Approvals

A5383

Primary Statistical Analysis Plan

Version 3.0

March 15, 2024

Randomized, Controlled Trial to Evaluate the Anti-inflammatory Efficacy of Letermovir (Prevymis) in Adults with Human Immunodeficiency Virus (HIV)-1 and Asymptomatic Cytomegalovirus (CMV) Who Are on Suppressive ART and Its Effect on Chronic Inflammation, HIV Persistence, and Other Clinical Outcomes (ELICIT)

ClinicalTrials.gov Identifier: NCT04840199

Protocol Version 3.0

This is the ACTG A5383 SAP Version 3.0 with names of authors, names of publication writing team members and analysis timeline redacted.

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Version History

Version	Changes Made	Date Finalized
1.0	Original Version	10 May 2022
2.0	Updated title page and header. Added new exploratory hypothesis/objective and updated language in Sections 2.2.3 and 2.3.3 to match the latest protocol. Updated text within Section 4 General Considerations.	10 Aug 2023
3.0	Due to the study closing early after the futility analysis and participants in the letermovir arm being brought in for treatment discontinuation visits the analysis approach was changed to account for participants in the letermovir arm having varying durations of treatment. Additionally, some of the original protocol objectives were abandoned by the team while others were changed from SDAC-led to outside-SDAC analyses.	15 Mar 2024

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary estimands that will address specific study objectives and interim monitoring of the A5383 study. The Primary SAP includes general analytic approaches for all primary estimands, 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.

All analyses which will be performed at SDAC have been outlined in this Primary SAP.

1.2 Version History

For SAP Version 3.0, major modifications are related to the planned analysis approach after the study was closed for futility. Due to the participants in the letermovir arm having to discontinue treatment after the SMC decision to close the study, the duration of treatment and the study week of final on-treatment evaluations differs by participant. The original cross-sectional analysis approach has been modified to a repeated measures approach with a treatment phase and a post-treatment phase to allow for varying time on treatment. Additionally, some analyses were abandoned and others were identified as outside-SDAC analyses.

For SAP Version 2.0, major modifications include updates to language throughout the SAP to align with A5383 protocol version 3.0, the addition of an exploratory hypothesis/objective, and clarification of population definitions under Section 4 General Considerations.

2 Study Overview (Protocol Version 3.0)

2.1 Study Design

A5383 is a phase II, randomized, open-label, controlled, multicenter trial being conducted at US sites to evaluate anti-inflammatory efficacy of letermovir 480 mg once daily for 48 weeks in adults with HIV and asymptomatic cytomegalovirus (CMV) on antiretroviral therapy (ART)-mediated suppression. A futility analysis will be performed after the first 40 participants, who have started study treatment, reach their 8-week study visit. Participants will be followed for 60 weeks (48 weeks on either letermovir or no anti-CMV treatment with 12 weeks of post-treatment period follow-up). We plan to enroll 180 participants (90 in each arm; our goal is that at least one third (30 participants in each arm) will be individuals assigned female sex at birth not on testosterone or individuals assigned male sex at birth on feminizing sex hormones and at least one half (45 participants in each arm) will have screening $CD4^+$ T cell counts <350 cells/mm^3). The target population for this study will be adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for ≥48 weeks on combination ART. Participants will be randomized 1:1 to receive either letermovir 480 mg once daily or no anti-CMV treatment for 48 weeks.

2.2 Hypotheses

2.2.1 Primary

Letermovir will cause a greater reduction in plasma soluble receptor for tumor necrosis factor type II (sTNFRII) levels than no anti-CMV treatment at weeks 46/48.

2.2.2 Secondary

- Letermovir (480 mg once daily) will be generally tolerable over the 48 week study treatment period as compared to no anti-CMV treatment.
- Letermovir will reduce the frequency of detection and levels of cytomegalovirus (CMV) DNA in mucosal samples (throat wash, seminal plasma, and cervicovaginal swabs) and in blood plasma compared to no anti-CMV treatment, through 48 weeks of treatment. This effect will persist for 4 weeks following treatment discontinuation (i.e., at week 52), and return to baseline by week 60.
- Letermovir will cause a greater reduction in plasma sCD163 levels than no anti-CMV treatment at weeks 8, 46/48, and 52, but not at week 60.
- Letermovir will cause greater reductions in plasma sTNFRII than no anti-CMV treatment at weeks 8 and 52, but not at week 60.

2.2.3 Exploratory

- Letermovir will cause a greater reduction in inflammatory and coagulation markers (sCD14, IL-6, hsCRP, and D-Dimer) than no anti-CMV treatment at weeks 8 and 46/48, differences that will persist at week 52, but return to baseline by week 60.
- Monocyte activation (cellular markers of monocyte activation, e.g., $CD14^{var}CD16+$): Letermovir will reduce monocyte activation at weeks 8 and 48 compared to no anti-CMV treatment, an effect that will persist for at least 4 weeks after discontinuing study treatment.
- CMV-specific response: Letermovir will reduce CMV immunoglobulin G (IgG) titer and CMV-specific T cell response (reduced clonality of T cell receptor [TCR]) at week 48 compared to no anti-CMV treatment.
- Microbial translocation markers (B-D-Glucan, I-FABP, LBP, Zonulin): Letermovir will reduce biomarkers of microbial translocation at weeks 46/48 compared to no anti-CMV treatment, an effect that will persist for at least 4 weeks after stopping study treatment.
- Multiplex-bead-array assay: Letermovir will modulate the cytokines network from baseline to weeks 8 and 46/48, compared to no anti-CMV treatment, an effect that will persist for at least 4 weeks after stopping study treatment.
- Detailed markers of coagulation: Letermovir will decrease markers of the coagulation cascade (including soluble urokinase plasminogen activator receptor [suPAR], plasmin-alpha2-antiplasmin complex [PAP], prothrombin fragment 1+2) at weeks 46/48 compared to no anti-CMV treatment.
- Letermovir will result in a greater reduction in soluble markers of endothelial activation at weeks 8 and 46/48 than no anti-CMV treatment (sICAM-1, sVCAM-1, sTF, E-selectin, P-selectin), an effect that will persist for at least 4 weeks after stopping study treatment.

