Approvals

A5415

Primary Statistical Analysis Plan

Version 2.0

July 18, 2024

A Limited-Center, Prospective, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Cenicriviroc Mesylate on Arterial Inflammation in People Living with HIV

ClinicalTrials.gov Identifier: NCT05630885

Protocol Version 2.0

This is ACTG A5415 SAP Version 2.0 with names of authors, names of publication writing team members, and analysis timeline redacted.

Table of Contents

Version History Table

Version	Changes Made	Date Finalized
1.0	Original Version per Protocol Version 1.0	Apr 5, 2023
1.1	Reviewed for Protocol version 2.0 with no changes needed.	Apr 15, 2024
2.0	Section 2: • Removed details on Interim monitoring • In Section 2.3.1, clarified outcome measure description (most diseased vessel) and revised analysis approach to use linear regression instead of t-test. • Added Section 2.3.3: exploratory analyses. • Added Section 2.6: regarding timing of final analyses. Section 3: • Added Section 3.1: Key definitions section. • Revised Section 3.1 for clarity, updated to Section 3.2. • Revised Section 3.2 to include other outcome measures and to update presentation structure into table-list. Updated to Section 3.3 Section 4.1: • Added Section 4.1.1 and 4.1.2: key dates and data inclusion/exclusion for data to be analyzed. • Revised Section 4.1.3 (previously 4.1): updated Day 1, week 4, and week 22 definition/range. Updated baseline definitions for outcomes to be based on entry instead of pre-entry/entry. • In Section 4.1.4 (previously 4.2.1): added complete-case set definition. • Revised Section 4.2: cleaned up sentences and moved details to be in Section 5. Section 5: • Added protocol deviation table to be reported. • Modified components of baseline characteristics summary. • Updated summary measures for baseline characteristics, study status, and treatment status from continuous to categorical. • Added analysis set to be used, groups, statistical tests, and other details relevant to each table to be generated. • Added sections on all listed outcomes and associated details.	July 18, 2024

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary, secondary, and other outcome measures that will address specific study objectives and interim monitoring of the A5415 study. The Primary SAP includes general analytic approaches for all primary, secondary, and other outcome measures that will be included in the primary manuscript(s), Conference on Retroviruses and Opportunistic Infections (CROI) submission, or submitted to ClinicalTrials.gov (regardless of the reporting timeline). The Primary SAP facilitates discussion of the statistical analysis components among the writing team and statisticians, helping them agree on the statistical analyses to be performed and presented in the final analysis report.

An Analysis Implementation Plan (AIP) will also be prepared to provide more detailed outlines of tables, figures, and coding descriptions.

1.2 Version History

Version 1.0: Original version based on Protocol Version 1.0 dated August 22, 2022.

Version 2.0: Prepared leading up to the final analysis.

- The study team revised baseline and week 24 testing for immunological outcomes from averaging pre-entry/entry and week 22/24 to only using entry and week 24 samples due to budget constraints.
- Other changes include updates to visit window definitions, adds more details and clarifications to analytic plans for the primary and secondary objectives, as well as providing analysis plans for exploratory objectives that will be included in the Primary Statistical Report. See Version History Table for more details.

2 Study Overview

2.1 Study Design

A5415 is a double-blind, randomized, placebo-controlled, phase II trial to evaluate 24 weeks of Cenicriviroc mesylate (CVC) to reduce arterial inflammation among individuals living with chronic HIV on ART with viral suppression. CVC or placebo for CVC will be administered for 24 weeks to participants. The target sample size was 93 participants (62 in the CVC arm and 31 in the placebo arm). The study enrolled between May 2023 and January 2024 with a final sample size of 110 participants.

2.2 Hypotheses

Cenicriviroc mesylate (CVC) will decrease vascular inflammation as measured by 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) cardiac imaging.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol as well as other study objectives in the protocol that will be analyzed for the primary statistical report.

2.3.1 Primary Objective and Estimand

See Section 3.1 for details about TBR-related terms.

