A5415

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

A Limited-Center Trial of the ACTG (Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections)

Sponsored by:

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22Mar2024

ACTG

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5415@fstrf.org via email. **The appropriate team member will generally respond within 1 working day.**

When sending messages to individual team members by role (e.g., Protocol Data Manager, Clinical Trials Specialist), sites should check the current roster on the ACTG Member Website.

Protocol Email Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5415 email group. Include the protocol number in the email subject line.

- Send an email message to actg.user.support@fstrf.org.

In order to remove site personnel from the actg.protoA5415 email group, contact the User Support Group at the DMC. Include the protocol number in the email subject line.

- **Send an email message to actg.user.support@fstrf.org.**

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the Clinical Management Committee (CMC).

- Send an email message to actg.cmcA5415@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to **laboratory element of the study (e.g., immunology, pharmacology, virology), contact the protocol team.**

- Send an email message to actg.teamA5415@fstrf.org (ATTN: Michael Lederman / Daniel Kuritzkes / Amelia Deitchman).
- **Include the study number and "laboratory question" in the email subject line.**

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the **study's protocol** data manager. Electronic CRFs (eCRFs) completion guidelines and participant completed CRFs can be downloaded from the **Frontier Science & Technology Research Foundation (**FSTRF**)** website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Kristine Coughlin and Jenna Meldrum directly.
- For other questions, send an email message to actg.teamA5415@fstrf.org (ATTN: Kristine Coughlin, Jenna Meldrum **and Anna Yoder**).
- Include the protocol number, PID, and **"Data Management Question" in the subject line.**

DMC Portal and Medidata Rave Problems
Contact DMC User Support:
- Send an email message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Randomization
For randomization questions or problems and study identification number SID lists**, contact the Randomization Desk at the Frontier Science Data Management Center (DMC).**
- Send an email message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900 x7301.

DMC Portal and Medidata Rave Problems
For questions about the DMC portal or Medidata Rave, contact DMC User Support.
- Send an email message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.
- Send an email message to actg.teamA5415@fstrf.org (ATTN: **Jhoanna Roa**).

Copies of the Protocol
To request a hard copy of the protocol, send a message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the **protocol-specific web page (PSWP) on the ACTG Member** Website (https://actgnetwork.org).

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, **contact DAIDS Protocol Registration.**
- **S**end an email message to Protocol@tech-res.com or call 301-897-1707.

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For questions related to protocol activation at US sites, contact the Clinical Trials Specialist **(CTS)**.
- Send an email message to **the study's CTS with a cc to actg.teamA5415@fstrf.org**.

For questions related to protocol activation at non-US sites, contact the ACTG Site Coordination Group.
- Send an email message **to** actgsitecoordination@dlhcorp.com **with a cc to the study's CTS.**

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For questions or problems regarding study product, dose, supplies, records, and returns, call Dapo Alli, Protocol Pharmacist, at 301-761-7269.

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Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741 **between 8 AM and 5 PM Eastern Time (ET). Outside of this timeframe, sites may use other contact information found in the CRPMC Online Site Management and Ordering System (COSMOS**).

IND (Investigational New Drug) Number or Questions
The IND number will be available on the PSWP **approximately** 30 days **after** the submission **of the final protocol version** to the FDA.

For **any** questions related to the IND submission, contact the DAIDS RSC.
- **Send an email message to** Regulatory@tech-res.com
  or
- **Call 1-800-537-9979 or 301-897-1709**
  or
- **Fax 1-800-275-7619 or 301-897-1710.**

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Phone Calls
Sites are responsible for documenting any phone calls made to A5415 team members.
- Send an email to actg.teamA5415@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the PSWP **on the ACTG Member Website**.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ADR/ADRs	adverse drug reaction/adverse drug reactions
ALT	alanine aminotransferase
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
CAC	coronary artery calcification
CAD	coronary artery disease
CCL2/CCL3/CCL4	chemokine ligand 2/chemokine ligand 3/chemokine ligand 4
CCR2/CCR5/CCR7	chemokine receptor 2/chemokine receptor 5/chemokine receptor 7
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CMC	Clinical Management Committee
COBI	cobicistat
CPK	creatine phosphokinase
CT	computed tomography
CVC	cenicriviroc mesylate
CVD	cardiovascular disease
DILI	drug-induced liver injury
DM	diabetes mellitus
FDG-PET	18F-fluorodeoxyglucose-positron emission tomography
FIB-4	Fibrosis-4
GFR	glomerular filtration rate
HLA-DR	human leukocyte antigen-DR
HOMA-IR	homeostasis model assessment-estimated insulin resistance
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
IL-6/hsIL-6	interleukin-6/high sensitivity interleukin 6
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IUD	intrauterine device
MCP-1	monocyte chemoattractant protein-1
MDS	most diseased segment
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mSv	milliSieverts

NASH	non-alcoholic steatohepatitis
PPI	proton pump inhibitor
RTV	ritonavir
sCD14/sCD163	soluble CD14/soluble CD163
SUV	standardized uptake value
TBR	target-to-background ratio
TEAE/TEAEs	treatment-emergent adverse event/treatment-emergent adverse events
ULN	upper limit of normal

SCHEMA

A5415

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

DESIGN

Double-blind, placebo-controlled phase II clinical trial comparing the intervention of cenicriviroc mesylate (CVC) versus placebo for arterial inflammation.

DURATION

Approximately 24 weeks

SAMPLE SIZE

Target Accrual= 93 participants
(62 in the CVC arm [Arm A], 31 in the placebo for CVC arm [Arm B])

Actual Accrual= 110 participants

On October 27, 2023, the study closed to screening, and participants who were in screening prior to that point were permitted to enroll if eligible. All screenings that were ongoing at the time of screening closure were completed on January 5, 2024, and the study closed to accrual. This resulted in over-enrollment of 110/93 participants.

POPULATION

Individuals living with HIV

- ≥45 years of age
- On stable non-nucleoside reverse transcriptase inhibitor (NNRTI)-based or unboosted integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) regimen, defined as no within-class changes in ART regimen within 12 weeks prior to entry and no between-class changes for 24 weeks prior to entry
- With suppressed HIV-1 RNA for ≥48 weeks prior to entry
- With at least one of the following cardiovascular risk factors (current diagnosis or receiving treatment):
  - Clinical atherosclerotic disease
  - Subclinical atherosclerotic disease
  - Diabetes mellitus (DM) or prediabetes or impaired fasting glucose or insulin resistance
  - Obesity or enlarged iliac waist circumference
  - History of hypertension or blood pressure ≥130/80 mmHg
  - Elevated low-density lipoprotein (LDL) cholesterol
  - Low high-density lipoprotein (HDL) cholesterol
  - Smoking (any current tobacco smoking)

- Family history of premature coronary artery disease (CAD; first degree relative with CAD prior to age 55 for male relative and 65 for female relative)
- High sensitivity C-reactive protein (hsCRP) >2.0 mg/L

STRATIFICATION

Randomization will be stratified by current use of statins (defined as statin use within the past 90 days prior to study entry versus none) to ensure even distribution of statin use between the treatment arms.

REGIMEN

Participants will be randomized 2:1 to either the CVC arm (Arm A) or placebo for CVC arm (Arm B). CVC 150 mg or placebo for CVC by mouth once a day for at least 24 weeks will be added to the participants' pre-existing antiretroviral (ARV) regimens.

For participants who are on an efavirenz (EFV)-based regimen, dosing will be 300 mg once a day.

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

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

1.2 Primary Objective

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.

1.3 Secondary Objectives

1.3.1 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.

1.3.2 To assess changes in plasma chemokine receptor 5 (CCR5) and CCL2 (previously known as MCP-1) levels (MIP-1α, MIP-1β and RANTES for CCR5; MCP-1 for CCR2) after treatment with CVC compared to placebo.

1.3.3 To evaluate the safety of CVC in virally suppressed antiretroviral therapy (ART)-treated, individuals living with HIV.

1.4 Exploratory Objectives

1.4.1 To measure the effects of CVC on adipocytokines including adiponectin and on noninvasive assessments of liver fibrosis, including AST to Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4).

1.4.2 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.

1.4.3 To determine the association between CVC trough exposure and the primary treatment outcome (i.e., reduced arterial inflammation).

1.4.4 To evaluate the effects of CVC on markers of monocyte and T cell homing and activation as well as on myeloid cells.

1.4.5 To assess changes in occupancy of the CCR5 and CCR2 receptors on T cells and monocytes after treatment with CVC compared to placebo.

1.4.6 To evaluate the effects of CVC on fibrinogen and other coagulation markers.

1.4.7 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.

2.0 INTRODUCTION

2.1 Background and Rationale

The incidence of cardiovascular disease (CVD) and mortality from CVD are increased among people living with HIV [1, 2, 3]. Traditional risk factors for atherosclerosis including dyslipidemia, diabetes mellitus, abdominal adiposity, and smoking are very common among people living with HIV. Furthermore, activation of the innate immune system and increased inflammation are likely to contribute to increased cardiovascular risk in individuals with chronic HIV [4]. Chemokines are important in the recruitment of leukocytes and their adhesion and migration, leading to the formation of atherosclerotic plaque [5]. CCR2 and CCR5 both are posited to have roles in the pathogenesis of atherosclerosis development [6, 7]. CVC is an orally active and potent inhibitor of CCR5 that was previously being developed as a therapeutic agent for HIV. In addition to CCR5 antagonistic activity, CVC is also a CCR2 antagonist. CVC was initially developed as an anti-HIV drug by Takeda and then Tobira, prior to acquisition by Allergan for investigation in liver disease, namely liver fibrosis with NASH. (Allergan subsequently acquired by AbbVie.) CVC displays potent, selective anti-HIV-1 activity via binding to CCR5 as a coreceptor of HIV-1 to prevent virus entry into the cell [8, 9]. CVC showed efficacy in treating HIV infection with HIV-suppressive activity at doses associated with a highly favorable safety profile as demonstrated in a comprehensive Phase 2b clinical study compared with the then standard of care (SoC) comparator efavirenz [8]. High-level dual-receptor blockade was demonstrated as highlighted by the high levels of viral suppression (not achievable without complete CCR5 occupancy [10] and dose-dependent increases of CCL2 [8]. Elevation of CD4 count was numerically greater in the CVC arms than SoC comparator arms (no statistical analysis reported), and the myeloid inflammatory marker sCD14 was reduced in the CVC arms, but elevated in the SoC arms, with this difference being statistically significant. Despite this encouraging profile as a direct-acting, antiviral candidate agent for HIV infection, it was not further developed as an HIV clinical candidate following its acquisition by Allergan, but investigated instead for potential therapy of NASH with liver fibrosis, due to the pharmacologies associated with CCR2 and CCR5 in this disease [11, 12]. In a Phase 2b study, CVC showed an improvement in liver fibrosis compared to placebo after 1 year of therapy with similar

safety profiles between both CVC and placebo groups. It was also associated with reduced levels of markers of cardiovascular outcomes such as C-reactive protein and fibrinogen and biomarkers of inflammation such as IL-6 and IL-1β [13, 14]. Despite mechanistically associated evidence of efficacy, the AURORA Phase 3 study was terminated early due to lack of efficacy based on the results of the planned interim analysis of Part 1 data. Therefore, we propose to investigate the effects of CCR2 and CCR5 antagonism on arterial inflammation using CVC in a prospectively recruited cohort of individuals living with HIV on stable suppressive ART. We will further investigate the changes in insulin resistance, adipocytokines, altered adipose tissue distribution, monocyte activation, and chemokine receptor occupancy in response to CVC.