- T cell dysfunction: Letermovir will reduce T cell dysfunction (including but not limited to decreased activation [$CD38^+$/HLA-DR co-expression], and exhaustion [PD-1] markers) in blood at weeks 8 and 48 and both decrease senescence markers (CD28-$CD57^+$ T cells) and increase $CD4^+/CD8^+$ ratio at week 48, when compared to those receiving no anti-CMV treatment, differences that will persist for at least 4 weeks after study treatment discontinuation.
- Insulin resistance: Letermovir will result in greater reductions in insulin resistance than no anti-CMV treatment at week 46 by homeostatic model assessment-insulin resistance (HOMA-IR) and plasma levels of free fatty acids, differences that will persist for at least 4 weeks after study treatment discontinuation.
- Plasma free fatty acids: Letermovir will result in greater reductions in fasting free fatty acids, an indirect measure of adipocyte insulin sensitivity and lipid storage, than no anti-CMV treatment at week 46, differences that may persist for at least 4 weeks after study treatment discontinuation.
- Letermovir will result in greater improvements than no anti-CMV treatment in physical function as assessed by chair rise time and frailty score (gait speed, grip strength) at week 46, differences that will persist for at least 4 weeks after study treatment discontinuation.
- Veterans Aging Cohort Study (VACS) index: Letermovir will result in greater improvements in VACS index than no anti-CMV treatment at weeks 46 and 60.
- HIV Reservoir: Letermovir will reduce the size of the HIV-1 reservoir as measured by cell-associated HIV-1 DNA at weeks 8 and 48 when compared to those receiving no anti-CMV treatment.
- HIV Reservoir Sequencing: Letermovir will reduce the clonality of the HIV reservoir in blood at week 48 when compared to those receiving no anti-CMV treatment.
- Letermovir will reduce the transcriptional activity of the HIV-1 reservoir as measured by single copy assays of plasma HIV-1 RNA and cell-associated HIV-1 RNA at the week 8 and 48 time points when compared to those receiving no anti-CMV treatment.
- Letermovir will not have clinically significant (i.e., requiring dose adjustment) interactions with common ART drugs (i.e., TDF/TAF and integrase inhibitors) or allowed statins.
- Plasma letermovir levels during treatment will correlate with the extent of reduction in sTNFRII and CMV DNA shedding levels.
- Letermovir will alter the plasma proteome as assessed by a modified aptamer assay (SOMAscan), including pathways linked to cardiovascular risk.
- Central nervous system (CNS) tolerability of letermovir: Change in neurocognitive performance, mood, sleep quality, concentrations will each be similar to or better than no anti-CMV treatment at week 46. Change in Neurofilament light (NFL) in blood plasma will be similar or better than no anti-CMV treatment at weeks 46/48.
- Letermovir resistance: Among letermovir-treated participants with persistent detectable CMV shedding, the emergence of letermovir resistance mutations will be observed in mucosal sites, but not plasma, and will no longer be detected at week 60.
- Flu vaccine responsiveness: Letermovir will reduce the humoral response to seasonal influenza vaccination obtained in the course of clinical care compared to no anti-CMV treatment (fold change from the last pre-vaccine time point to the first available time point between 4-12 weeks post-vaccine).

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 study, all queries have been resolved, and the study database closure/data lock has been completed.

2.3.1 Primary Objectives

- To determine whether letermovir 480 mg daily at weeks 46/48 will result in decreased plasma sTNFRII levels compared to no anti-CMV treatment in treated individuals with HIV.

2.3.2 Secondary Objectives

- Tolerability: To determine whether letermovir 480 mg daily for 48 weeks is safe and tolerable in treated individuals with HIV.
- CMV DNA levels: To determine if letermovir reduces mucosal and plasma levels of CMV DNA in treated individuals with HIV through 48 weeks of therapy and following treatment discontinuation.
- To evaluate if letermovir reduces plasma sCD163 levels at weeks 8, 46/48, 52, and 60.
- To evaluate if letermovir reduces plasma sTNFRII levels at weeks 8, 52 and 60.

2.3.3 Exploratory Objectives

- To evaluate if letermovir affects inflammatory and coagulation markers (sCD14, IL-6, hsCRP, and D-Dimer) at weeks 8, 46/48, 52, and 60.
- Monocyte activation (cellular markers of monocyte activation): To evaluate if letermovir reduces monocyte activation at weeks 8, 48, 52, and 60.
- CMV-specific response: To evaluate if letermovir affects CMV IgG titer and CMV-specific T cell response (reduced clonality of TCR) at week 48. [*NOTE: The CMV-specific T cell response outcome will be analyzed outside of SDAC*]
- Microbial translocation markers (B-D-Glucan, I-FABP, LBP, Zonulin): To evaluate if letermovir affects biomarkers of microbial translocation at weeks 8, 46/48, 52, and 60. [*NOTE: This outcome will be analyzed outside of SDAC*]
- Multiplex-bead-array assay: To evaluate if letermovir affects the cytokines network at weeks 8, 46/48, 52, and 60. [*NOTE: This outcome was abandoned*]
- Detailed markers of coagulation: To evaluate if letermovir affects the coagulation cascade (including suPAR, plasmin antiplasmin complexes, prothrombin fragment 1+2) at weeks 8, 46/48, 52, and 60. [*NOTE: This outcome will be analyzed outside of SDAC*]
- To evaluate if letermovir reduces soluble markers of endothelial activation at weeks 8, 46/48, 52, and 60. [*NOTE: This outcome will be analyzed outside of SDAC*]
- To evaluate if letermovir affects T cell dysfunction in blood at study weeks 8, 48, 52, and 60.
- To evaluate if letermovir reduces insulin resistance at weeks 46 and 60.