<table>
<tr><th colspan="2">Primary Objective 1: To assess whether CVC treatment results in reduced arterial inflammation by comparing the changes in arterial target-to-background ratio (TBR) in the carotid arteries and aorta after treatment with CVC versus placebo.</th></tr>
<tr><td>Estimand description</td><td>Percentage change in the arterial 18-FDG-PET TBR in the most diseased segment (MDS) of the carotid arteries and aorta following 24 weeks of CVC therapy among virally suppressed people living with HIV with at least one cardiovascular risk factor.</td></tr>
<tr><td>Treatment</td><td>Addition of CVC to background ART compared to ART alone.</td></tr>
<tr><th>Target population</th><th>Analysis set</th></tr>
<tr><td>Individuals living with HIV who are ≥45 years old, have at least one cardiovascular risk factor, and are on stable NNRTI-based or unboosted INSTI-based ART regimen, with suppressed HIV-1 RNA for ≥48 weeks prior to CVC start and who remain on the same ART drug class over an additional 24 weeks of CVC.</td><td>Participants who remain on study treatment for at least 22 weeks, and remain on the same ART drug class during the study.</td></tr>
<tr><th>Variable(s)</th><th>Outcome measure(s)</th></tr>
<tr><td>Fold change in 18-FDG-PET TBR, measured in the MDS of the most diseased vessel between the left and right carotid arteries and aorta over 24 weeks of CVC treatment</td><td>Fold change from baseline to week 24 in 18-FDG-PET TBR of the MDS of the most diseased vessel between the left and right carotid arteries and aorta.
MDS TBR will be $\log_{10}$ transformed ($\log_{10}$[week 24] – $\log_{10}$[pre-entry]) for analysis and back transformed for a fold change interpretation.</td></tr>
<tr><th>Handling of intercurrent events</th><th>Handling of missing data</th></tr>
<tr><td>The following intercurrent events are relevant to the estimand:
- Change in background ART regimen not within the same drug class: excluded (principal stratum)
- Change in background ART regimen within the same drug class: ignored (treatment policy)
- Treatment interruption or missed doses: ignored (treatment policy)
- Permanent discontinuation of treatment or background ART: Excluded (principal stratum)
- Death – excluded (principal stratum)
- Prohibited medications – excluded (principal stratum)
- Pregnancy or breast-feeding – excluded (principal stratum)</td><td>Missing data due to unreadable or missed scans will be handled by using multiple imputation.
A sensitivity analysis for the primary analysis will include complete case analysis.</td></tr>
<tr><th>Population-level summary statistic</th><th>Analysis approach</th></tr>
<tr><td>Geometric mean fold change (expressed as a percentage) in arterial MDS TBR after 24 weeks of treatment with and without CVC.</td><td>Fold change in TBR (1 - the geometric mean change) will be summarized by treatment groups with a 95% confidence interval.
The relative treatment difference will be described as a geometric mean difference (active compared to placebo) and compared with a linear regression, stratified by statin use.</td></tr>
<tr><td colspan="2">A supplementary analysis to the primary analysis will include participants who remain on treatment for at least 12 weeks and remain on the same ART drug class. A second supplementary analysis will exclude participants with confirmed HIV-1 RNA > 200 copies/mL or ART interruption for 14 or more consecutive days at any time during the course of the study.</td></tr>
</table>

2.3.2 Secondary Objectives

1) To assess changes in metabolic parameters including fasting glucose, fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), inflammatory markers including high sensitivity interleukin 6 (hsIL-6) and hsCRP, and markers of monocyte/macrophage activation including soluble CD14 (sCD14), soluble CD163 (sCD163), and monocyte chemoattractant protein-1 (MCP-1) after treatment with CVC compared to placebo.
2) To assess changes in cellular chemokine receptor 5 (CCR5) and CCR2 levels and changes in their plasma ligands (MIP-1α, MIP-1β and RANTES for CCR5; MCP-1 [CCL2] for CCR2) after treatment with CVC compared to placebo.
3) To evaluate the safety of CVC in virally suppressed antiretroviral therapy (ART)-treated, HIV-infected individuals.