Atherosclerosis is an inflammatory disease where immune mechanisms interact with metabolic factors [15-18]. Chronic HIV is associated with a state of systemic inflammation and immune activation. HIV causes alterations in the monocyte repertoire [19] with expansion of the $CD14^{+}CD16^{+}$ monocyte subset. Tilton and colleagues found individuals living with HIV, with or without ART, have elevated monocyte production of inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 when compared to findings among controls without HIV, and that individuals living with HIV on ART with effective viral suppression still have markedly elevated frequency of monocytes producing inflammatory cytokines [20]. We propose a physiologic interventional study using CVC, a CCR5 and CCR2 inhibitor, to investigate its effects on arterial inflammation as well as its immunomodulatory effects on monocyte activation in individuals living with HIV.

The ligand for CCR2, MCP-1, is important in monocyte migration into the vascular intima during the development of atherogenesis [21]. Participants living with HIV with MCP-1 2518G allele were found to have an associated 5-fold increased risk for atherosclerosis, and individuals with atherosclerosis had higher plasma concentrations of MCP-1 than individuals without atherosclerosis [22]. This same polymorphism has also been associated with severity of coronary artery disease (CAD) in individuals without HIV [23]. Prior reports have suggested that the HIV-1 *Tat* protein, an early viral protein critical in HIV-1 replication, may promote MCP-1 secretion, leading to increased transmigration of monocytes across the vascular endothelium [24] and may cause endothelial dysfunction in porcine coronary arteries [25]; however, the clinical implication of these published data is not fully clear, as monocyte infection with HIV is rare and we do not yet have evidence of *Tat* protein being present in abundance in extracellular space to stimulate monocytes. MCP-1's receptor, CCR2, is also one of the co-receptors that could be used by HIV to enter CD4 lymphocytes [26]. Polymorphisms of CCR2 have been associated with increased risk of acute coronary events and interestingly, polymorphisms in CCR2 have also been associated with differences in HIV disease progression [27-35]. Signaling via CCR2 and CCR5 also drives recruitment of myeloid-derived suppressor cells, which are profoundly immune-suppressive, elevated in HIV+ and in acute coronary syndrome [33-35].

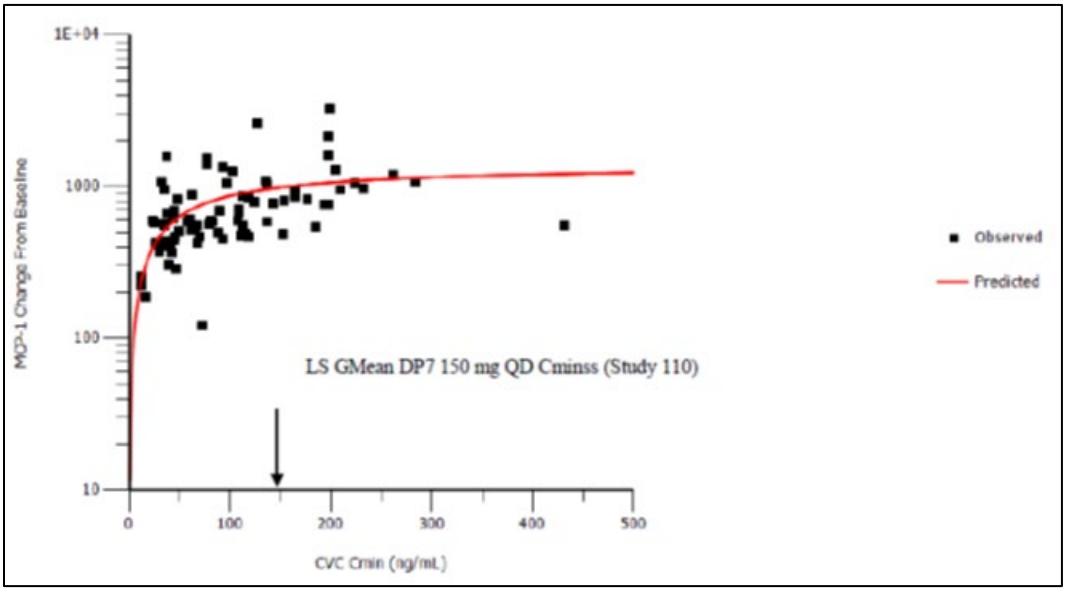

Figure 2.1-1: Relationship between CVC levels and MCP-1 concentrations.

MCP-1 is a chemokine that is produced by adipocytes and is overexpressed in obesity and hyperinsulinemic states [36]. In mice with obesity, treatment with an antagonist of CCR2 reduced adipose tissue macrophage content and improved insulin sensitivity [37]. As visceral obesity and insulin resistance is highly prevalent in individuals living with HIV on chronic ART treatment, the potential beneficial effects of blocking MCP-1 actions at the CCR2 receptor in ameliorating insulin resistance and visceral adiposity as well as decreasing inflammation within visceral adipose tissue will also be investigated in this study. In a clinical study conducted by Allergan, plc. (Study 202), higher CVC plasma concentration levels were associated with greater increases from baseline to week 48 in bound plasma MCP-1 levels, suggesting concentration-dependent CCR2 blockade by CVC. Using peripheral blood mononuclear cells from participants treated with CVC, T cells from these participants were unable to bind MCP-1, indicating receptor occupancy (*unpublished data from A5415 Protocol Immunologist, Dr. Michael Lederman*).

To investigate the effects of CVC on arterial inflammation, we propose to use FDG-PET. In contrast to imaging approaches that assess structural components of atherosclerosis, FDG-PET allows functional imaging of macrophage activity in vivo. FDG competes with glucose for uptake into metabolically active cells, including macrophages in atherosclerotic plaques, and is trapped inside cells after phosphorylation. FDG-PET can image metabolic activity (as a marker of plaque inflammation) quantitatively in atherosclerotic plaques [38, 39], has been shown to have high reproducibility [40], and correlates with histologic macrophage accumulation [39]. Macrophages play a key role in plaque destabilization and thrombus formation [41], thus, measurement of its activity may help to identify risk for cardiovascular events [13]. Furthermore, individuals living with HIV have been shown to have increased FDG uptake in the aorta compared to Framingham risk score-matched controls and measures of FDG uptake correlated with

sCD163, a marker of monocyte/macrophage activation [14] among individuals living with HIV. FDG-PET can also be used to image macrophage activity within adipose tissue depots [42]. Preliminary data from a clinical trial investigating effects of statin therapy on arterial inflammation at Massachusetts General Hospital (MGH) in participants living with chronic HIV on ART demonstrate that 49 out of 50 (98%) participants living with HIV have aortic target-to-background ratio (TBR) >1.6 and 46 out of 50 (92%) have TBR >1.8 at baseline prior to randomization. Thus, a very significant proportion of persons living with chronic HIV have a high degree of vascular inflammation. TBR ≥1.6 has previously been considered to define inflamed and active atheroma [39, 42].

Monocyte subpopulations will be characterized by expression of CD14 and CD16 as described previously [43]. Within each population, expression of the CVC binding chemokine receptors, CCR5 and CCR2, will be examined, as will their occupancy by CVC. In each monocyte subpopulation, we will also monitor the expression of the fractalkine binding receptor CX3CR1 that promotes binding to endothelial fractalkine. Monocyte activation will be monitored by measuring density of human leukocyte antigen-DR (HLA-DR) and CD69. Further characterizations of the myeloid population may be undertaken with collected or archived frozen samples to include investigation into MDSC population effects. MDSCs are classified as CD14+HLA-DR-/lo, in contrast to the monocyte subsets, which are HLA-DR+, and are increased in the blood of patients with acute coronary syndrome [33].

Lymphocyte populations ($CD4^+$ and $CD8^+$ T cells, B cells, and NK [natural killer] cell numbers) will also be monitored by flow cytometry as will T cell maturation subsets (determined by expression of CCR7 and CD45RA). In these populations, the expression of the CVC-binding chemokine receptors CCR5 and CCR2 will be monitored. Among the circulating $CD4^+$ and $CD8^+$ T cells, occupancy of these receptors by CVC will be monitored by assays we have developed that identify occupied receptors that are recognized by their inability to bind CCR5 ligands (RANTES analogues) and CCL2 that each block binding of co-receptor binding monoclonal antibodies. An effect of CVC on T cell activation will be explored by monitoring expression of CD38 and HLA-DR on T cell maturation subsets and on T cell subsets that express CCR5 and CCR2.

<u>Rationale for 150 mg Dose</u>
CVC is a well-tolerated oral formulation with most adverse events considered mild or moderate; the most common side effects reported are nausea, headache, and diarrhea [14, 40]. CVC should be administered with food for optimal absorption. There were no major safety signals in over 2,000 patients exposed to CVC, including vulnerable patient populations, such as patients with HIV-1 or patients with liver cirrhosis, in CVC clinical trials. Optimal responses on CCR2 blockade (as evidenced by increase in MCP-1 [chemokine ligand 2 {CCL2}] level) were seen with a 150 mg dose of CVC in Phase IIa study (Study 652-2-201) in participants living with HIV [44]. Furthermore, in participants with nonalcoholic steatohepatitis (NASH), CVC at a 150 mg dose significantly increased MCP-1 (CCL2), CCL3, and CCL4 (consistent with CCR2 and CCR5 blockade), and reduced sCD14, IL-6, hsCRP, and fibrinogen compared to placebo [45]. Due to the effectiveness of a CVC 150 mg dose at reducing monocyte activation, we believe this

dose could be effective in reducing arterial inflammation, which is reflective of macrophage infiltration and metabolism in the arterial wall.

Furthermore, this dose (150 mg) was evaluated in the CENTAUR (phase 2) and AURORA (Phase 3) studies (Study 652-2-203 and 3152-301-002, respectively) and selected based on the clinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and safety data from prior studies (652-1-110, 652-1-111, 652-120, 652-1-121, 652-1-122, 652-123, 652-124, 652-2-202, and 652-2-201), which together support:

- Evidence of meaningful clinical efficacy of CVC 150 mg in participants with NASH and liver fibrosis in the CENTAUR study (Study 652-2-203)
- Evidence that CVC 150 mg is safe and well tolerated in participants with NASH and liver fibrosis in the CENTAUR study (Study 652-2-203)
- CVC dose of 150 mg provides an expectation of effective primary pharmacology (i.e., CCR2 and CCR5 antagonism)
- Evidence of improvement in systemic inflammation biomarkers support underlying CVC pharmacology

In CENTAUR, the CVC dose of 150 mg daily exposed >77% of participants to minimum plasma concentration (Cmin) values that exceed the ECmin50 (Cmin associated with half-maximal response; using most conservative ECmin50 of 50 ng/mL, based on data from the HIV Phase II program), providing an expectation of substantial and near maximal antagonism of CCR2/CCR5 in most participants at this dose. When using the ECmin50 of 40 ng/mL, which was based on changes in CCL2 and CCL4 levels (i.e., reciprocal increases in CCL2 and CCL4 levels observed due to effective CCR2 and CCR5 blockade by CVC) observed in the CENTAUR study, >84% of CVC-treated participants achieved this target drug concentration. Results from a drug interaction study (Study 652-123) have shown that administration of a proton pump inhibitor (PPI) 90 minutes prior to CVC, dosed at 150 mg, resulted in significantly decreased CVC concentrations. In the CENTAUR study, PPIs were allowed with specific dosing instructions (i.e., dosing of PPIs at least 2 hours after CVC 150 mg daily dose) and were used in 44% of all participants. Although fewer participants achieved an ECmin50 of 40 ng/mL when using PPIs (84.5%) compared to those who did not (94.3%), a similar proportion of participants in both groups achieved the key efficacy endpoint of improvement in fibrosis by at least 1 stage and no worsening of steatohepatitis: 21.0% for PPI users versus 25.0% for nonusers, respectively (mITT). Therefore, the dose of 150 mg appears sufficient when managing coadministration of CVC with commonly used concomitant medications, such as PPIs. Taken together, prior PK/PD analyses further support that the CVC 150 mg dose was able to maximize CCR2/CCR5 blockade in most participants and support its evaluation in the current study.