- To evaluate if letermovir reduces plasma fasting free fatty acids at weeks 46 and 60.
- To evaluate if letermovir improves physical function and frailty at weeks 46 and 60.
- VACS index: To evaluate if letermovir improves the VACS index at weeks 46 and 60.
- HIV Reservoir: To evaluate if letermovir reduces the size of the HIV-1 reservoir as measured by cell-associated HIV-1 DNA at study weeks 8 and 48.
- HIV Reservoir Sequencing: To evaluate if letermovir reduces the clonality of the HIV reservoir in blood at study week 48. [*NOTE: This outcome will be analyzed outside of SDAC*]
- To evaluate if letermovir affects the transcriptional activity of the HIV-1 reservoir as measured by single copy assays of plasma HIV-1 RNA and cell-associated HIV-1 RNA at the week 8 and 48 time points. [*NOTE: This outcome will be analyzed outside of SDAC*]
- To evaluate interactions between letermovir and common ART drugs and statins. [*NOTE: This outcome was abandoned*]
- To evaluate correlations between plasma letermovir levels during treatment with the extent of reduction in sTNFRII and CMV DNA shedding levels. [*NOTE: This outcome was abandoned*]
- To evaluate if letermovir affects plasma proteome, including pathways linked to cardiovascular risk. [*NOTE: This outcome will be analyzed outside of SDAC*]
- To evaluate the CNS tolerability of letermovir: The tolerability measures will include change in neurocognitive performance, mood, sleep quality, and NFL concentrations in blood plasma.
- Letermovir resistance: To evaluate emergence of letermovir resistance mutations in participants with persistent detectable CMV shedding during study period. [*NOTE: This outcome was abandoned*]
- Flu vaccine responsiveness: To evaluate if letermovir affects the humoral response to seasonal influenza vaccination obtained in the course of clinical care (fold change from the last pre-vaccine time point to the first available time point between 4-12 weeks post-vaccine). [*NOTE: This outcome was abandoned*]

2.4 Overview of Sample Size Considerations

Determined based on the primary endpoint of change in levels of plasma sTNFRII, the sample size for A5383 is calculated to be 180 participants with a 1:1 randomization to letermovir 480 mg : no anti-CMV treatment ratio, 90 participants will receive letermovir 480 mg and 90 will receive no anti-CMV treatment. Note that this resulting sample size of 180 has been inflated to account for the 15% 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, 154 participants (77 letermovir, 77 no anti-CMV treatment) would provide 90% power to detect a 0.065 $\log_{10}$ pg/mL difference in sTNFRII between the arms, using a two-sample t-test, a change SD of 0.123 $\log_{10}$ pg/mL (accounting for reduced variability due to averaging two sTNFRII results pre-treatment and two sTNFRII results at weeks 46 and 48), and a two-sided 5% alpha.

2.5 Overview of Formal Interim Monitoring

The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC), although the SMC may elect to deviate from this timeline. In the event that

enrollment for the first 40 participants takes longer than 6 months, a separate SMC meeting will be held 6 months after the first participant is enrolled. SMC reviews will then continue every 6-12 months after this point. The SMC will review summaries of accrual, baseline characteristics, conduct of the study (including premature study and premature study treatment discontinuations), adverse events (AEs) by study treatment arm, $CD4^+$ T cell counts and HIV-1 RNA levels/suppression, and plasma CMV DNA levels (and if applicable, letermovir resistance results) over time by study treatment arm, and data/sample availability.

The first interim SMC review for tolerability will occur at the time of futility analysis. We expect this to occur at approximately 9 months after the enrollment of the first study participant, once the 40^{th} enrolled participant has reached 8 weeks on study, plasma samples have been tested for an initial protocol-specified assessment of immunologic futility, and data have been analyzed. Enrollment will pause after the 40^{th} participant has started study treatment and until (and if) the SMC deems the intervention not to be futile, but enrolled participants will be allowed to continue on study (i.e., beyond week 8) while the interim analysis is being conducted.

An interim review should also be convened if, at any time, CMV DNA levels are detectable in plasma in 12 or more participants while taking study medications (letermovir arm only), letermovir resistance is detected in plasma specimens in two participants (letermovir arm only), new grade ≥2 atrial fibrillation or atrial flutter of any grade is identified in four participants, a participant experiences a grade 4 AE related to study treatment, or 3 or more participants experience HIV-1 virologic failure in the letermovir arm or any concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team.

3 Outcome Measures (Modified Due to Early Study Termination)

3.1 Primary Outcome Measures

- Absolute change from baseline to week 46/48 (or the latest result in the treatment phase) in sTNFRII.

3.2 Secondary Outcome Measures

- Occurrence of Grade ≥3 AEs or confirmed HIV-1 virologic failure after initiation of study treatment (letermovir arm) or the IOT visit (no anti-CMV treatment arm).
- Mucosal and plasma CMV DNA levels at baseline and weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52, and 60.
- sCD163 at baseline and weeks 8, 24, 46, 48 (and/or the latest result in the treatment phase), 52, and 60.
- sTNFRII at baseline and weeks 8, 24, 46, 48 (and/or the latest result in the treatment phase), 52, and 60.

3.3 Other Outcome Measures

- Coagulation markers (sCD14, IL-6, hsCRP, and D-Dimer) at baseline and weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52 and 60.