2.3.3 Exploratory Objectives

1) To measure the effects of CVC on adipocytokines (adiponectin) and on noninvasive assessments of liver fibrosis, including AST to Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4).
2) To assess changes in FDG uptake in visceral fat and to quantify changes in visceral adipose tissue area and volume, subcutaneous adipose tissue area and volume, fat density, and liver to spleen attenuation ratio (as a noninvasive measure of hepatosteatosis) by noncontrast CT after treatment with CVC compared to placebo.
3) [PK/PD] To determine the association between CVC trough exposure and the primary treatment outcome (i.e., reduced arterial inflammation).
4) To evaluate the effects of CVC on markers of monocyte and T cell homing and activation as well as on myeloid cells.
5) To assess changes in occupancy of the CCR5 and CCR2 receptors on T cells and monocytes after treatment with CVC compared to placebo.
6) [PK/PD] To evaluate potential drug interactions by a) investigating the impact of INSTI- and NNRTI-based ART on CVC trough estimates and to compare these estimates across regimens and b) investigating the impact of CVC treatment versus no treatment on the trough exposure of ART.
Note: The Study Pharmacologist is evaluating currently available data on the effects of CVC on ART exposures to determine ARTs would be of interest for part b) of this objective.

2.4 Overview of Sample Size Considerations

The target sample size is 75 participants (50 in the CVC arm and 25 in the placebo arm) with baseline and follow-up PET/CT. To allow for some loss to follow-up and participants unwilling or unable to complete 2 scans, the study planned to enroll 93 participants (62 in the CVC arm and 31 in the placebo arm). Final enrollment was 110 participants.

The primary analysis will focus on between-treatment arm differences in the within-participant changes in arterial MDS TBR (the measure of arterial inflammation by PET/CT). Based on a superiority trial design with two-sided α=0.05, assuming a standard deviation (SD) of 0.065 $\log_{10}$ TBR for change in MDS TBR, a total of 75 participants providing complete, evaluable data sets will ensure 80% power to detect a between-groups difference of 0.046 $\log_{10}$ MDS TBR (which is a 10% reduction from baseline).

The assumptions underlying the power calculation are as follows:

1) The target effect size for the change in MDS TBR on therapy of 10% is based on the observation of a statin intensification study.
2) The assumed SD for change in ($\log_{10}$) MDS TBR of 0.065 is derived from the placebo arm of ACTG A5314.

3) The use of a two-sided, two-sample T-test with type-I error rate of 5%.

The assumption that 93 enrolled participants will provide 75 participants with evaluable data is derived by 20% total data loss due to drop-out after randomization (including premature discontinuation of study treatment and change in background ART drug class).

2.5 Timing of Final Analyses

[redacted]

[redacted]

[redacted]

3 Outcome Measures

3.1 Key Definitions Related to FDG-PET Imaging

Term(s)	Definitions at a Participant Level
Target vessel	Specific arterial vessels of interest: R carotid, L carotid, and aorta.
Background vessel	Internal jugular vein (JV) for carotids and superior vena cava (SVC) for aorta.
Standardized Uptake Value (SUV): 1. Target SUV 2. Background SUV 3. Average background SUV	Decay-corrected tissue concentration of FDG (in kBq/mL) divided by the injected dose per body weight (kBq/g). SUV is unitless. 1. Target SUV is the maxSUV measured for each of 10 slices of the target vessel. 2. Background SUV is the meanSUV measured for each of 10 slices of the background vessel. 3. Average background SUV is calculated as the average of the meanSUVs of the respective background vessel.
Most diseased segment (MDS)	2-3 slices of arterial segment, centered on the slice of the target vessel with the highest SUV ***at baseline.***
Index Vessel	Vessel with the highest vessel TBR (see definition below) ***at baseline*** (i.e., most diseased vessel).
Target-to-Background Ratio (TBR): 1. Vessel TBR 2. Vessel MDS TBR 3. Index vessel MDS TBR	Measure of FDG uptake, calculated as a ratio between the target and background SUV. 1. Vessel TBR is calculated as the ratio of the average target SUV (over 10 slices) and its associated average background SUV. 2. Vessel MDS TBR is calculated as the ratio of the average target SUV of the MDS of the vessel (over 2-3 slices) and its associated average background SUV. 3. Index vessel MDS TBR is defined as the vessel MDS TBR of the index vessel (i.e., the vessel with the highest vessel TBR).