This is also supported by data from the Phase 3, two-part AURORA study (3152-301-002), which aimed to confirm the antifibrotic benefit of CVC as compared with placebo in adults with NASH and Stage 2 or 3 fibrosis. Part 1 of the study was designed to demonstrate the superiority of CVC compared with placebo on liver histology at Month 12, relative to the screening biopsy in adult participants with a liver biopsy diagnosis of

NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system), as confirmed by an independent central pathologist. Part 1 assessed the proportion of participants with improvement in fibrosis by at least 1 stage (NASH CRN system), and no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) on liver histology at Month 12 relative to the screening biopsy. Upon interim analysis of the data from Part 1 completion, the study was terminated early, as no meaningful numerical or statistical difference was observed between CVC 150 mg once daily and placebo, with respect to the key efficacy endpoints regarding liver histology at Month 12 relative to the screening biopsy in adult participants with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system). CVC 150 mg once daily was, in general, well tolerated in this study, and there were no treatment-related TEAEs that were fatal or life-threatening.

Allergan also conducted a Phase 2 clinical study “Rollover” (3152-201-002) to provide open-label treatment and to assess the long-term safety of continued treatment with CVC for eligible participants who have previously participated in CVC studies (CENTAUR 652-2-203 and AURORA 3152-301-002). Following the analysis of the data from Part 1 of the AURORA study, the sponsor decided not to develop this product further for the treatment of NASH due to not achieving the primary efficacy endpoint, and the AURORA and Rollover studies were prematurely terminated. The CVC program was not terminated due to safety concerns. CVC 150 mg once daily was well tolerated in this study. No clinically significant safety information was identified. In overall terms coupling the mechanistic data generated and safety profile, the totality of information further support that the CVC 150 mg dose was able to maximize CCR2/CCR5 blockade in most participants and support its evaluation in the current study.

Rationale for CVC Dose with ART Regimen

Clinical drug-drug interaction studies have been performed by Allergan, plc, in healthy adult volunteers. To summarize, CVC exposure was increased when co-administered with protease inhibitors (ritonavir [RTV], darunavir/ritonavir [DRV/r], or atazanavir/ritonavir [ATV/r]). Although the PK profile of CVC in combination with cobicistat (COBI) has not been studied, it is assumed that there will be significant increase in CVC concentration when co-administered with regimens boosted with COBI since COBI is a potent CYP3A inhibitor. CVC exposure was decreased when co-administered with efavirenz (EFV) and dolutegravir (DTG), but not changed with tenofovir (TFV). Co-administration with CVC increased TFV and ATV/r exposure, and had no effect on EFV, DRV/r, or DTG exposure. For EFV specifically, there was a 23% reduction in CVC Cmax, a 43% reduction in AUC0-24, and a 48% reduction in Cmin with EFV co-administration, which is a large enough reduction in CVC exposure to warrant a CVC dosage adjustment when given with EFV. (See Cenicriviroc mesylate [CVC] Investigator’s Brochure [IB], Version 8.0, dated 04/2022)

Based on these data, dosing will be 150 mg once a day for participants who are on an INSTI- or rilpivirine (RPV)-based regimen, and 300 mg once a day in the morning with food for participants who are on an EFV-based regimen at bedtime. Although co-administration with DTG reduced CVC exposure, the effect was modest and not

expected to be clinically significant (CVC IB, Version 8.0, dated 04/2022), and thus does not warrant dose adjustment. As RPV is not a potent inducer of CYP3A, we believe it is unlikely to accelerate metabolism of CVC; therefore, no dose adjustment is proposed for participants who may be receiving an RPV-based ART regimen. At this time, we will exclude participants who are on protease inhibitors or on regimens boosted by RTV or COBI.

Rationale for 2:1 Randomization

At study entry, participants will be randomized at a 2:1 ratio (CVC arm:placebo arm). The 2:1 allocation is chosen so that more participants may potentially benefit from CVC (as opposed to no benefit from placebo). This is felt to be particularly important in the context of a placebo controlled study in which participants are being asked to undergo multiple imaging studies. This approach will also give us more statistical power to assess within group changes for the CVC arm.

Rationale for Per-protocol Analyses

The per-protocol analysis approach will be used in primary and key secondary analyses since the primary focus of the study is to determine the biological activity of CVC on vascular inflammation rather than clinical efficacy.

Rationale for Duration of 24 Weeks

In another study in participants living with HIV, Study 652-2-202, a Phase IIb study, CVC led to significant increases in MCP-1 (CCL2) at week 24 compared to EFV and CVC led to significant decreases in the monocyte activation marker sCD14 by 12 weeks that were sustained at week 24 and later. Prior studies examining arterial inflammation have shown that arterial inflammation can be reduced by 12 weeks using other interventions such as statin therapy and thus, we believe at least 12 weeks duration would be needed. Extending the intervention to 24 weeks will allow us to safely prolong exposure to CVC, which might produce a greater effect, and also examine the duration of the effect if maximum activity that is demonstrable at 12 weeks.

Rationale for Pharmacology Study

The majority of the prior PK information on drug-drug interactions (DDIs) was generated in healthy volunteers. Therefore, to provide information for CVC PK in individuals living with HIV on select ART regimens and to provide ART PK in the context of CVC, specifically in individuals living with HIV, a sparse PK design is included in the protocol.

CVC Safety Data

All safety data and information described here is taken from the Cenicriviroc Investigator's Brochure (CVC IB version 8.0 04/2022 – AbbVie Data on file) and has been selected in light of the dosing regimen similarity with this study.

Overall, to date, 1361 participants have been exposed to either single or multiple doses of CVC in AbbVie-Sponsored completed clinical studies. The overall safety experience of CVC is based on data from all the studies (including healthy participants, adult participants with NASH and liver fibrosis, participants with PSC, participants living with

HIV, and participants with COVID-19). CVC doses range from 25 mg to 900 mg across all CVC studies.

Adverse drug reactions (ADRs) included in this section were identified by the Sponsor, based on the nature and frequency of observed events (from all clinical studies) and reasonable evidence of causal association with CVC. The ADRs described in this section are considered non-serious.

CENTAUR (Study 652-2-203)
Safety in adult participants with liver fibrosis was evaluated in the CENTAUR Phase 2 study, "A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Multinational, 2-year Study" (Study 652-2-203). The 150 mg dose in the CENTAUR study was well tolerated. Overall, the safety profile of CVC (150 mg QD) was comparable to that in participants treated with placebo and was well tolerated over 2 years. The overall incidence of treatment-emergent adverse events (TEAEs) during the study was similar across the treatment groups (≥95.0% of participants in each group). No deaths occurred during the study. (See CVC IB, 8.0, dated 04/2022)

The adverse drug reactions (ADRs) for CVC in participants with NASH are listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term in Table 2.1-1. The overall frequency of the ADR represents the frequency for all ADRs regardless of seriousness. The information includes the nature of the ADR, including serious, life threatening, or fatal outcomes. For all events in the table, non-serious events are expected. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); and very rare (<1/10,000) (See CVC IB, 8.0, dated 04/2022).

Table 2.1-1: Expected Adverse Drug Reactions in Participants with NASH Treated with CVC in Clinical Studies (CVC IB, 8.0, dated 04/2022)

System Organ Class Preferred Term	Centaur Year 1		Centaur Year 1 + Year 2	
	CVC 150 mg N=144	Placebo N=144	CVC/CVC N=121	Placebo/ Placebo N=60
Adverse Reactions				
Gastrointestinal disorders				
Abdominal distention	10 (6.9%)	2 (1.4%)	11 (9.1%)	0 (0.0%)
Diarrhea	30 (20.8%)	21 (14.6%)	25 (20.7%)	14 (23.3%)
Flatulence	9 (6.3%)	5 (3.5%)	9 (7.4%)	1 (1.7%)
Nausea	25 (17.4%)	13 (9.0%)	23 (19.0%)	8 (13.3%)
Vomiting	14 (9.7%)	6 (4.2%)	14 (11.6%)	5 (8.3%)
General disorders and administration site conditions				
Asthenia	6 (4.2%)	3 (2.1%)	6 (5.0%)	1 (1.7%)
Pyrexia	8 (5.6%)	3 (2.1%)	6 (5.0%)	1 (1.7%)

System Organ Class Preferred Term	Centaur Year 1		Centaur Year 1 + Year 2	
	CVC 150 mg N=144	Placebo N=144	CVC/CVC N=121	Placebo/ Placebo N=60
Musculoskeletal and connective tissue disorders				
Arthralgia	18 (12.5%)	6 (4.2%)	20 (16.5%)	4 (6.7%)
Joint swelling	5 (3.5%)	0 (0.0%)	5 (4.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders				
Dermatitis contact	5 (3.5%)	0 (0.0%)	6 (5.0%)	0 (0.0%)
Rash*	16 (11.1%)	8 (5.6%)	16 (13.2%)	7 (11.7%)

* Rash, rash macular, rash maculopapular, rash erythematous, rash pustular, rash pruritic and rash generalized.

The frequency and types of TEAEs reported were comparable between treatment groups during Year 1 and Year 2 (Table 2.1-2 and Table 2.1-3).

Table 2.1-2: Summary of Treatment Emergent Adverse Events (≥10% of Participants in any Treatment Arm) by System Organ Class and Preferred Term – Safety Analysis Set Year 1 (CVC IB, 8.0, dated 04/2022)

System Organ Class Preferred Term	Placebo[a] (Arm B + C) (N = 144) n (%)	CVC 150 mg (Arm A) (N = 144) n (%)	Total (N = 288) n (%)
Any TEAE[b]	133 (92.4)	134 (93.1)	267 (92.7)
Gastrointestinal disorders	73 (50.7)	77 (53.5)	150 (52.1)
Diarrhea	21 (14.6)	30 (20.8)	51 (17.7)
Nausea	13 (9.0)	25 (17.4)	38 (13.2)
Abdominal pain upper	19 (13.2)	14 (9.7)	33 (11.5)
Abdominal pain	13 (9.0)	15 (10.4)	28 (9.7)
Musculoskeletal and connective tissue disorders	51 (35.4)	57 (39.6)	108 (37.5)
Back pain	17 (11.8)	11 (7.6)	28 (9.7)
Arthralgia	6 (4.2)	18 (12.5)	24 (8.3)
General disorders and administration site conditions	34 (23.6)	47 (32.6)	81 (28.1)
Fatigue	20 (13.9)	18 (12.5)	38 (13.2)
Nervous system disorders	33 (22.9)	41 (28.5)	74 (25.7)
Headache	24 (16.7)	19 (13.2)	43 (14.9)

[a] The Placebo column includes all participants randomized to placebo during Treatment Period 1.
[b] TEAEs include all events with a start date/time after the date of first dose of study medication during the treatment period.