- $CD14^{var}CD16+$ cells at baseline and weeks 8, 48 (and/or the latest result in the treatment phase), 52, and 60.
- Absolute change from baseline to week 48 (and/or the latest result in the treatment phase) in CMV IgG titer.
- CD4+/CD8+ ratio at baseline and weeks 8, 48 (and/or the latest result in the treatment phase), 52, and 60.
- (CD8+)CD38+HLA-DR+ T cells at baseline and weeks 8, 48 (and/or the latest result in the treatment phase), 52, and 60.
- CD8+CD28-CD57+ T cells at baseline and weeks 8, 48 (and/or the latest result in the treatment phase), 52, and 60.
- HOMA-IR and plasma levels of free fatty acid at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- Gait speed time at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- Grip strength at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- Chair rise time at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- VACS index score at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- Single copy assay of HIV-1 RNA and cell-associated HIV-1 RNA and total HIV DNA at baseline and weeks 8 and 48 (or the latest result in the treatment phase).
- Neurocognitive functioning (Trail Making A & B, Digit Symbol, and HVLT-R [HAILO Battery]) at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- PHQ9 at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- GAD7 at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- Pittsburgh Sleep Quality Index at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.
- Plasma NFL at baseline and weeks 46 (and/or the latest result in the treatment phase) and 60.

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 summarized on the $\log_{10}$ scale, as appropriate, if determined not to 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 and all eligible participants in the control arm.
- Confirmed virologic failure is defined as two consecutive HIV-1 RNA levels ≥200 copies/mL by real-time HIV-1 RNA testing. Participants with a plasma HIV-1 RNA ≥200 copies/mL at any

visit will have a confirmatory viral load obtained as soon as possible but within 14 days after the first sample was drawn, if possible. If the consecutive measurement of HIV-1 RNA is also ≥200 copies/mL, the participant will be considered to have confirmed virologic failure.

- "Treatment phase" refers to the time from study entry to 1) discontinuation of study treatment in the letermovir arm + 10 days, and 2) the last study visit on/prior to Week 48 in the control arm.
- 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 (same as efficacy set in estimand tables below) limited to participants who 1) do not prematurely discontinue study product prior to Week 8 and have self-reported adherence >50% (letermovir arm only), and 2) do not have a confirmed virologic failure during the treatment phase.
- Unless otherwise noted, PP analyses will exclude outcome data collected 1) after initiating a prohibited medication, 2) within 7 days of receiving a vaccination (vaccine administration on the same day as specimen collection will be assumed to have occurred after the specimen collection), 3) during or within 7 days of the resolution of influenza and COVID-19 diagnoses, and 4) within 7 days of a reported fever (≥38° C).
- Any participants determined to be ineligible for A5383 will not be included in any of the safety or efficacy analyses.
- Absolute change refers to the value at the follow-up time point minus the value at baseline.
- The screening visit window will be [randomization date - 90 days, randomization date - 1 day].
- The entry visit window will be [randomization date, initiation of treatment visit date - 2 days]. If the initiation of treatment visit date is missing the window will be [randomization date, randomization date + 30 days].
- The initiation of treatment visit window will be [initiation of treatment visit date, earliest of 1) initiation of treatment visit + 2 days or 2) treatment initiation date].
- Baseline refers to the most recent study evaluation at or prior to the treatment initiation visit.
- Post-baseline, visit weeks will be calculated as weeks since treatment initiation and visit week windows will be ± 2 weeks for Week 4, -2 to +4 weeks for Week 8 and ± 4 weeks for Weeks 16, 24, 32 and 40. Weeks 46 and 48 will share a window which will span week 44 to week 50. Week 52 will have a -2 to +4 week window and Week 60 will have a ± 4 week window.
- For post-baseline visit weeks other than 46 and 48, in the event of multiple results within a study window the result closest to the scheduled evaluation week will be used, with priority given to on-treatment results.
- Results within the weeks [44, 50] visit window will use the following logic to determine Week 46 and Week 48 results:
    - If two results are collected the earlier will be Week 46 and the latter Week 48.
    - If one result is collected on treatment and one result is collected off treatment the on treatment will be Week 46 and the off treatment will be Week 48.
    - If only one result is collected it will be Week 48.
    - If three or more results are available priority will be given to those collected on treatment and assigned Weeks based on the above rules.
- For markers run in duplicate (for the purpose of averaging) at study entry and treatment initiation and also at Weeks 46 and 48, "baseline" will refer to the average of study entry and treatment initiation and "Week 46/48" will refer to the average of Week 46 and Week 48. If

only one result is available at either of these time points the single result will be used. For the per-protocol analyses the "Week 46/48" calculation will only use results collected while on treatment (letermovir arm only).

- The VACS index score outcome will use the VACS 2.0 Index equation. The eGFR component will use the CKD-EPI 2021 equation.
- Gait speed will be calculated as the average two gait speeds if both 4-meter walks were completed.
- Grip strength will be calculated as the mean of the available trial results (up to 3).
- PHQ9 will be scored as outlined at https://www.mdcalc.com/calc/1725/phq9-patient-health-questionnaire9.
- GAD7 will be scored as outline at https://www.mdcalc.com/calc/1727/gad7-general-anxiety-disorder7
- Pittsburgh sleep quality index will be scored as outlined in PMID: 2748771 DOI: 10.1016/0165-1781(89)90047-4.
- VACS 2.0 Index will be calculated using SAS code provided by Janet Tate.

5 Estimand and Estimation

5.1 Primary Estimand

Primary Objective 1: To determine whether letermovir 480 mg daily will result in decreased plasma sTNFRII levels compared to no anti-CMV treatment in treated individuals with HIV.	
Estimand description	Change in sTNFRII during the treatment phase after initiating letermovir, among HIV-infected adults with asymptomatic CMV who remain on study treatment (with ≥50% adherence) without virologic failure or use of prohibited medications.
Treatment	Letermovir 480 mg once daily
Target population	**Analysis set**
Adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for at least the prior 48 weeks on combination ART.	Efficacy set (Participants who remained on study treatment during the treatment phase for at least 8 weeks with self-reported adherence >50% (letermovir arm only) and did not have confirmed virologic failure)
Variable(s)	**Outcome measure(s)**

Change in sTNFRII during the treatment phase.	Absolute change from baseline to Week 46/48 (or the latest result in the treatment phase) in sTNFRII. "Baseline" refers to the average of two pre-treatment phase results. "Week 46/48" refers to the average of two results within one day of treatment discontinuation and within the week [44, 50] window. If two results are not available for averaging within a time point, a single result will be used.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 8 (letermovir arm only): excluded (principal stratum) 5. Self-reported treatment adherence <50% (letermovir arm only): excluded (principal stratum) 6. Confirmed HIV virologic failures: excluded (principal stratum) 7. Vaccination or concurrent acute illness within 1 week of sTNFRII assessments: excluded (principal stratum) 8. Pregnancy: excluded (principal stratum)	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.
Population-level summary measure	**Analysis approach**
The average change in sTNFRII during the treatment phase after initiating letermovir compared to the average change had no treatment been given.	Linear regression of sTNFRII change (log_{10}-transformed prior to calculating change) on treatment arm adjusted for stratification factors.