3.2 Primary Outcome Measure

Primary Outcome Measure			
	Expected Reporting Timeline	**Outcome Measure(s)**	**Associated Objective(s)**
1	CROI	Change in the Index vessel MDS TBR of the index vessel from baseline to week 24	Primary

3.3 Secondary and Other Outcome Measures

Secondary Outcome Measures			
	Expected Reporting Timeline	**Outcome Measure(s)**	**Associated Objective(s)**
1	CROI	Change in vessel TBR of the bilateral carotid artery and aorta from baseline to week 24 from baseline to week 24 *For the bilateral carotid, the mean of the maxSUV for both the right and left carotid arteries will be combined.*	Further investigation of Primary
2	CROI	Change in average vessel SUV of the bilateral carotid artery and aorta from baseline to week 24 *For the bilateral carotid, the mean of the maxSUV for both the right and left carotid arteries will be combined.*	
3	CROI	Change in fasting glucose from baseline to week 24	Secondary 1
4	FINAL	Change in fasting insulin and HOMA-IR from baseline to week 24	Secondary 1
5	CROI	Change from baseline to week 24 in • IL-6, hsCRP, MCP-1 (inflammatory biomarkers) • sCD14, sCD163 (markers of monocyte/macrophage activation)	Secondary 1
6	FINAL	Change from baseline to week 24 in: • Cellular levels of CCR5 and CCR2 • Plasma levels of RANTES, MIP-1α, MIP-1β (CCR5 plasma ligands) • Plasma levels of MCP-1 (CCR2 plasma ligand) *Note: MCP-1 is the same outcome measure described above, it is retained here as it will be repeated in tabular summaries related to CVC effects on CCR5 and CCR2.*	Secondary 2
7	CROI	• Occurrence of at least one SAE • Occurrence of at least one treatment related AE • Occurrence of at least one treatment limiting AE	Secondary 3
Other Outcome Measures			
	Expected Reporting Timeline	**Outcome Measure(s)**	**Associated Objective(s)**
1	FINAL	Change in FDG uptake in visceral fat and lymph nodes from baseline to week 24.	Exploratory 2
2	FINAL	Change in adipocytokines (such as adiponectin) from baseline to week 24.	Exploratory 1

3	FINAL	Change from baseline to week 24 in myeloid derived suppressor cell (MDSC) frequencies Change from baseline to week 24 in monocyte subsets: • % CD14+, CD16- (Classical); % CD14+, CD16+ (Inflammatory); % CD14-, CD16+ (Non-classical) *where % is % of total monocytes* • Expression of CX3CR1, CCR5, CCR2 (homing receptors) on total monocytes and on monocyte subsets. • HLA-DR density and CD69 expression (monocyte activation) on total monocytes and on monocyte subsets.	Exploratory 4, 5
4	FINAL	Changes from baseline to week 24 in CD4 and CD8 T cell expression of CX3CR1, CCR2, CCR5 Changes from baseline to week 24 in CD4 and CD8 T cell expression CD38 and HLA-DR	Exploratory 5
5	FINAL	[PK/PD] CVC trough concentration measured at weeks 4, 8, 12, and 24.	Exploratory 3, 6
6	FINAL	[PK/PD] ART trough concentration measured at pre-entry, weeks 4, 8, 12, and 24. *Measured only in participants randomized to CVC.*	Exploratory 6

4 Statistical Principles

4.1 General Considerations

4.1.1 Data for Analysis

Key Timepoints	
Date	**Timepoint**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4.1.2 Participant Exclusions

Participants who had any events below will be excluded from efficacy data to be analyzed, per handling of intercurrent events (Section 2.3.1):

- Never started treatment
- Deemed clinically ineligible for the study
- Took prohibited medication(s) during the study
- Died
- Became pregnant

4.1.3 Analysis Windows

Defined as follows:

- Day 1 = study treatment initiation date
- Week 4: -21 / +14 days
- Weeks 8, 12, 16: +/- 14 days
- Week 22: -14 / +7 days
- Week 24: -7 days up to maximum days observed

Baseline refers to study evaluation closest to Week 0 prior to initiation of study treatment unless otherwise stated.

In the event of multiple results within a study window, the result closest to the scheduled evaluation week based on the time since study treatment initiation date will be used. Exceptions may include repeat visits for confirmation of events such as virologic failures.

4.1.4 Analysis Sets

Efficacy set (per-protocol set): All eligible participants who remain on study treatment for at least 22 weeks and remain on the same ART drug class during their entire study period.

Complete-case set: Efficacy set participants who have baseline-week 24 pair of PET/CT scan data.

Supplementary efficacy set one: All eligible participants in the efficacy set as well as participants who remained on study treatment for at least 12 weeks and remained on the same ART drug class during their entire study period.