Table 2.1-3: Summary of Treatment Emergent Adverse Events (≥5% of Participants in any Treatment Arm) by System Organ Class and Preferred Term – Year 2 – Safety Analysis Set Year 2 (CVC IB, 8.0, dated 04/2022)

System Organ Class Preferred Term	Placebo/ Placebo (Arm C) (N=60) n (%)	CVC 150 mg/ CVC 150 mg (Arm A) (N=121) n (%)	Placebo/ CVC 150 mg (Arm B) (N=61) n (%)	Total (N=242) n (%)
Any TEAE*	50 (83.3)	105 (86.8)	46 (75.4)	201 (83.1)
Infections and infestations	18 (30.0)	62 (51.2)	22 (36.1)	102 (42.1)
Nasopharyngitis	2 (3.3)	11 (9.1)	5 (8.2)	18 (7.4)
Upper respiratory tract infection	3 (5.0)	8 (6.6)	5 (8.2)	16 (6.6)
Urinary tract infection	0 (0.0)	9 (7.4)	3 (4.9)	12 (5.0)
Sinusitis	4 (6.7)	6 (5.0)	1 (1.6)	11 (4.5)
Bronchitis	3 (5.0)	4 (3.3)	0 (0.0)	7 (2.9)
Ear infection	3 (5.0)	1 (0.8)	1 (1.6)	5 (2.1)
Gastrointestinal disorders	18 (30.0)	31 (25.6)	12 (19.7)	61 (25.2)
Abdominal pain	4 (6.7)	4 (3.3)	2 (3.3)	10 (4.1)
Abdominal pain upper	3 (5.0)	4 (3.3)	3 (4.9)	10 (4.1)
Diarrhea	5 (8.3)	2 (1.7)	3 (4.9)	10 (4.1)
Nausea	2 (3.3)	7 (5.8)	0 (0.0)	9 (3.7)
Musculoskeletal and connective tissue disorders	11 (18.3)	28 (23.1)	8 (13.1)	47 (19.4)
Arthralgia	2 (3.3)	6 (5.0)	0 (0.0)	8 (3.3)
Back pain	3 (5.0)	0 (0.0)	4 (6.6)	7 (2.9)
Pain in extremity	0 (0.0)	7 (5.8)	0 (0.0)	7 (2.9)
Injury, poisoning and procedural complications	10 (16.7)	20 (16.5)	8 (13.1)	38 (15.7)
Procedural pain	4 (6.7)	4 (3.3)	2 (3.3)	10 (4.1)
General disorders and administration site conditions	11 (18.3)	18 (14.9)	5 (8.2)	34 (14.0)
Fatigue	3 (5.0)	11 (9.1)	2 (3.3)	16 (6.6)
Skin and subcutaneous tissue disorders	11 (18.3)	15 (12.4)	8 (13.1)	34 (14.0)
Rash	4 (6.7)	6 (5.0)	1 (1.6)	11 (4.5)
Pruritus	3 (5.0)	3 (2.5)	1 (1.6)	7 (2.9)
Investigations	6 (10.0)	15 (12.4)	7 (11.5)	28 (11.6)
Alanine aminotransferase increased	2 (3.3)	6 (5.0)	2 (3.3)	10 (4.1)
Respiratory, thoracic and mediastinal disorders	8 (13.3)	14 (11.6)	1 (1.6)	23 (9.5)
Cough	0 (0.0)	6 (5.0)	1 (1.6)	7 (2.9)

* TEAEs include all events with a start date/time after the date of first dose of study medication during the treatment period.

CVC in Participants Living with HIV

In participants living with HIV in Study 652-2-201, CVC was generally well tolerated at the doses studied and no safety concerns were identified. There were no SAEs, deaths,

or other significant AEs, and there were no discontinuations because of an AE. Most TEAEs were mild or moderate in severity. Participants who received 150 mg of CVC (i.e., the highest dose studied) had more AEs compared with participants in the other dose groups, although the severity of AEs was comparable across all dose groups. The most common (>2 participants) TEAEs reported on CVC were diarrhea (n=9), nausea (n=8), headache (n=6), fatigue (n=6), flatulence (n=3), vomiting (n=3), cough (n=3), and pyrexia (n=3). (See CVC IB, 8.0, dated 04/2022)

In participants living with HIV in Study 652-2-202, doses of 100 mg and 200 mg of CVC were generally well tolerated during the entire study period (up to 48 weeks of treatment followed by a 4-week follow-up period). No participants died. One participant in each treatment arm experienced SAEs, all unrelated to study drug. AEs leading to discontinuation of study medication occurred in one participant (2%) in the CVC 200 mg arm and in six participants (21%) in the EFV arm. Most AEs were mild or moderate (Grade 1 or Grade 2) in severity. The percentage of participants who experienced a Grade ≥3 AE was lower in the CVC arms (total of 4%) than in the EFV arm (15%). No Grade 4 AEs were reported in CVC-treated participants. The percentage of participants with AEs that were at least Grade 2 and at least possibly related to study medication was lower in the CVC arms (9% in both CVC arms) than in the EFV arm (36%). Headache, fatigue, and upper respiratory tract infection were reported more frequently in the CVC arms than in the EFV arm (Table 2.1-4). The most frequently reported study drug-related clinical TEAEs of at least moderate (Grade 2) severity occurring in ≥2% of participants in any treatment group were nausea (2%) in the CVC groups combined, and abnormal dreams (11%), insomnia (11%), nausea (7%), and rash (7%) in the EFV group. Most laboratory abnormalities were Grade 1 or Grade 2 in severity. Except for abnormalities in creatine phosphokinase (CPK) that were observed more frequently in the CVC 200 mg arm, there were no differences in percentages of participants with Grade 3 or Grade 4 laboratory abnormalities between the treatment arms. All cases of CPK elevations were transient and were not associated with clinical symptoms. No Grade 4 ALT or AST elevations were observed. A decrease was observed during CVC treatment in total cholesterol, mainly due to decreases in low density lipoprotein cholesterol. No clinically relevant changes in ECG or vital sign parameters were observed during the treatment period in any of the treatment arms [8]. (See CVC IB, 8.0, dated 04/2022)

Table 2.1-4: Treatment-Emergent Adverse Events Occurring in ≥10% of Participants in CVC or EFV Arms - Study 652-2-202 (CVC IB, 8.0, dated 04/2022)

Preferred Term n (%)	CVC 100 mg	CVC 200 mg	All CVC	EFV
	(N = 58)	(N = 57)	(N = 115)	(N = 28)
Mean (SE) duration of intake study medication (weeks)[a]	41.2 (1.89)	40.9 (1.88)	41.1 (1.33)	36.2 (3.64)
Any AE	51 (88%)	48 (84%)	99 (86%)	27 (96%)
Nausea	10 (17%)	8 (14%)	18 (16%)	6 (21%)

Preferred Term n (%)	CVC 100 mg (N = 58)	CVC 200 mg (N = 57)	All CVC (N = 115)	EFV (N = 28)
Upper respiratory tract infection	9 (16%)	9 (16%)	18 (16%)	2 (7%)
Diarrhea	7 (12%)	10 (18%)	17 (15%)	3 (11%)
Headache	9 (16%)	7 (12%)	16 (14%)	0
Rash[b]	7 (12%)	7 (12%)	14 (12%)	5 (18%)
Fatigue	6 (10%)	8 (14%)	14 (12%)	1 (4%)
Dizziness	5 (9%)	6 (11%)	11 (10%)	8 (29%)
Nasopharyngitis	2 (3%)	8 (14%)	10 (9%)	1 (4%)
Abnormal dreams	6 (10%)	3 (5%)	9 (8%)	6 (21%)
Insomnia	0	7 (12%)	7 (6%)	4 (14%)
Lymphadenopathy	3 (5%)	4 (7%)	7 (6%)	4 (14%)
Depression	2 (3%)	1 (2%)	3 (3%)	3 (11%)
Syphilis	1 (2%)	0	1 (1%)	3 (11%)

[a] Note that exposure is based on ITT population.
[b] Included rash, rash maculopapular, rash pruritic, rash generalized, and rash papular.

Safety data originating from the four studies completed in 2021 (Aurora, Rollover, Tandem, and CLJC242A2101) are aligned with the current knowledge of the safety profile of CVC and are summarized below.

AURORA (Study 3152-301-002)
Full Cohort
TEAEs reported by 22% participants in the CVC group and that occurred at an incidence rate of 22% greater than in the placebo group were nausea (104 [8.8%] participants in the CVC group versus 39 [6.6%] participants in the placebo group), alanine aminotransferase increase (45 [3.8%] participants in the CVC group versus 9 [1.5%] participants in the placebo group), aspartate aminotransferase increase (38 [3.2%] participants in the CVC group versus 6 [1.0%] participants in the placebo group), and nephrolithiasis (25 [2.1%] participants in the CVC group versus 0 participants in the placebo group). CVC 150 mg once daily was, in general, well tolerated in this study, there were no treatment-related TEAEs that were fatal or life-threatening. The nature and incidence rates of AEs observed with CVC were similar to those observed with placebo, except for nausea, elevation in transaminases, and nephrolithiasis, the latter, a finding inconsistent with previous safety data. The proportion of participants who experienced DILI (cases adjudicated as possible or probable DILI) was higher in the CVC group (4 participants [0.3%]) compared to placebo group (0 participants [0%]), suggesting a possible causal relationship between CVC and DILI. Nevertheless, all these cases were non-serious, non-clinically significant, and reversible after CVC discontinuation.

ROLLOVER (Study 3152-201-002)
The incidence of all Treatment-emergent Adverse Events (TEAEs) reported during the study was 140 of 167 participants (83.8%). Treatment-related TEAEs, as determined by

the investigator, were reported for 28 participants (16.8%). The majority of TEAEs were mild in intensity. Severe TEAEs were reported for 40 participants (24.0%). There were no clinically meaningful findings regarding clinical laboratory. The most common events reported in ≥10% of participants were arthralgia (13.2%), diarrhea (12.0%), and nasopharyngitis (10.2%).

TANDEM (Study CLJC242A2201J)
The safety profiles of the combination therapies of tropifexor 140 mcg + CVC 150 mg and tropifexor 90 mcg + CVC 150 mg were similar to those of each monotherapy, with no additional emergent safety signals compared to those identified and reported in previous monotherapy studies. Overall, pruritus, nausea, and fatigue were the most frequently experienced AEs. The proportion of participants who experienced pruritus was highest in the tropifexor 140 mcg alone group and notably lower with tropifexor 140 mcg + CVC 150 mg combination treatment. Similar patterns are noted for fatigue and urinary tract infection, and this pattern may be explained by the DDI by which CVC treatment reduces tropifexor levels.

No deaths were reported in the study. Most SAEs were single occurrences. The AEs most frequently leading to discontinuation from study treatment were pruritus (tropifexor 140 mcg group: 4, 8.0%; tropifexor 140 mcg + CVC 150 mg group: 2, 4.3%) and flatulence (tropifexor 140 mcg + CVC 150 mg group: 2, 4.3%); all other AEs leading to discontinuation were single occurrences.

Study CLJC242A2101
There were no deaths reported during this study, and one SAE (unrelated ovarian torsion) was reported after the cut-off date for TEAEs in the clinical database. One participant who received tropifexor + CVC discontinued from the study due to a TEAE (rash), which was suspected to be definitely related to the study drugs. None of the 4 TEAEs reported for tropifexor alone or the 10 TEAEs reported for CVC alone were considered related to the study drugs. The most commonly reported PTs were abdominal pain reported for two (14.3%) participants after receiving tropifexor alone, and dermatitis contact and headache each reported for two (14.3%) participants, after receiving CVC alone.

<u>Radiation Safety Considerations</u>
The FDG-PET/CT imaging will be associated with radiation exposure of ~19 to 21 milliSieverts (mSv). This exposure is similar amount of radiation that a person is exposed to when undergoing a single exercise stress test with myocardial perfusion imaging (~15 mSv for technetium studies, and ~21 to 24 mSv for thallium studies), and is substantially below the 50 mSv limit that is established by Institutional Review Boards (IRBs) in the United States (the annual limit established for radiation workers). To further limit the radiation risks to participants, anyone who reports any significant radiation exposure over the course of the year prior to study entry (defined in the exclusion criteria) or who has a history of radiation therapy will be excluded. There may be rare instances when imaging has to be repeated because the initial image obtained was deemed uninterpretable. If this occurs, the exposure may approach 28 to 32 mSv.

Biomarkers
As CVC binds and inhibits function of CCR2 and CCR5, interference with binding and clearance of CCL2 and MIP-1a, MIP-1b, and RANTES (CCR5 ligands) might be anticipated. As we hypothesize that monocyte/macrophage activation may be attenuated by CVC administration, we also plan to monitor levels of sCD14 and sCD163, indices of monocyte/macrophage activation.