5.2 Secondary Estimands

5.2.1 First Secondary Estimand

Secondary Objective 1: To determine whether letermovir 480 mg daily is safe and tolerable in treated individuals with HIV.	
Estimand description	The change in the probability of Grade ≥3 adverse events or HIV-1 virologic failure after initiating letermovir among HIV-infected adults with asymptomatic CMV.
Treatment	Letermovir 480 mg once daily
Target population	**Analysis set**
Adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for at least the prior 48 weeks on combination ART.	Safety set (Participants who initiate study treatment (letermovir arm only) and all participants in the no anti-CMV treatment arm)
Variable(s)	**Outcome measure(s)**
Occurrence of a Grade ≥3 AE or HIV-1 virologic failure.	Outcome measure as defined by the Variable. Only events occurring after the initiation of study treatment are included in the letermovir arm. All post-IOT visit events are included in the no anti-CMV treatment arm.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Change in background ART regimen: ignored (treatment policy) 2. Use of prohibited medications: ignored (treatment policy) 3. Treatment discontinuation prior to week 48 (letermovir arm only): ignored (treatment policy) 4. Self-reported treatment adherence <50% (letermovir arm only): ignored (treatment policy) 5. Pregnancy: ignored (treatment policy)	Participants who discontinue follow-up before week 60 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 [60 weeks]). A sensitivity analysis will use the Kaplan-Meier estimator of time to first event with participants censored at the time of study discontinuation.

Population-level summary measure	Analysis approach
For any Grade ≥3 adverse event or HIV-1 virologic failure (yes/no), the change in the probability of an event after initiating letermovir compared to the probability of an event had letermovir not been given.	Absolute difference (letermovir arm relative to no anti-CMV treatment arm) in the proportion of participants with any Grade ≥3 adverse event or virologic failure (yes/no) while on study. 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 (Chan-Zhang method).

Supplementary Analyses

A supplementary analysis will examine all reported AEs, regardless of grade. The highest AE grade per participant will be summarized by treatment arm. A two-sided Wilcoxon rank sum test will be used to assess differences in the highest grade distribution between arms.

5.2.2 Second Secondary Estimand

Secondary Objective 2: To determine if letermovir reduces mucosal and plasma levels of CMV DNA in treated individuals with HIV during therapy and following treatment discontinuation.	
Estimand description	The change in the probability of CMV DNA shedding over 60 weeks after initiating letermovir among HIV-infected adults with asymptomatic CMV.
Treatment	Letermovir 480 mg once daily
Target population	**Analysis set**
Adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for at least the prior 48 weeks on combination ART.	Efficacy set
Variable(s)	**Outcome measure(s)**
Mucosal and plasma CMV DNA levels baseline and weeks 8, 46, 48, 52, and 60.	1) Plasma CMV DNA shedding (detectable CMV DNA levels) at baseline, weeks 8, 46, 48

	(and/or the latest result in the treatment phase), 52, 60. 2) Oral CMV DNA shedding (detectable CMV DNA levels) at baseline, weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52, 60. 3) Genital (seminal/cervicovaginal) CMV DNA shedding (detectable CMV DNA levels) at baseline, weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52, 60.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 8 (letermovir arm only): excluded (principal stratum) 5. Self-reported treatment adherence <50% (letermovir arm only): excluded (principal stratum) 6. Confirmed HIV virologic failures: excluded (principal stratum) 7. Vaccination or concurrent acute illness within 1 week of CMV DNA assessments: excluded (principal stratum) 8. Pregnancy: excluded (principal stratum)	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.
Population-level summary measure	**Analysis approach**
The change in the probability of CMV DNA shedding during the treatment phase and post-treatment phase compared to the probability had letermovir not been given.	For each of plasma and mucosal shedding, a generalized estimating equations (GEE) model with binary outcomes and an appropriate covariance structure. The covariates will be study arm and the stratification factors, as well as a three-level period effect (early treatment phase [through Week 8], late treatment phase, post-treatment phase) and its interaction with the study arm.

5.2.3 Third Secondary Estimand

Secondary Objective 3: To evaluate if letermovir reduces plasma sCD163 levels at weeks 8, 24, 46, 48, 52, and 60.	
Estimand description	Change in sCD163 over 60 weeks after initiating letermovir, among HIV-infected adults with asymptomatic CMV.
Treatment	Letermovir 480 mg once daily
Target population	**Analysis set**
Adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for at least the prior 48 weeks on combination ART.	Efficacy set
Variable(s)	**Outcome measure(s)**
sCD163 at baseline and weeks 8, 24, 46, 48, 52 and 60.	sCD163 at baseline and weeks 8, 24, 46, 48 (and/or the latest result in the treatment phase), 52 and 60. "Baseline" refers to the average of two pre-treatment results. If two results are not available for averaging within a time point, a single result will be used.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 8 (letermovir arm only): excluded (principal stratum) 5. Self-reported treatment adherence <50% (letermovir arm only): excluded (principal stratum) 6. Confirmed HIV virologic failures: excluded (principal stratum)	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.