Supplementary efficacy set two: All eligible participants in the efficacy set excluding participants with confirmed HIV-1 RNA > 200 copies/mL or ≥ 14 consecutive days of ART interruption at any time during the course of the study.

Safety set: All enrolled participants who initiate study treatment.

4.2 Analysis Approaches

- Descriptive summaries in Section 5 will be presented for both the Safety set and Efficacy set, unless otherwise specified.
- Summary statistics for discrete and continuous outcomes will be detailed under each report-content in Sections 5 - 9.
- All statistical tests will be two-sided with a nominal alpha level of 0.05.
  - No adjustment for multiple testing will be performed.
- Stratification will be taken into account in efficacy outcome analyses unless stated otherwise.
- No statistical comparisons across groups for baseline characteristics are planned.
- Missing data for TBR analyses will be handled using multiple imputation; sensitivity analyses will be complete case where missing data are ignored.
- Missing data for biomarker analyses will be ignored (i.e., all analyses will be complete case).

Report Contents

5 Participant Characteristics and Disposition

5.1 Screening

1) Table of N (%) of participants screened.
2) Table of N (%) of participants failed screening, with reasons for failed screening.

5.2 Accrual

1) Figure: Bar chart of number of accrual by month
   - By sex
   - By treatment arm
2) Table of N (%) accrual by site

5.3 CONSORT diagram

Flowchart of number of participants from screening up to analyses by treatment arms, including information on exclusions from each step.

5.4 Protocol Deviations

	Cenicriviroc Mesylate (CVC) (N=xx)	Placebo (N=xx)	Total (N=xx)
Overall Deviation	**xx (xx%)**	**xx (xx%)**	**xx (xx%)**
Deviation Reason Category	**xx (xx%)**	**xx (xx%)**	**xx (xx%)**
Reason 1	xx	xx	xx
Reason 2	xx	xx	xx
…	…	…	…

[All contents below will be by treatment groups, unless otherwise mentioned]

5.5 Baseline characteristics

Analysis set(s): Safety set, Efficacy set

Table 1a	Demographics
Characteristic	**Summary Statistic(s)**
Age	Median (Q1, Q3), and P10, P90 N (%): 45-54, 55-64, 65-74, 75+
Sex at Birth	N (%): Male, female
Gender Identity	N (%): Cisgender, transgender spectrum
Race	N (%): White, Black or African American, unknown
Ethnicity	N (%): Hispanic or Latino, Not Hispanic or Latino
BMI	Median (Q1, Q3), and P10, P90 N (%): Underweight (< 18.5), normal (18.5 – 24.9), overweight (25 – 29.9), obese (30+)

Current-use of statins at entry	N (%): Current use of statins, no current use of statins.
Statin agents	N (%): statins
eGFR	Median (Q1, Q3), and P10, P90
Table 1b	**HIV Characteristics**
Characteristic	**Summary Statistic(s)**
CD4 Count	Median (Q1, Q3), and P10, P90
CD4 %	Median (Q1, Q3), and P10, P90
HIV-1 RNA	Median (Q1, Q3), and P10, P90 N (%): < LLQ, ≥ LLQ (lower limit of quantification)
ART Class at entry	N (%): INSTI and NNRTI-based, INSTI-based, NNRTI-based
ART Regimens	N (%): ARV regimens at entry
Table 1c	**Cardiovascular Risk Factors**
Characteristic	**Summary Statistic(s)**
Participants' number of cardiovascular risk factors	N (%): 1, 2, 3, 4+ CV risk factors
High-risk cardiovascular risk factors (*see Protocol Section 4.1.6 for the list*)	*For each CV risk factor:* N (%): With, without

5.6 Study status

Table	**Study Status**
Characteristic	**Summary Statistic(s)**
Study Status	N (%): completed study, prematurely discontinued study
Last Clinic Visit	N (%): No follow-up, < 12 weeks, 12 - < 24 weeks, 24+ weeks
Study Discontinuation Reasons	N (%): Reasons