Supporting Pharmacokinetic Data from Allergan/**AbbVie**
In Study 104, there was a 2.39-fold increase in CVC Cmax, a 3.55-fold increase in CVC AUC from time 0 to 24 hours post dose (AUC0-24), and a 5.24-fold increase in CVC Cmin with RTV co-administration.

In Study 105, there was no evidence of a drug-drug interaction on CVC by tenofovir disoproxil fumarate (TDF); however, co-administration with CVC increased plasma TDF exposure by approximately 28%-36%.

In Study 107, there was a 2.17-fold increase in CVC Cmax, a 3.13-fold increase in CVC AUC0-24, and a 4.17-fold increase in Cmin with DRV/r co-administration, which is comparable to the effect seen with co-administration of RTV alone in Study 104. In Study 113, there was no meaningful effect of CVC on plasma darunavir (DRV) or RTV exposure.

In Study 108, there was a 2.55-fold increase in CVC Cmax, a 3.89-fold increase in AUC0-24, and a 5.75-fold increase in Cmin with ATV/r co-administration, which is comparable to the effect seen with co-administration of RTV alone in Study 104. In Study 112, there were modest effects of CVC on RTV Cmin (1.50-fold increase) and on atazanavir (ATV) Cmax (1.19-fold increase), AUC0-24 (1.33-fold increase), and Cmin (1.55-fold increase). There were no statistically significant effects of CVC on RTV Cmax or AUC0-24.

In Study 109, there was a 23% reduction in CVC Cmax, a 43% reduction in AUC0-24, and a 48% reduction in Cmin with EFV co-administration. CVC did not result in a meaningful change in plasma EFV exposure.

In Study 110, there was a 28% reduction in CVC Cmax, a 29% reduction in AUC0-24, and a 23% reduction in Cmin with DTG co-administration. CVC did not result in a meaningful change in plasma DTG exposure.

A summary of detailed results of these studies performed is shown in Appendix I.

3.0 STUDY DESIGN

This is a double-blind, placebo-controlled phase II clinical trial comparing the intervention of CVC versus placebo for a duration of 24 weeks on arterial inflammation evaluated by FDG-PET/CT imaging. Image analysis will be performed by imaging specialists at the

central imaging core laboratory at the Massachusetts General Hospital (MGH) Imaging Trials Center (MITC). The imaging specialists at the core laboratory are blinded to the clinical history and treatment group classification of the participant.

A total of 93 participants will be randomized 2:1 to the CVC arm (Arm A) or placebo for CVC arm (Arm B). Stratification by statin use at randomization will ensure even distribution of statin use between the treatment groups.

Blood samples will be collected per the SOE.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by:

- Any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry
  AND
- Confirmed by one of the following:
- A licensed Western blot
- A second antibody test by a method other than the initial rapid HIV and/or E/CIA
- HIV-1 antigen, plasma HIV-1 RNA viral load, or
- Two HIV-1 RNA >1,000 copies/mL.

NOTE: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.2 Currently on a stable, continuous NNRTI-based or unboosted INSTI-based ART regimen for ≥48 weeks prior to study entry with no ART interruption longer than 7 consecutive days and with no plans to change ART during the course of the study.

NOTE A: Stable is defined as no within-class changes in ART regimen within 12 weeks prior to study entry and no between-class changes for 24 weeks prior to study entry.

NOTE B: Unboosted ART is defined as an ART regimen that does not include the pharmacologic booster COBI or RTV.

NOTE C: Modifications of ART formulation within 12 weeks prior to study entry (e.g., from standard formulation to fixed-dose combination of the same drugs), are permitted.

4.1.3 Screening HIV-1 RNA level below the limit of quantification (e.g., <20, <40, <50, or <75 copies/mL, depending on the assay) using an FDA-approved assay with a quantification limit of 75 copies/mL or lower performed by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs within 90 days prior to study entry.

4.1.4 All HIV-1 RNA levels within 48 weeks prior to study entry below the limit of quantification (e.g., <20, <40, <50, or <75 copies/mL, depending on the assay) using an FDA-approved assay with a quantification limit of 75 copies/mL or lower performed by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

NOTE A: Up to two HIV-1 RNA determinations that are between the assay quantification limit and 500 copies/mL (i.e., “blips”) are allowed as long as the preceding and subsequent determinations are below the level of quantification.

NOTE B: The screening value may serve as the subsequent undetectable value following a blip.

4.1.5 CD4+ cell count >200 cells/mm^3 obtained within 90 days prior to study entry at any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that is IQA certified.

4.1.6 At least <u>one</u> of the following cardiovascular risk factors (current diagnosis or receiving treatment, except where a time period is specified):

- Clinical atherosclerotic disease (symptomatic atherosclerotic lesions in any vessel)
- Subclinical atherosclerotic disease (coronary artery calcification [CAC] >10 or presence of non-obstructive plaques)
- DM or prediabetes (hemoglobin A1c [HbA1c] ≥5.7%) or impaired fasting glucose (documented fasting glucose of >100 mg/dL within 6 months prior to study entry) or insulin resistance (HOMA-IR ≥2.6) or any one of these

laboratory values within 6 months prior to study entry

- Obesity (body mass index [BMI] ≥30 kg/m^2) or enlarged iliac waist circumference (>40 inches in males, >35 inches in females)

  NOTE A: BMI calculator is available at the Data Management Center (DMC) website: https://www.fstrf.org/ACTG/ccc.html.

- History of hypertension or blood pressure ≥130/80 mmHg measured during screening
  NOTE: See the A5415 Manual of Procedures (MOPS) for **blood pressure measurement guidance.**
- Elevated LDL cholesterol (fasting LDL of >160 mg/dL; result from sample taken within 90 days prior to study entry can be used)
- Low HDL cholesterol (<40 mg/dL; result from sample taken within 90 days prior to study entry can be used)
- Smoking (any current tobacco smoking)
- Family history of premature CAD (first degree relative with CAD prior to age 55 for male relative and 65 for female relative; participant report is acceptable)
- hsCRP >2.0 mg/L within 90 days prior to study entry without an active infection or acute illness at the time the sample was obtained

4.1.7 The following laboratory values obtained within 90 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

- Absolute neutrophil count (ANC) >750/mm^3
- Platelet count >100,000/mm^3
- Aspartate aminotransferase (AST) (SGOT) ≤5x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) (SGPT) ≤5x ULN
- Alkaline phosphatase ≤5x ULN
- Estimated glomerular filtration rate (GFR) ≥60 mL/min/1.73 m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation

NOTE: See the A5415 MOPS for further information and a link to the CKD-Epi equation and calculator.

4.1.8 Pre-entry FDG-PET/CT imaging (within 60 days prior to study entry) that has been deemed:

- Interpretable as assessed by the central imaging core laboratory
  AND
- Without incidental findings that will preclude participation in the study at the discretion of the site investigator

4.1.9 No plans to receive immunizations 7 days prior to the week 24 study visit.

4.1.10 For study candidates of child-bearing potential, negative serum or urine pregnancy test within 90 days prior to study entry and prior to starting study treatment at study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test, or at any network-approved non-US laboratory or clinic that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

NOTE: Reproductive potential is defined as individuals who have reached menarche and individuals who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available, or have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy).

4.1.11 If participating in sexual activity that could lead to pregnancy, willingness of person of childbearing potential to use two forms of contraception while receiving study medication and for 3 months after stopping study medication as required.

NOTE A: Acceptable forms of contraception include:
- Barrier methods (condoms [male or female] with or without a spermicidal agent, diaphragm, or cervical cap [with spermicide])
- Hormone-based contraception (oral, patch, parenteral, implants, or vaginal ring)
- Intrauterine device (IUD)

NOTE B: If the participant is not of reproductive potential (individuals who are post-menopausal as defined above, or individuals who have undergone surgical sterilization [e.g., hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy]), they are eligible without requiring the use of a contraceptive method. Acceptable documentation of surgical sterilization and menopause is by participant-reported history.

4.1.12 Individuals ≥45 years of age.

4.1.13 Ability and willingness of participant or legal guardian/representative to provide informed consent.

4.2 Exclusion Criteria

4.2.1 Acute coronary syndrome, defined as myocardial infarction (MI) or unstable angina, within 90 days prior to study entry.

4.2.2 A current diagnosis of latent or active tuberculosis (TB) infection, any prior untreated TB infection, inadequate treatment of active TB, or inadequate treatment of latent TB.

NOTE A: Individuals with cases of active infection and latent TB infection with a history of adequate treatment may be considered for enrollment provided the individual has a negative chest X-ray following treatment and within 1 year prior to study entry.

NOTE B: Written documentation of prior TB treatment and negative chest x-ray is required.

4.2.3 Current diagnosis with other intracellular pathogens (*Mycobacterium avium complex*, *Listeria monocytogenes*, *Toxoplasma gondii*, and *Cryptococcus neoformans*) within 90 days prior to study entry.

4.2.4 Untreated hepatitis B virus (HBV) infection with detectable HBV DNA within 6 months prior to study entry.

4.2.5 Current hepatitis C virus (HCV) infection (i.e., detectable HCV RNA within 6 months prior to study entry).

NOTE: Individuals with successfully treated HCV, and are at least 6 months post treatment completion, are not excluded.

4.2.6 Acute or clinically significant infection or illness requiring IV antibiotics or hospitalization within 90 days prior to study entry.

4.2.7 History of cirrhosis with severe hepatic impairment and/or hepatic decompensation including ascites, hepatic encephalopathy, or variceal bleeding.

4.2.8 Active malignancy, except squamous cell skin cancer.

4.2.9 Hemoglobin A1c >8% within 90 days prior to study entry by any laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory or clinic that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

4.2.10 Initiation of statin therapy or change in statin dose within 90 days prior to study entry.

4.2.11 Current use of any of the statins at the doses indicated:

- Atorvastatin, >40 mg/day dose
- Rosuvastatin, ≥20 mg/day dose

4.2.12 Anticipated addition of any lipid lowering medication during the course of the study.

4.2.13 Concurrent use of drugs with potential drug-drug interactions with CVC within 90 days prior to study entry (refer to the prohibited medications list in section 5.4.2).

4.2.14 Known allergy/sensitivity or any hypersensitivity to components of study drug(s) or their formulation.

4.2.15 Treatment within 30 days prior to study entry or anticipated treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons, cyclosporine, and tacrolimus).

4.2.16 Immunization within 7 days prior to the pre-entry FDG-PET/CT imaging (refer to section 6.3.9).

4.2.17 History of radiation therapy.

4.2.18 High radiation exposure within one year prior to entry, defined as having undergone more than two of any of the procedures below (includes having undergone the same procedure twice within one year prior to study entry):

- Coronary artery catheterization with or without percutaneous coronary intervention (PCI)
- Myocardial perfusion stress test
- Coronary CT angiography
- CT of the chest and abdomen
- Barium enema

4.2.19 Currently pregnant, breastfeeding, or planning to become pregnant during the length of the study and three months after completing the study.

4.2.20 Body weight >300 pounds or >136 kilograms.

4.2.21 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE) responsible for oversight of the study. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will

review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL BE reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed. The participant (or, when necessary, the legal representative if the participant is under guardianship) will be asked to read and sign the approved protocol consent form.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC Participant Enrollment System.

4.3.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.3 Randomization

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, an ACTG Screening Failure Results form must be completed and keyed into the database.

Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

4.4 Coenrollment Guidelines

- US sites are encouraged to coenroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Coenrollment in A5128 does not require permission from the A5415 protocol chair.
- Coenrollment is not allowed for participants in A5332, “Randomized Trial to Prevent Vascular Events in HIV – REPRIEVE.”
- For specific questions and approval for coenrollment in other studies, sites should first check the PSWP or contact the protocol team via email as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as CVC or placebo for CVC, both of which will be provided by the study.