7. Vaccination or concurrent acute illness within 1 week of sCD163 assessments: excluded (principal stratum) 8. Pregnancy: excluded (principal stratum)	
Population-level summary measure	**Analysis approach**
The average change in sCD163 during the treatment phase and post-treatment phase compared to the average change had letermovir not been given.	A generalized estimating equations (GEE) model with continuous outcomes and an appropriate covariance structure. The covariates will be study arm and the stratification factors, as well as a three-level period effect (early treatment phase [through Week 8], late treatment phase, post-treatment phase) and its interaction with the study arm.

5.2.4 Fourth Secondary Estimand

Secondary Objective 4: To evaluate if letermovir reduces plasma sTNFRII levels at weeks 8, 24, 46, 48, 52 and 60.	
Estimand description	Change in sTNFRII over 60 weeks after initiation letermovir, among HIV-infected adults with asymptomatic CMV.
Treatment	Letermovir 480 mg once daily
Target population	**Analysis set**
Adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for at least the prior 48 weeks on combination ART.	Efficacy set
Variable(s)	**Outcome measure(s)**
sTNFRII at baseline and weeks 8, 24, 46, 48, 52 and 60.	sTNFRII at baseline and weeks 8, 24, 46, 48 (and/or the latest result in the treatment phase), 52 and 60. "Baseline" refers to the average of two pre-treatment results. If two results are not

	available for averaging within a time point, a single result will be used.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 8 (letermovir arm only): excluded (principal stratum) 5. Self-reported treatment adherence <50% (letermovir arm only): excluded (principal stratum) 6. Confirmed HIV virologic failures: excluded (principal stratum) 7. Vaccination or concurrent acute illness within 1 week of sTNFRII assessments: excluded (principal stratum) 8. Pregnancy: excluded (principal stratum)	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.
Population-level summary measure	**Analysis approach**
The average change in sTNFRII during the treatment phase and post-treatment phase compared to the average change had letermovir not been given.	A generalized estimating equations (GEE) model with continuous outcomes and an appropriate covariance structure. The covariates will be study arm and the stratification factors, as well as a three-level period effect (early treatment phase [through Week 8], late treatment phase, post-treatment phase) and its interaction with the study arm.

6 Analysis of Objectives

6.1 Primary Analysis

1. sTNFRII analysis:
    a. Using the PP population, absolute changes in sTNFRII from baseline to the latest result in the treatment phase will be compared between the letermovir arm and the no anti-CMV treatment arm by linear regression. For this model each participant will have a single outcome measure of sTNFRII change from baseline

to the end of the treatment phase. The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors).

b. A supplemental logistic regression will be done to estimate the odds of achieving the targeted sTNFRII reduction of 0.065 log_{10} pg/mL which, as previously stated, has been associated with a clinically relevant 22.5% reduction in CAD events. For this model, each participant will have a single outcome measure (last treatment phase sTNFRII change of ≤ -0.065 log_{10} pg/mL vs > -0.065 log_{10} pg/mL). The covariates will be study arm with screening CD4+ cell count and sex plus hormonal therapy (the stratification factors).

c. Five supplemental linear regression analyses will be performed. The first will perform the primary analysis using a modified intent-to-treat population (mITT) consisting of all participants who have been exposed to letermovir and all no anti-CMV treatment arm participants. The remaining four will use the PP population and will assess differential letermovir effects by 1) baseline sTNFRII tertile, 2) CD4 strata, 3) sex and hormonal therapy strata, and 4) presence versus absence of mucosal CMV shedding at baseline by additionally adjusting for these main effects and the study arm by main effect interaction.

6.2 Secondary and Exploratory Analyses

1. Safety secondary analysis:
    a. Using the mITT population, Grade 3+ AEs or HIV-1 virologic failures through Week 48 will be summarized by treatment arm. The proportion of participants in each arm with a Grade 3+ AE or HIV-1 virologic failure will be provided along with the difference in proportions and associated exact 95% CI and p-value.
    b. Using the mITT population, Kaplan-Meier curves of time from the IOT visit to first Grade 3+ AE or HIV-1 virologic failure (participants will be censored at time of study discontinuation) will be provided along with the corresponding log-rank test p-value.
    c. Using the mITT population, the highest grade AE for each participant through Week 48 will be summarized by treatment arm. The associated Wilcoxon rank-sum test p-value will be provided.
2. CMV DNA shedding secondary analysis:
    a. Using the PP population, binary CMV DNA shedding (yes/no) from baseline, weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52 and 60 will be analyzed by GEE regression. For this model each participant will have up to seven outcomes of shedding at the above weeks. The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors) as well as a three-level period effect (early treatment phase [through Week 8], late treatment phase, post-treatment phase) and its interaction with the study arm.
    NOTE: this analysis will be done three times, once for each of the following: blood plasma CMV DNA, throat CMV DNA, and genital (seminal/cervicovaginal) CMV DNA.
3. sCD163 secondary analysis:

   a. Using the PP population, sCD163 from baseline, weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52 and 60 will be analyzed by GEE regression. For this model each participant will have up to six outcomes of sCD163 at the above weeks. The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors) as well as a three-level period effect (early treatment phase [through Week 8], late treatment phase, post-treatment phase) and its interaction with the study arm.
4. sTNFRII secondary analysis:
   a. Using the PP population, sTNFRII from baseline, weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52 and 60 will be analyzed as the secondary sCD163 analysis above.
5. Inflammatory and coagulation marker exploratory analysis:
   a. Using the PP population, sCD14, IL-6 hsCRP and D-Dimer ~~change~~ from baseline, weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52 and 60 will each be analyzed as the secondary sCD163 analysis above.
6. Monocyte activation exploratory analysis:
   a. Using the PP population, $CD14^{var}$CD16+ cells from baseline, weeks 8, 48 (and/or the latest result in the treatment phase), 52 and 60 will each be analyzed as the secondary sCD163 analysis above.
7. CMV-specific response exploratory analysis:
   a. Using the PP population, absolute changes in CMV IgG titer from baseline to Week 48 (or the latest result in the treatment phase) will be compared between the letermovir arm and the no anti-CMV treatment arm by linear regression. For this model each participant will have a single outcome measure of clonality change from baseline to Week 48 (or the latest result in the treatment phase). The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors).
8. T-cell exploratory analysis:
   a. Using the PP population, continuous (CD8+)CD38+HLA-DR+, PD-1, CD38+CD28-CD57+ and CD4+/CD8+ ratio from baseline, weeks 8, 48 (and/or the latest result in the treatment phase), 52 and 60 will each be analyzed as the secondary sCD163 analysis above.
9. Insulin resistance exploratory analysis:
   a. Using the PP population, continuous HOMA-IR and plasma free fatty acid from baseline, ~~to~~ weeks 46 (and/or the latest result in the treatment phase) and 60 will each be analyzed by GEE regression. For this model each participant will have up to four outcomes at the above weeks. The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors) as well as a two-level period effect (treatment phase, post-treatment phase) and its interaction with the study arm.
10. Physical function exploratory analysis:
    a. Using the PP population, continuous chair rise time, gait speed and grip strength from baseline, weeks 46 (and/or the latest result in the treatment phase) and 60 will each be analyzed as the insulin resistance analysis above.
11. VACS 2.0 Index exploratory analysis:

a. Using the PP population, continuous VACS index score from baseline, weeks 46 (and/or the latest result in the treatment phase) and 60 will be analyzed as the insulin resistance analysis above.

12. HIV reservoir exploratory analysis:
    a. Using the PP population, continuous single copy assay of HIV-1 RNA, cell-associated HIV-1 RNA and cell-associated HIV-1 DNA from baseline, weeks 8 and 48 (or the latest result in the treatment phase) will each be analyzed by GEE regression. For this model each participant will have three outcome measures ~~of change~~ at the above weeks. The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors) as well as a two-level period effect (early treatment phase [through Week 8], late treatment phase).
        i. For each of the three outcome measures, if over one third of the data are below the lower limit of quantification (LLoQ) at either baseline, week 8 or week 48 (end of the treatment phase), the data will also be analyzed as binary (<LLoQ vs. ≥LLoQ) outcomes by GEE regression.
13. CNS tolerability exploratory analysis:
    a. Using the PP population, continuous trail making A & B, digit symbol, HVLT-R, PHQ9, GAD7, Pittsburgh sleep quality index and plasma NFL from baseline, ~~to~~ weeks 46 (and/or the latest result in the treatment phase) and 60 will each be analyzed as the insulin resistance analysis above.

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, summaries will be pooled over treatment arms. For the SMC Closed Interim Report as well as for final analysis, summaries will be presented both pooled (overall) and by 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 prior SMC reviews.
2. Study entry (randomized population)
    a. Accrual: Tables of accrual by month and by site.
3. Study status (reported in ClinicalTrials.gov)
    a. Number of participants off study with off study reasons.
    b. Study visit of last clinic visit.
    c. Weeks from study entry to last clinic visit.
4. Treatment status (not included in SMC Open Interim Report)
    a. Number of participants who did not start study treatment and reason why treatment was not started.
    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 treatment initiation to permanent discontinuation of study treatment.
5. Baseline characteristics (for mITT and PP populations, reported in ClinicalTrials.gov)
   a. Demographics: age, sex, gender, sex and use of gender-affirming hormones, race, ethnicity
   b. Weight and BMI
   c. HIV status: ARV regimen, CD4 count, HIV-1 RNA
   d. Laboratory results: Hemoglobin, platelet count, AST/SGOT, ALT/SGPT, alkaline phosphatase, bilirubin, and eGFR/CrCl.
6. Pregnancies
   a. Listing and description of all available information related to pregnancy and outcome.
7. Virologic failures
   a. Number of confirmed virologic failures.
   b. Listing of all available HIV-1 RNA data for participants who had virologic failures.
8. Adverse events (mITT population) and deaths (randomized population) (reported in ClinicalTrials.gov)
   a. Summary of all reportable AEs through Week 48 by MedDRA PT grouped by SOC and grade.
   b. Summary of SAEs through Week 48 by MedDRA PT grouped by SOC and grade.
   c. Summary of SAEs that are EAEs through Week 48 by MedDRA PT grouped by SOC and grade.
   d. Summary of all reportable AEs through Week 60 by MedDRA PT grouped by SOC and grade.
   e. Summary of SAEs through Week 60 by MedDRA PT grouped by SOC and grade.
   f. Summary of SAEs that are EAEs through Week 60 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.
9. CD4 cell counts
   a. Summary of cross-sectional CD4 cell counts and changes from entry.
10. Futility analysis (first closed SMC report after 40 participants have been enrolled, PP population)
   a. Summary of 8 week change in sTNFRII and sCD163 by treatment arm and difference between arms.
   b. Using observed and simulated future data for various simulation assumptions the following will be provided: predicted interval plots (PIPs), summary statistics of the final treatment effect, conditional power.
      NOTE: If the above summaries determine letermovir is futile for both sTNFRII and sCD163 they will be repeated in the subset of participants with screening CD4 <350 cells/mm^3.
   c. Participant listing of baseline and 8 week changes in sTNFRII and sCD163.