5.7 Treatment status

Table 1	**Treatment Status**
Characteristic	**Summary Statistic(s)**
Treatment Status	N (%): Completed, did not start, prematurely discontinued
Days from Entry to First Dose of Treatment	N (%): 0, 1, 2, 3, 4+ days
Reasons for Treatment Discontinuation	N (%): Reasons
Week of Treatment Discontinuation	N (%): Did not start, < 12 weeks, 12 - < 24 weeks, 24+ weeks
Treatment Interruption Reason	N (%): Reason
Week of Initial Interruption	N (%): Did not start, < 12 weeks, 12 - < 24 weeks, 24+ weeks
Total Interruption Duration	N (%): 1-7, 8-14, 15+ days

6 Adverse and Targeted events (AE)

6.1 Adverse Events

Analysis set(s): Safety set
Statistics: N (%)
Listing: Public ID, AE start day, AE term, Grade, Action taken with treatment, Relationship to treatment.

1) Table of all new, post-entry AEs by MedDRA PT grouped by SOC (reported in ClinicalTrials.gov)
2) Listing of longitudinal creatinine and eGFR with creatinine-related AEs
3) Table/listing of SAEs by MedDRA PT grouped by SOC, excluding those related to PET/CT
4) Listing of all AEs related to study treatment by MedDRA PT grouped by SOC, excluding those related to PET/CT
5) Table/listing of all AEs related to PET/CT scan by MedDRA PT grouped by SOC

6.2 Pregnancies

Listing of participants who become pregnant while on study, with public ID, treatment arm, weeks of positive pregnancy test, weeks of study treatment discontinuation, and pregnancy outcomes

6.3 Mortality

Listing of participants who died, with public ID, treatment arm, primary cause of death, and weeks of death, and relationship to study treatment

6.4 Virologic failures

Table of N (%) of participants with virologic failure. If N is small, listing of virologic failures with public ID, treatment arm, weeks of initial and confirmed virologic failure, and HIV-1 RNA copies/mL at initial and confirmed virologic failure may be provided in lieu of summary table.

7 Arterial Inflammation

7.1 Inclusion/Exclusion for Efficacy Analyses

1) Table of N (%) of participants included or excluded, by reasons and treatment arm, in:
   a. Efficacy set
   b. Complete-case set
   c. Supplementary set 1
   d. Supplementary set 2

Inclusion/Exclusion for xxx Analysis Set					CVC (N=xxx)	Placebo (N=xxx)	Total (N=xxx)
Safety Population Flag	**On-treatment for at least 12 weeks**	**Per-Protocol Population Flag**	**On-treatment for at least 22 weeks**	**No change in ART class from baseline**			
Included	Included	Included	Included	Included	xx (xx%)	xx (xx%)	xx (xx%)
		Excluded	Excluded	Included	xx (xx%)	xx (xx%)	xx (xx%)
				Excluded	xx (xx%)	xx (xx%)	xx (xx%)
	Excluded	Excluded	Excluded	Included	xx (xx%)	xx (xx%)	xx (xx%)

7.2 TBR-related Outcomes

- TBRs will be $\log_{10}$-transformed for analyses and back-transformed to fold-change for interpretation and presentation.
- Missing data due to unreadable or missed week 24 scans will be handled using multiple imputation (MI) with regression (details will be provided in the AIP).

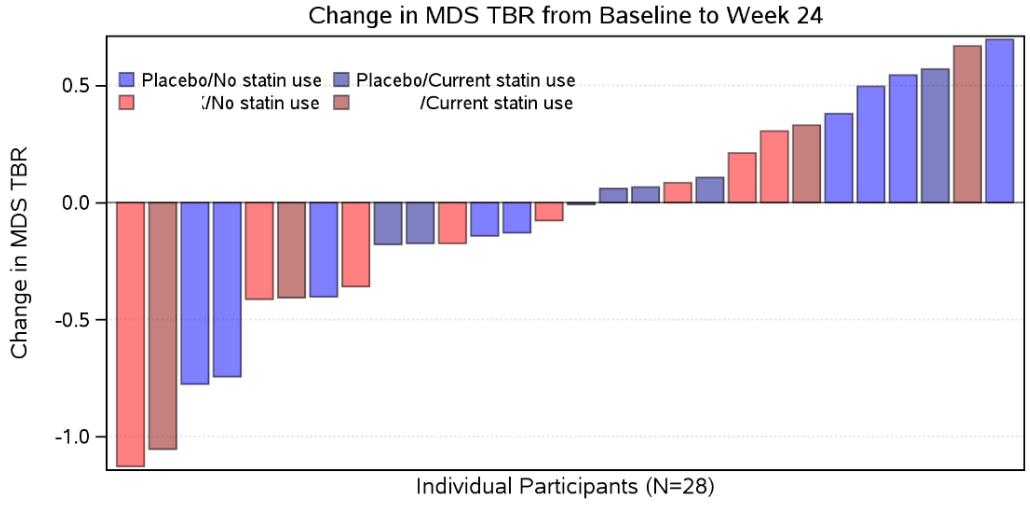
7.2.1 Descriptive Statistics for TBR Outcomes