The study treatment will be added to the current NNRTI-based or unboosted INSTI-based antiretroviral (ARV) regimen. The background ART will not be provided by the study.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

At study entry, participants will be randomized 2:1 to oral CVC (Arm A) or oral placebo for CVC (Arm B) once a day. The study treatment will be added to the participants’ pre-existing ARV regimens.

Table 5.1.1-1: Pre-existing ART Regimen and CVC or Placebo for CVC Dose

Pre-existing ART regimen	Arm A	Arm B
EFV	CVC 300 mg	Placebo for CVC 300 mg
All other ARTs	CVC 150 mg	Placebo for CVC 150 mg

5.1.2 Administration

CVC 150 mg or Placebo: Administered as one 150-mg tablet/placebo.

CVC 300 mg or Placebo: Administered as two 150-mg tablets/placebo.

The appropriate dose of CVC or placebo for CVC will be administered by mouth once a day with food. The dose should be taken as close to the same time of day as possible.

For participants who are on EFV-based regimen, CVC or placebo for CVC will be administered in the morning with food.

5.1.3 Treatment Duration

Study participants will remain on study treatment for at least 24 weeks. Study treatment may be extended if needed to ensure that treatment is not discontinued before the end of study evaluations at week 24 are completed (see section 6.2.3).

5.2 Study Product Formulation and Preparation

CVC and placebo for CVC are available as 150 mg yellow-coated, immediate-release tablets for oral administration, and packaged in high-density polypropylene (HDPE) bottles with child-resistant screw caps.

CVC and placebo for CVC should be stored at 15°C to 30°C (59°F to 86°F) with transient excursions permitted between -20°C (-4°F) and 60°C (140°F).

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

CVC and placebo for CVC will be manufactured and provided by AbbVie and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The clinical research site (CRS) pharmacist should obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for Division of AIDS (DAIDS) Clinical Trials Networks.*

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions. Investigators must also review the study agent's prohibited and precautionary medications list in sections 5.4.2 and 5.4.3.

Additional drug information may be found on the Precautionary and Prohibited Medications Database located at: **https://www.ppmdb.org/PPMD**.

5.4.1 Required Medications

NNRTI-based or unboosted INSTI-based ART.

NOTE: Refer to section 4.1.2 for the definition of unboosted ART.

5.4.2 Prohibited Medications

Caution should always be exercised when administering concomitant medications based on the individual medication profile and clinical risk-benefit assessment.

The participant **should** not take the following prohibited medications at any time during the study**.**

- Immunomodulating agents (such as systemic corticosteroids*, interleukins, interferons, cyclosporine, and tacrolimus)

  *If there are plans to start a participant on systemic corticosteroids while on study, contact the A5415 Clinical Management Committee (CMC) (actg.cmca5415@fstrf.org) for additional guidance.

- Immunizations 7 days prior to the week 24 study visit.

- High-dose statins (see Table 5.4.2-1)

  Table 5.4.2-1: Prohibited High-Dose Statins

Statin	Prohibited Dose
Atorvastatin	>40 mg/day
Rosuvastatin	≥20 mg/day

  Contact the A5415 CMC (actg.cmca5415@fstrf.org) for any question regarding allowed statin doses.

- Drugs with potential drug-drug interactions with CVC (see Table 5.4.2-2)

Table 5.4.2-2: Drugs with Potential Drug-Drug Interactions with CVC

Antibacterial	rifampin nafcillin clarithromycin erythromycin telithromycin
Anticonvulsant	carbamazepine phenytoin
Antidiabetic	pioglitazone
Antidepressant	nefazodone
Antifungal	voriconazole itraconazole ketoconazole posaconazole
Antihistamine	astemizole
Anti-inflammatory	sulfasalazine
Antimetabolite	methotrexate
Antipsychotic	pimozide
Antiviral	all antivirals for treatment of HCV HIV protease inhibitors Cobicistat **Maraviroc** **Nirmatrelvir/ritonavir usage ≥10 days is considered prohibited, and participants should be permanently discontinued from study treatment, per section 6.2.4. Short term (<10 days) use of nirmatrelvir/ritonavir is considered precautionary. See section 5.4.3.**
Ergot alkaloid	dihydroergotamine ergonovine ergotamine methylergonovine
Immunosuppressant	cyclosporine tacrolimus
Lipid-lowering agent	gemfibrozil
Opioid	fentanyl alfentanil

Sedative/hypnotic	midazolam* triazolam **Midazolam* *is allowed for sedation for surgical procedures; however, the lowest dose possible should be used and titrated according to the desired clinical response. Contact the A5415 CMC (actg.cmca5415@fstrf.org) for any questions.*
Other	cisapride obeticholic acid high-dose (i.e., >400 IU/day) vitamin E

5.4.3 Precautionary Medications

Table 5.4.3-1: Precautionary Medications

Medicinal Product Class	Drugs that are Allowed but Must be Taken with Precaution During Intake of CVC *(Mechanism)*
Acid-reducing agents (H2 receptor antagonists, antacids, and PPIs)	When required, acid-reducing agents should be administered at least 2 hours after the CVC dose to ensure that adequate CVC concentrations are maintained. When possible, use of an H2 receptor antagonist (except cimetidine) or antacids is preferred over a PPI. It is recommended to start with the lowest dose of these agents and titrate according to clinical response. • *H2 receptor antagonists* (e.g., famotidine or ranitidine) should preferably be given from 2 to 12 hours after administration of CVC at a dose that does not exceed doses comparable to famotidine 40 mg daily. • *Antacids* (e.g., aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, or bismuth subsalicylate) should preferably be given at least 4 hours after administration of CVC due to their immediate effect in increasing gastric pH. • *PPIs* (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, or dexlansoprazole) should preferably be given approximately 3 hours after administration of CVC at a dose that does not exceed doses comparable to omeprazole 20 mg daily. Due to the prolonged acid-reducing effect of PPIs (~16 to 24 hours), it is advised to follow these dosing recommendations to reduce their potential impact on CVC absorption at subsequent dosing.
Lipid-lowering agents	Refer to Table 5.4.2-1 for the statin doses that are not allowed. Contact the A5415 CMC (actg.cmca5415@fstrf.org) for any question regarding statin doses.

Medicinal Product Class	Drugs that are Allowed but Must be Taken with Precaution During Intake of CVC *(Mechanism)*
PDE5 enzyme inhibitors	sildenafil, tadalafil, vardenafil *(CYP3A4 substrates)* The recommended starting doses for these medications are as follows: – sildenafil 25 mg – tadalafil 2.5 mg – vardenafil 2.5 mg
Short term (<10 days) use of nirmatrelvir/ritonavir	**When required, the study treatment should be stopped during the time the participant is receiving the medication and can be restarted after it is stopped. The participant should remain off study treatment for at least 5 days after stopping nirmatrelvir/ritonavir. The participant should remain on study and complete all protocol evaluations. Please consult with the CMC regarding study treatment hold, restarting study treatment, and the timing of key study evaluations.**

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations

Evaluation	Screening	Pre-Entry	Entry	Post-Entry Evaluations (weeks, see section 6.2.3 for visit windows)						Confirmation of Suspected Virologic Failure	Confirmation of Grade ≥3 Toxicity	Premature Treatment Discontinuation	Premature Study Discontinuation
				4	8	12	16	22	24				
Documentation of HIV-1	X												
Medical History	X		X										
Medication History	X		X										
Complete Physical Exam	X												
Targeted Physical Exam			X	X	X	X	X	X	X		(X) (see section 6.3.4)	X	X
Weight	X					X			X			X	
Height	X												
Waist Circumference	X					X			X			X	
Concomitant Medications				X	X	X	X	X	X				
Study Treatment Modifications				X	X	X	X	X	X			X	
Hematology	X	X	X			X		X	X		(X) (see section 8.1)	X	(X) (see section 6.2.4)

Evaluation	Screening	Pre-Entry	Entry	Post-Entry Evaluations (weeks, see section 6.2.3 for visit windows)						Confirmation of Suspected Virologic Failure	Confirmation of Grade ≥3 Toxicity	Premature Treatment Discontinuation	Premature Study Discontinuation
				4	8	12	16	22	24				
Blood Chemistries	X		X	X		X			X		(X) (see section 8.1)	X	(X) (see section 6.2.4)
Glucose (fasting)	X		X			X			X		(X) (see section 8.1)	X	(X) (see section 6.2.4)
Insulin (fasting, real-time)	X												
Lipid Panel (fasting)	X								X		(X) (see section 8.1)	X	(X) (see section 6.2.4)
Liver Function Tests	X		X	X		X			X		(X) (see section 8.2.1)	X	(X) (see section 6.2.4)
HbA1C (real-time)	X								X			X	
Prothrombin Time and International Normalized Ratio			X								(X) (see section 8.2.1)		(X) (see section 6.2.4)
hsCRP (real-time)	X												
Estimated GFR	X		X	X		X			X		(X) (see section 8.2.2)	X	(X) (see section 6.2.4)
Pregnancy Testing	X		X (see section 6.3.5)	If suspected								If suspected	
$CD4^+/CD8^+$		X	X			X		X	X			X	

Evaluation	Screening	Pre-Entry	Entry	Post-Entry Evaluations (weeks, see section 6.2.3 for visit windows)						Confirmation of Suspected Virologic Failure	Confirmation of Grade ≥3 Toxicity	Premature Treatment Discontinuation	Premature Study Discontinuation
				4	8	12	16	22	24				
Plasma HIV-1 RNA	X		X	X		X			X	X		X	
Stored Plasma		X	X			X		X	X			X	
Stored Serum (fasting)			X			X			X			X	
Stored PBMC		X	X			X		X	X			X	
FDG-PET with CT		X							X			(X) (see section 6.2.4)	
Pharmacokinetic Studies		X		X	X	X			X				
Adherence Assessment			X	X	X	X	X	X	X			X	
Food Diary (D=distribute, C=collect)		X[D]	X[C]					X[D]	X[C]				
Perceived Stress Scale-10		X							X				

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Screening and pre-entry evaluations must occur prior to participants starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 90 days prior to study entry unless otherwise specified. Screening evaluations must be completed, and the results confirmed as meeting eligibility requirements based on screening evaluations, before the FDG-PET/CT imaging at pre-entry is performed.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on participants who do not enroll will be captured in a Screening Failure Results form and entered into the ACTG database.

Pre-Entry
Pre-entry evaluations must be performed after all screening evaluations have been completed and within 60 days prior to entry evaluations unless otherwise specified. The FDG-PET/CT imaging must be performed only after it is confirmed that a candidate meets eligibility requirements based on the screening evaluations. It is encouraged that all pre-entry evaluations occur on the same day. If evaluations cannot occur on the same day as the FDG-PET/CT imaging, evaluations must occur ±7 days of imaging.

6.2.2 Entry Evaluations

Entry evaluations must occur within 60 days from the date of the pre-entry FDG-PET/CT imaging unless otherwise specified. Participant must begin treatment within 72 hours after randomization.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations
All post-entry evaluations must be scheduled as per section 6.1.

Weeks 4 through 22 have a visit window of ±7 days. Week 24 has a visit window of -7 and +14 days.

Study Completion Evaluations
The week 24 evaluations will be the participant's final on-study visit. Participants must continue taking the study treatment until all week 24 evaluations are completed. If needed, study treatment will be extended until the week 24

evaluations are completed. It is encouraged that all week 24 evaluations occur on the same day. If evaluations cannot occur on the same day as the FDG-PET/CT imaging, evaluations must occur ±7 days of imaging. Site personnel should notify the A5415 CMC via email (actg.cmca5415@fstrf.org) if study treatment is anticipated to require extension past the week 24 visit window to complete the required evaluations.

Event-Driven Evaluations
Evaluations must be scheduled as per section 8.0.

Confirmation of Suspected Virologic Failure
Virologic failure is defined as two consecutive plasma HIV-1 RNA levels ≥200 copies/mL at any visit.