   d. Summary of 8 week odds of achieving hypothesized treatment effects (-0.0325 log_{10} pg/mL for sTNFRII and -0.023 log_{10} µg/mL for sCD163) by treatment arm and odds ratio between arms.
   e. Summary of 8 week change in sTNFRII and sCD163 by treatment arm and difference between arms within CD4 (≤ vs > 350 cells/mm3) and baseline level (≤ vs > observed median sTNFRII or sCD163) subgroups.
11. Concomitant medications (final report only)
   a. Summary of concomitant medications continued at study entry and started on study.
12. Analysis of primary sTNFRII outcome (final report only, PP population unless otherwise noted, reported in ClinicalTrials.gov)
   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 (or the latest result in the treatment phase) absolute change in sTNFRII with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
   c. Summary of the logistic regression model of 48 week (or the latest result in the treatment phase) absolute change in sTNFRII (≤ -0.065 vs >-0.065 log_{10} pg/mL) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
   d. Summary of the supplemental linear regression model of 48 week (or the latest result in the treatment phase) absolute change in sTNFRII with treatment arm and stratification factor covariates using the mITT population. The estimated effects, 95% CIs, and associated p-values will be provided.
   e. Similar linear regression summary for the supplemental subgroup linear regression models assessing differential letermovir effects by 1) baseline sTNFRII tertile, 2) CD4 strata, 3) sex and hormonal therapy strata and 4) presence of mucosal CMV shedding at baseline.
13. Analysis of secondary safety outcome (final report only, mITT population, reported in ClinicalTrials.gov)
   a. Summary of the number of participants with a Grade 3+ AE or HIV-1 virologic failure through Week 48 by treatment arm and associated difference in proportions and associated exact 95% CI and p-value.
   b. Kaplan-Meier curves of time from the IOT visit to first Grade 3+ AE or HIV-1 virologic failure (participants will be censored at time of study discontinuation) will be provided along with the corresponding log-rank test p-value.
   c. Summary of the number of participants with an AE through Week 48 by their highest grade and treatment arm and associated two-sided Wilcoxon rank sum p-value.
14. Analysis of secondary CMV DNA shedding outcomes (final report only, PP population, reported in ClinicalTrials.gov)
   a. Summary of CMV DNA shedding (yes/no) in blood plasma, throat and genital secretion compartments.

   b. For each compartment, summary of the GEE model of CMV DNA shedding at baseline, Weeks 8, 46, 48 (and/or the latest result in the treatment phase), 52 and 60. The estimated risk ratio, 95% CIs, and associated p-values will be provided for each follow-up period.

15. Analysis of secondary sCD163 outcome (final report only, PP population, reported in ClinicalTrials.gov)
    a. Summary of sCD163 at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of sCD163 (baseline, weeks 8, 24, 46, 48 (and/or the latest result in the treatment phase), 52 and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
16. Analysis of secondary sTNFRII outcome (final report only, PP population, reported in ClinicalTrials.gov)
    a. Summary of GEE model of sTNFRII (baseline, weeks 8, 24, 46, 48 (and/or the latest result in the treatment phase), 52 and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
17. Analysis of exploratory inflammatory and coagulation marker outcomes (final report only, PP population)
    a. Summary of sCD14, IL-6, hsCRP and D-Dimer at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of sCD14, IL-6, hsCRP and D-Dimer (baseline, weeks 8, 46/48 (and/or the latest result in the treatment phase), 52 and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
18. Analysis of exploratory monocyte activation outcomes (final report only, PP population)
    a. Summary of CD14^{var}CD16+ cells at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of CD14^{var}CD16+ cells (baseline, weeks 8, 48 (and/or the latest result in the treatment phase), 52 and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
19. Analysis of exploratory CMV-specific response outcomes (final report only, PP population)
    a. Summary of CMV IgG titer at each time point as well as changes from baseline by treatment arm.
    b. Summary of the linear regression models of 48 week (or the latest result in the treatment phase) absolute change in CMV IgG titer with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
20. Analysis of exploratory T-cell outcomes (final report only, PP population)
    a. Summary of (CD8+)CD38+HLA-DR+, PD-1, CD38+CD28-CD57+ and CD4+/CD8+ ratio at each time point as well as changes from baseline by treatment arm.

   b. Summary of GEE model of (CD8+)CD38+HLA-DR+, PD-1, CD38+CD28-CD57+ and CD4+/CD8+ ratio (baseline, weeks 8, 48 (and/or the latest result in the treatment phase), 52 and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.

21. Analysis of exploratory insulin resistance outcomes (final report only, PP population)
    a. Summary of HOMA-IR and plasma free fatty acid at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of HOMA-IR and plasma free fatty acid (baseline, weeks 46 (and/or the latest result in the treatment phase) and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
22. Analysis of exploratory physical function outcomes (final report only, PP population)
    a. Summary of chair rise time, gait speed and grip strength at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of chair rise time, gait speed and grip strength (baseline, weeks 46 (and/or the latest result in the treatment phase) and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
23. Analysis of exploratory VACS index outcome (final report only, PP population)
    a. Summary of VACS index score at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of VACS index score (baseline, weeks 46 (and/or the latest result in the treatment phase) and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.
24. Analysis of exploratory HIV reservoir outcomes (final report only, PP population)
    a. Summary of single copy assay of HIV-1 RNA, cell-associated HIV-1 RNA and cell-associated HIV-1 DNA at each time point as well as changes from baseline by treatment arm.
    b. Summary of GEE model of single copy assay of HIV-1 RNA, cell-associated HIV-1 RNA and cell-associated HIV-1 DNA (baseline, weeks 8 and 48 (or the latest result in the treatment phase)) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
        i. If required, summary of GEE model of unquantifiable (<LLoQ) HIV-1 RNA, cell-associated HIV-1 RNA or cell-associated HIV-1 DNA (baseline, weeks 8 and 48 (end of the treatment phase)) with treatment arm and stratification factor covariates. The estimated risk ratio, 95% CIs, and associated p-values will be provided.
25. Analysis of exploratory CNS tolerability outcomes (final report only, PP population)
    a. Summary of trail making A & B, digit symbol, HVLT-R, PHQ9, GAD7, Pittsburgh sleep quality index and plasma NFL at each time point as well as changes from baseline by treatment arm.

8 Summary of GEE model of trail making A & B, digit symbol, HVLT-R, PHQ9, GAD7, Pittsburgh sleep quality index and plasma NFL (baseline, weeks 46 (and/or the latest result in the treatment phase) and 60) with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided for each follow-up period.