Analysis set(s): Efficacy set
Stratification: Overall, by statin-use
Grouped by: Baseline, Week 24, Change
Analysis method: (change-outcomes only) stratified, within-arm paired two-sample t-test between baseline and week 24 with null hypothesis of no difference between baseline and week 24 TBRs.

Table	Columns for each group: Total (baseline group only), Cenicriviroc, Placebo	
Characteristic	**Baseline, Week 24 Statistic(s)**	**Change Statistic**
Index vessel MDS TBR	Mean (st.dev.), Median (Q1, Q3), and P10, P90	Mean, 95% confidence interval
Index vessel	N (%): Aorta, R Carotid, L Carotid	
Aortic Vessel TBR	Mean (st.dev.), Median (Q1, Q3), and P10, P90	Mean, 95% confidence interval
Bilateral Carotid Vessel TBR	Mean (st.dev.), Median (Q1, Q3), and P10, P90	Mean, 95% confidence interval

7.2.2 Figure of changes in TBR from Baseline to Week 24 versus participants

Analysis set(s): Efficacy set
Grouped by: by statin-use and treatment arm



7.2.3 Regression Analysis of Difference in Change in TBR between Treatment Arms

- Analysis set(s):
  1. Outcome: Efficacy set
  2. (Primary only) Sensitivity analysis: Complete-case set
  3. (Primary only) Supplementary analysis 1: Supplementary set 1
  4. (Primary only) Supplementary analysis 2: Supplementary set 2

- Analysis method:
  a) Linear regression of change in TBR on treatment arm, adjusted by statin-use.
  b) Linear regression above with interaction between treatment arm and statin-use.

NOTE: Linear regression with interaction (b) for secondary outcomes will be done only if linear regression with interaction of primary outcome shows that change in MDS TBR is different by statin-use.

Table	**Regression Analysis Results**		
Outcome	**Characteristic**	**Summary Statistic(s)**	**Statistical Test**
PRIMARY	Change in Index vessel MDS TBR (a)	Treatment parameter estimate	95% confidence interval, p-value
	Change in Index vessel MDS TBR given statin-use (b)	Treatment parameter estimate	95% confidence interval, p-value of interaction effect of statin-use
	Change in Index vessel MDS TBR given no statin-use (b)	Treatment parameter estimate	
Outcome	**Characteristic**	**Summary Statistic(s)**	**Statistical Test**
Secondary	Change in aortic vessel TBR (a)	Treatment parameter estimate	95% confidence interval, p-value
	Change in bilateral carotid vessel TBR (a)	Treatment parameter estimate	95% confidence interval, p-value

7.2.4 Modification of CVC effect by Sex and Race

Analyses 1b above will be repeated replacing statin-use with a) sex assigned at birth b) race (Black versus non-black).

7.3 Correlates of MDS TBR of the Index Vessel

These analyses are planned for the Final Report.

- Analysis set(s): Efficacy set
- Outcomes: 1) Baseline MDS TBR of the index vessel 2) Change in MDS TBR of the index vessel
- Covariates: Age, sex, race, BMI, use of statins at entry, ART (INSTI vs NNRTI), perceived stress scale, diet, average CVC trough (analysis of change only)
  With the exception of average CVC trough, all measures are at entry. In the event of a positive effect of CVC, analyses of change will be limited to participants in the CVC arm.
- Analysis method:
  a) Descriptive graphic displays of the distribution TBR by each of the covariates of interest
  b) Linear regression of TBR adjusted for each covariate in turn (i.e., unadjusted analyses).
  Analyses of change in MDS TBR will also adjust for baseline MDS TBR.
  c) Linear regression of TBR adjusted for each covariate with evidence of association with TBR in unadjusted analyses. Given the relatively small sample size, evidence of association will be judged with either relaxed type 1 error or clinically meaningful effect sizes.
- Presentation of results: Forest plot for each outcome showing parameter estimates and 95% confidence interval.