If the HIV-1 RNA level is ≥200 copies/mL at any visit, a repeat HIV-1 RNA will be performed (per section 6.1) within 2 weeks of receipt of the result. If the Confirmation of Suspected Virologic Failure visit coincides with a regularly scheduled visit, the evaluations should be combined. If the repeat HIV-1 RNA level is ≥200 copies/mL, the participant will be considered to have confirmed virologic failure and the A5415 CMC must be notified via email CMC (actg.cmca5415@fstrf.org) within 48 hours.

If a participant is confirmed to have virologic failure, the participant must return to the clinic to complete the premature treatment discontinuation evaluations as described in **section 6.2.4** and then taken off study treatment. If an evaluation is not completed at the premature treatment discontinuation visit, effort should be made to obtain the evaluation as soon as possible and within the evaluation window. The participant will be followed on study/off study treatment through completion of the study.

Confirmation of Grade ≥3 Toxicity
Toxicities are defined in section 8.0. Evaluation of Grade ≥3 laboratory toxicity must follow instructions outlined in sections 8.1 and 8.2. Only the evaluations required to assess the toxicity are required at this visit.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the Entry visit.

No follow-up evaluations are required for randomized participants who do not start the study treatment.

Premature Treatment Discontinuation Evaluations
The premature treatment discontinuation evaluations, as noted in section 6.1, will be performed in the following situations:

- Combined premature treatment and study discontinuation
- Premature treatment discontinuation **(see section 9.1)** but continuing with study follow-up (i.e., on study/off study treatment)**.**

Site personnel should notify the A5415 CMC via email CMC (actg.cmca5415@fstrf.org) within 48 hours of learning of any participant who prematurely discontinues study treatment.

Stored samples must be drawn as soon as possible, preferably within 7 days after the last study treatment dose. All other evaluations must be performed as soon as possible, preferably within 14 days after the last study treatment dose.

The FDG-PET/CT imaging is not required if the participant prematurely discontinues study treatment before week 12. If premature treatment discontinuation is at or after week 12 and before week 24, the FDG-PET/CT imaging must be performed as soon as possible, preferably within 7 days after the last study treatment dose. The participant should be instructed to return to clinic in a fasting state. Refer to the A5415 MOPS for the pre-imaging dietary instructions and section 6.3.5 for the fasting instructions. If premature treatment discontinuation is not due to pregnancy, refer to section 6.3.5 for the pregnancy test guidelines and section 6.3.9 for pregnancy testing prior to conducting the FDG-PET/CT imaging. A participant who is found to be pregnant at the premature treatment discontinuation visit will not have the FDG-PET/CT imaging performed.

A participant who prematurely discontinues study treatment because of pregnancy will NOT have the FDG-PET/CT imaging performed and is NOT required to fast prior to the discontinuation visit.

Participants should be encouraged to continue to attend all study visits and receive study evaluations as per section 6.1, with the exception of the FDG-PET/CT imaging at week 24 and the PK evaluation. They will be followed on study/off study treatment through completion of the study.

Participants who prematurely discontinue treatment and the study at the same time will have no further visits other than follow-up of ongoing adverse events and toxicities until resolution to Grade ≤2 (refer to section 8.0).

Evaluations for Premature Study Discontinuation during On Study/Off Study Treatment Follow-up

A participant who prematurely discontinues from the study (i.e., prior to completing the week 24 visit) during on study/off study treatment follow-up will have no additional evaluations performed other than follow-up of ongoing adverse events and toxicities (see section 8.0).

Site personnel should notify the A5415 CMC via email CMC (actg.cmca5415@fstrf.org) within 48 hours of any participant who prematurely discontinues from the study during on study/off study treatment follow-up.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the DAIDS AE Grading Table and adverse event (AE) reporting of AE requirements.

The protocol team and/or study monitoring entity (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Medical History

The medical history will be recorded per the SOE unless otherwise specified.

At screening, all signs and symptoms regardless of grade within the past 30 days must be documented, however only Grade ≥2 signs and symptoms must be recorded. At entry, all new signs and symptoms regardless of grade that occurred since the screening visit must be documented, however only Grade ≥2 signs and symptoms must be recorded.

At screening, all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days must be recorded. In addition, the following diagnoses must be recorded regardless of the date when they occurred:

- AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
- Bone fractures (verbal history accepted)
- Coronary heart disease or stroke

- Cancer (exclusive of basal/squamous cell skin cancer)
- Tuberculosis
- Chronic hepatitis C virus infection
- Chronic hepatitis B virus infection
- Lowest known CD4 cell count (participant report accepted)
- Clinical or subclinical atherosclerotic disease
- DM or prediabetes or impaired fasting glucose or insulin resistance
- Obesity
- Hypertension
- Dyslipidemia
- Smoking and vaping (tobacco), current and in past three years

At entry, all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade that occurred since the screening visit must be recorded.

Any allergies to any medications and their formulations must also be documented but are not recorded on the eCRF.

A family history of premature CAD (first degree relative with CAD prior to age 55 for male relative and 65 for female relative) must be recorded on the eCRF.

6.3.3 Medication History

A medication history must be present and recorded on the eCRF, including start and stop dates. Table 6.3.3-1 below lists the medications that must be included in the history.

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Within 12 months prior to entry
Statins and other lipid-lowering agents	Complete History
Immune-based therapy	Complete History
Immunizations	60 days prior to entry
Prescription drugs for treatment of opportunistic infections	Within 12 months prior to entry
Prescription drugs for prophylaxis of opportunistic infections	Within 12 months prior to entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Within 12 months prior to entry, except for hormone-releasing IUDs
Prescription drugs (other)	Current
Non-prescription drugs†	Within 90 days prior to entry

Medication Category	Complete History or Timeframe
Alternative therapies	Current
Dietary supplements	Current

* Includes hormone-releasing IUDs (e.g., Mirena) inserted in the last 5 years; oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors, or any other androgen, estrogen, or progesterone analogue or antagonist therapy.
† Includes over-the-counter (OTC) and complementary medicines.

6.3.4 Clinical Assessments

At screening and entry, refer to section 6.3.2 Medical History for reporting requirements. Post-entry, refer to section 7.2 for AE collection requirements and section 8.5 for collection requirements for pregnancy.

Complete Physical Exam
A complete physical examination will be performed per the SOE and is to include, at a minimum:

- Examination of the skin, head, mouth, and neck
- Auscultation of the chest
- Cardiac exam
- Abdominal exam
- Examination of the lower extremities for edema
- Signs and symptoms
- Diagnoses
- Vital signs (temperature, pulse, respiration rate, and blood pressure). Blood pressure should be measured following the **procedure in** the A5415 MOPS**.**

Targeted Physical Exam
A targeted physical examination includes vital signs (temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms and diagnoses. Blood pressure should be measured following the **procedure in** the A5415 MOPS**.**

For confirmation of Grade ≥3 toxicity, perform a targeted physical examination if the investigator feels it is clinically indicated.

Height, Weight, and Waist Circumference
Record height, weight, and waist circumference per the SOE.

Height and weight should be measured using the ACTG Metabolic Study Group Procedures for Standardized Measurement of Height and Weight. Waist

circumference should be measured **following the procedure in** the A5415 MOPS**.**

Concomitant Medications
Post-entry, any new and discontinued prescription and non-prescription medications including immunizations and ARVs taken/received since the last study visit must be recorded.

Study Treatment Modifications
Record all study drug modifications, including initial doses and treatment interruptions (inadvertent and deliberate) since the last visit. Record any permanent discontinuation of treatment.

6.3.5 Laboratory Evaluations

At screening, pre-entry, and entry, all protocol-required laboratory values must be recorded regardless of grade.

For post-entry assessments, record all of the following values regardless of grade:
- Hemoglobin
- White blood cell (WBC) count with differential
- Platelet count
- Creatinine
- Fasting glucose
- HbA1c
- Total cholesterol (fasting)
- HDL cholesterol (fasting)
- LDL cholesterol (fasting)
- Triglycerides (fasting)
- AST
- ALT
- Total bilirubin
- Direct bilirubin
- Prothrombin Time (PT)
- International Normalized Ratio (INR)
- Estimated GFR

NOTE: Refer to the A5415 MOPS for the link to the CKD-Epi equation and calculator.

Refer to section 7.2 for AE reporting requirements for post-entry abnormal laboratory findings.

Refer to the current A5415 Laboratory Processing Chart (LPC) for the collection and processing instructions.

Fasting Instructions
Fasting is defined as nothing to eat or drink except prescription medications and water for at least 8 hours, preferably 10 hours. If participants are in a non-fasting state, they should be instructed to return to the clinic within 3 days of the original scheduled visit for fasting evaluations (as indicated in section 6.1).

Fasting is NOT required for pregnant participants.

For the fasting requirements for the FDG-PET/CT imaging: See section 6.3.9.

Hematology
Hemoglobin, hematocrit, red blood cells (RBCs), WBCs with differential, absolute neutrophil count (ANC), and platelets

Blood Chemistries
Serum electrolytes (sodium, potassium, and chloride), BUN, creatinine, and amylase.

Fasting Glucose
Fasting blood sample for glucose will be collected per section 6.1. **All glucose collections** should be collected in a gray top tube (sodium fluoride). Refer to the current A5415 LPC for the collection and processing instructions.

Insulin
At screening, fasting blood sample for insulin will be collected and insulin testing will be performed in real time.

After screening, insulin testing will be performed on stored serum (see sections 3.0 and 6.3.8).

Fasting Lipid Panel
Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides

Liver Function Tests (LFTs)
AST (SGOT), ALT (SGPT), alkaline phosphatase (ALP), total bilirubin, and direct bilirubin

HbA1C
HbA1c will be done in real-time per section 6.1.

Prothrombin Time (PT) and International Normalized Ratio (INR)
PT will be performed to support calculation of the INR when needed to confirm elevated liver enzymes that occur on study (see section 8.2.1).

hsCRP
At screening, hsCRP will be performed in real-time.

After screening, hsCRP will be performed on stored plasma (see sections 3.0 and 6.3.8).

Estimated GFR
GFR will be estimated using the CKD-Epi equation per section 6.1. Refer to the A5415 MOPS for further information and a link to the CKD-Epi equation and calculator.

Pregnancy Testing
For people of childbearing potential: Serum or urine β-HCG at screening and entry. Urine test must have a sensitivity of <25 mIU/mL. The pregnancy test at entry must be performed within 15 days of the visit and the result must be available at the site at the time of entry.

At all other visits, perform as indicated in section 6.1 and if pregnancy is suspected.

In the event of a positive pregnancy test result, refer to section 8.5 for pregnancy and pregnancy outcome reporting requirements.

For pregnancy testing prior to conducting the FDG-PET/CT imaging: See section 6.3.9.

6.3.6 Immunologic Studies

NOTE: Because of the diurnal variation in biomarkers that may be measured as part of the study (e.g., $CD4^+$ and $CD8^+$ T cell counts and other biomarkers that may be measured on stored samples), blood draws for individual participants should be performed consistently in either the morning or the afternoon throughout the study, if possible.

$CD4^+/CD8^+$
At pre-entry, obtain absolute CD4+/CD8+ count and percentages from a laboratory that possesses a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

For entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent or equivalent (US sites) or IQA certification (non-US sites).

6.3.7 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 90 days prior to study entry at a laboratory that possesses a CLIA certification or equivalent (US sites) or VQA certification (non-US sites). Eligibility will be determined based on the screening value.

At the entry and post-entry visits, HIV-1 RNA testing must be performed at the protocol-designated laboratory. Refer to the A5415 LPC.

6.3.8 Stored Plasma/Serum and PBMC

For collection, processing and shipping instructions, refer to the A5415 LPC.

Stored Plasma
Plasma will be collected per section 6.1 and stored. The stored plasma will be used for the following batched assays: inflammatory markers, adiponectin, fibrinogen, and other coagulation markers.