7.4 SUV Outcomes

Analysis set(s): Efficacy set

Same analyses as Primary outcome (Section 7.2) on aorta, carotid arteries.

8 Soluble and Cellular Biomarkers

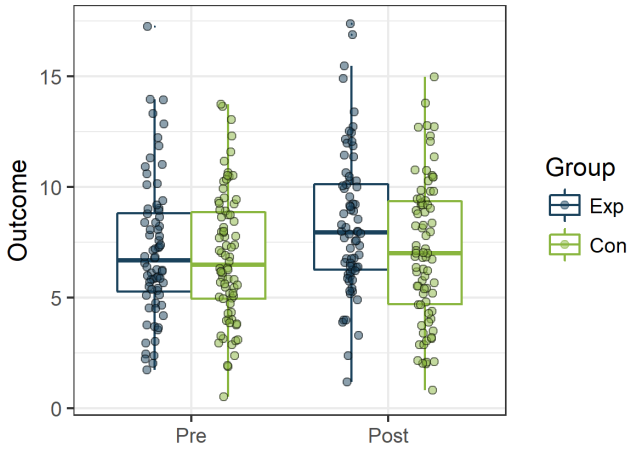
Analysis set(s): Efficacy set, Supplementary analysis set 1.

- All change-from-baseline-to-week-24 outcomes described in Section 3.3 will be analyzed in the same manner as the Primary outcome (Section 7.2).
- Soluble biomarkers may be transformed for analyses on the $\log_{10}$ scale and back transformed to fold change for interpretation and presentation, as appropriate.
- Missing data will be ignored; all analyses will be complete case including only participants with paired values of each given biomarker available.

8.1.1 Distribution Plot of Biomarkers by Visit Week

Analysis set(s): Efficacy set
Stratification: Overall, by statin-use
Grouped by: Baseline, Week 24, Change

- Figure: Jitter and boxplot of biomarkers at baseline and week 24 by treatment arms (with a 3rd group of boxplots showing the within-participant change)



9 Pharmacokinetic (PK) / Pharmacodynamic (PD) Outcomes

Analyses in this section are subject to change based on pending review of current literature of CVC and ART drug-drug interactions. Based on review of participant regimens, only bictegravir (BIC), dolutegravir (DTG), rilpivirine (RPV), tenofovir alafenamide (TAF), emtricitibine (FTC), and lamiviudine (3TC) have exposure by at least 10 participants.

All PK outcomes are limited to participants in the CVC arm.

9.1.1 Descriptive Statistics of CVC Trough Estimates by ART Class

Analysis set(s): Complete case set (cenicriviroc arm only)
Grouped by: a) ART Class (INSTI, NNRTI, both); b) ART Agent

Table	CVC Trough Estimates by ART Class / Agent
Characteristic	**Summary Statistic(s)**
Participant-level average CVC trough concentration	Median (Q1, Q3), and P10, P90
CVC trough concentration by week	Median (Q1, Q3), and P10, P90

9.1.2 Change in ART Trough Estimates

Analysis set(s): Complete case set
Grouped by: Specific ART Bictegravir, Dolutegravir, Rilpivirine
Stratification: None
Analysis method: paired t-test of pre-study treatment and participant-level average post-study treatment ART trough estimates with null hypothesis of no difference between pre- and post- study measures.

Table	Columns for each group: Pre, Post, Change	
Characteristic	**Pre-, Post- Treatment Statistic(s)**	**Change Statistic**
Average <DRUG> trough concentration	Mean (st.dev.), Median (Q1, Q3), and P10, P90	Mean, 95% confidence interval, p-value

9.1.3 Correlation between CVC Trough Exposure versus Index Vessel MDS TBR

Analysis set(s): Complete case set
Stratification: Overall, by statin-use
Analysis method: Spearman's rank-based correlation

- Figure: Scatterplot of Index Vessel MDS TBR vs CVC trough exposure
  - CVC exposure is based on composite time-adjusted CVC exposure estimate over the 24-week study period obtained from mixed-effect modelling based on measured concentrations at weeks 4, 8, 12, and 24 (see Protocol Section 11.3.2).