If a participant experiences an acute inflammatory condition (including colds and sexually transmitted diseases [STDs]), receives a vaccine, or experiences a severe concurrent illness during the study, plasma must be collected with as much interval as possible between the illness or vaccination and blood draw while staying within the visit window. Sites should contact the A5415 CMC (actg.cmca5415@fstrf.org) with any questions regarding whether an interval between a specific situation and plasma collection is required.

Stored Serum (fasting)
Fasting blood sample will be collected for serum per section 6.1 and stored. Refer to the fasting instructions in section 6.3.5 if a participant arrives in clinic in the non-fasting state. The stored serum will be used for batched insulin assay.

Stored PBMC
PBMC will be collected per section 6.1 and stored. The stored samples will be used for batched advanced flow analysis.

Advanced Flow
Advanced flow analysis requires a $CD4^+/CD8^+$ and WBC with differential from a sample obtained at the same time (see section 6.1).

6.3.9 18F-Fluorodeoxyglucose (FDG)-positron Emission Tomography (PET) / Computed Tomography (CT)

FDG-PET/CT imaging will be performed per section 6.1 following the FDG-PET/CT procedure described in the image acquisition protocol. Sites should follow their

local IRB requirement for pregnancy testing prior to the imaging. Participants will be asked not to exercise for 24 hours before the scan and must fast for at least 8 hours, preferably 10 hours, before the procedure. If the procedure will be performed in the afternoon, participants are allowed to have a low-carbohydrate breakfast in the morning (after fasting overnight for at least 8 hours, preferably 10 hours) and then must fast for at least 4 hours before the procedure. Fasting blood glucose will be obtained prior to the imaging following the local imaging center procedure. The results of the pregnancy and fasting blood glucose tests are not reported on an eCRF. Refer to the A5415 MOPS for the pre-imaging dietary instructions for participants, and the image acquisition protocol for pre-imaging preparation and safety tests, imaging procedure, and submission guidelines.

The imaging at pre-entry must be performed only after confirming that the participant meets all screening eligibility requirements. If participants have received any immunizations prior to the pre-entry (baseline) FDG-PET/CT imaging, the imaging must be performed at least 7 days after the immunization(s). For participants receiving any immunizations during the study, the imaging must be performed at least 7 days after the immunization(s). The site must notify the A5415 CMC (actg.cmca5415@fstrf.org) if the imaging may have to be performed outside the visit window to achieve the required separation between an immunization and the imaging. If participants interrupted their ART for ≥5 days prior to the pre-entry FDG-PET/CT or their ART or study drug for ≥5 days prior to the week 24 FDG-PET/CT, sites must notify and consult the A5415 CMC (actg.cmca5415@fstrf.org) prior to performing the FDG-PET/CT.

The pre-entry FDG-PET/CT imaging is valid for 60 days prior to study entry. All imaging at pre-entry and on study must be evaluated by the local radiologist for incidental findings and the central reading laboratory for overall completeness and image quality. Any incidental findings in the pre-entry imaging must be reviewed by the site investigator to determine if it is safe for the participant to proceed with entry into the study. Refer to section 8.4 for additional guidance regarding the management of any clinically relevant incidental findings in the pre-entry and on study imaging. The site investigator should contact the CMC via email (actg.cmca5415@fstrf.org) if there are any concerns.

The imaging at pre-entry or week 24 may be repeated once and only once if the image is deemed not interpretable. The site must have permission from the A5415 CMC (actg.cmca5415@fstrf.org) before the repeat imaging is scheduled and performed.

Refer to section 6.2.4 for the instructions for performing FDG-PET/CT imaging at premature treatment discontinuation.

6.3.10 Pharmacokinetic Studies

At each visit indicated in section 6.1, a single PK sample will be drawn and stored.

Participants should be stable on ART for at least 10 days (i.e., no ART regimen change for 10 days) prior to PK draws. The ART dose prior to the PK evaluations should be given as close to 12 hours prior to the PK evaluation as is feasible. Blood should be drawn before the morning dose of CVC/CVC placebo (as applicable) and ART. In the case where a morning CVC/CVC placebo or ART dose is taken prior to the trough measurements or if any of the four preceding doses have been missed, the PK sampling should be rescheduled during the same week, if possible. If this is not possible, contact the A5415 CMC (actg.cmca5415@fstrf.org) for guidance. Dates and times of the last four doses of ART and CVC will be recorded.

For processing and shipping instructions, refer to the A5415 LPC. Refer to section 11.0 for assay details.

6.3.11 Adherence Assessment

Adherence to ART by self-report will be assessed at entry, all post entry visits, and at premature treatment discontinuation. Adherence to CVC by self-report and pill count will be assessed at all post entry visits and at premature treatment discontinuation. Sites will provide adherence reinforcement, according to standard practice, throughout the study. Participants with poor adherence will be provided counseling by the site.

The adherence eCRF is posted on the DMC Portal in the Forms Management Utility.

6.3.12 Food Diary

A 4-day food record (3 weekdays and 1 weekend day) will be collected per section 6.1. The food diary does not have to be collected on consecutive days and should represent the participant's usual diet. Refer to the A5415 MOPS for the instructions for completing the food diary. The date the food diary was collected will be recorded.

6.3.13 Perceived Stress Scale-10

The Perceived Stress Scale-10 will be completed by participants within 7 days of the FDG-PET with CT scan at pre-entry and at week 24. If the participant has not completed the scale prior to the FDG-PET with CT scan, the participant may complete it during the FDG-PET with CT scan visit.

The Perceived Stress Scale-10 is posted on the DMC Portal in the Forms Management Utility.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met.

- All new Grade ≥2 diagnoses and the following targeted events regardless of grade:
  - AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
  - Bone fractures (verbal history accepted)
  - Coronary heart disease
  - Cancer (exclusive of basal/squamous cell skin cancer)
  - Diabetes
  - Tuberculosis, active or latent
  - Hepatitis C virus infection
  - Hepatitis B virus infection
  - SARS-CoV-2 infection
  - Any infection
- All Grade ≥3 signs and symptoms, except fever and chills, which should be reported regardless of grade
- All Grade ≥2 laboratory findings
  - NOTE: Creatinine and eGFR should be graded using the categorical mL/min values from the DAIDS AE Grading Table. The percent change criteria from baseline will not apply to A5415.
- Any Grade ≥3 AE that occurs due to or during the FDG-PET/CT imaging
- All AEs that led to a change in study treatment regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be

found on the DAIDS RSC Web site: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions, and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

DAERS, an internet-based reporting system, must be used for expedited EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at **https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.**

For questions about DAERS, please contact NIAID Clinical Research Management System (CRMS) Support at CRMSsupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are: cenicriviroc (CVC) and placebo for cenicriviroc (CVC).

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC Web site at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the DAIDS EAE manual.
- After the protocol-defined EAE reporting period, unless otherwise noted, only suspected, *unexpected* serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol team will monitor the conduct and safety of the study via monthly summaries of accrual and reportable AEs. This summary will be pooled over the treatment arms. In addition, baseline characteristics, early study treatment and study discontinuations, and virologic failures, pooled over arms, will be reviewed regularly by the leadership team, at a minimum of once a month.

The DAIDS Clinical Representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs, as applicable.

The study will undergo interim review yearly by the CTSG Study Monitoring Committee (SMC). The first interim review will occur approximately 8 months after enrollment of the first participant. An interim review may also be convened if a concern is identified by the DAIDS Clinical Representative, the study chairs, or study statistician in consultation with the team. See section 10.5 for statistical considerations related to interim monitoring.

Detailed plans for study monitoring will be outlined in a Study Progress, Data, and Safety Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Management of abnormal liver enzymes and GFR are explained in section 8.2.

8.1.1 Grades 1 and 2 Toxicity

Participants who develop a Grade 1 or 2 laboratory abnormality or AE may continue the study treatment at the discretion of the site investigator and managed according to local guidelines.

8.1.2 Grade 3 Toxicity

If a participant develops a Grade 3 laboratory abnormality, a confirmatory measurement should be obtained within 5 days after the laboratory result becomes available.

A Grade 3 laboratory abnormality that is not confirmed upon repeat testing will be managed according to the toxicity management guidance for the new toxicity grade.

If the Grade 3 laboratory abnormality is confirmed or the participant has a Grade 3 clinical AE, the study treatment may be continued if the laboratory abnormality or clinical AE is considered to be unrelated to study drug after discussion with the A5415 CMC (actg.cmca5415@fstrf.org).

If a confirmed Grade 3 laboratory abnormality or an AE is considered to be related to study treatment, the study treatment should be interrupted. The AE should be monitored and/or the laboratory test repeated regularly as clinically indicated. The study treatment may be resumed once the toxicity returns to Grade ≤2.

If a laboratory abnormality or AE recurs to Grade ≥3 following rechallenge with study drug and is considered related to study treatment, the study treatment will be permanently discontinued and the participant managed according to local practice. The decision to continue a participant on study/off study treatment until completion of all other study visits for assessment of clinical outcomes must be agreed upon by the site investigator and the A5415 CMC. Refer to section 6.2.4 for the instructions for following participants on study/off study treatment.

Recurrence of a laboratory abnormality or AE considered unrelated to study treatment may not require permanent treatment discontinuation. Continuing the study drug after a recurrent Grade 3 laboratory abnormality or AE considered not related to study treatment should be discussed with the A5415 CMC (actg.cmca5415@fstrf.org) prior to continuing the study drug.

The study treatment may be continued without dose interruption for a clinically nonsignificant Grade 3 laboratory abnormality (e.g., glucose elevation in participants with pre-existing diabetes; glucose, cholesterol or triglyceride elevation that is non-fasting or that can be medically managed).

8.1.3 Grade 4 Toxicity

If a participant develops a Grade 4 laboratory abnormality, a confirmatory measurement should be obtained within 5 days after the laboratory result becomes available.

The study treatment may be continued without dose interruption for a clinically nonsignificant Grade 4 laboratory abnormality (e.g., glucose elevation in participants with pre-existing diabetes; glucose, cholesterol, or triglyceride elevation that is non-fasting or that can be medically managed).

A Grade 4 laboratory abnormality that is not confirmed upon repeat testing will be managed according to the toxicity management guidance for the new toxicity grade.

If the Grade 4 laboratory abnormality is confirmed or the participant has a Grade 4 clinical AE, the study treatment may be continued if the laboratory abnormality or clinical AE is considered to be unrelated to study treatment after discussion with the A5415 CMC (actg.cmca5415@fstrf.org).

If a confirmed Grade 4 laboratory abnormality or an AE is considered to be related to study treatment, the study treatment should be permanently discontinued and the participant managed according to local guidelines. The participant should be followed as clinically indicated until the AE or laboratory abnormality returns to Grade ≤2, if applicable, or is otherwise explained, whichever occurs first.

The decision to continue on study/off study treatment until completion of all other study visits for assessment of clinical outcomes must be agreed upon by the site investigator and the A5415 CMC. Refer to section 6.2.4 for the instructions for following participants on study/off study treatment.

8.2 Specific Management of Toxicities Related to Study-Provided Treatment

8.2.1 Elevated Liver Enzymes

Site personnel must report treatment-emergent (i.e., not present at screening or baseline) and confirmed ALT and/or AST elevations meeting any of the following criteria for suspected drug-induced liver injury (DILI), with special consideration given to baseline transaminase values:

- When the baseline ALT or AST values are <2 x ULN, and the ALT and/or AST increases to >3 × ULN and >5 x the baseline value (confirmed upon repeat testing).

- When the baseline ALT or AST values are <2 x ULN, and ALT and/or AST increases to >3 x ULN but ≤5 x the baseline value (confirmed upon repeat testing) AND the increase is accompanied by total bilirubin >2 x ULN (in participants with Gilbert's syndrome use direct bilirubin >2 x baseline) AND/OR if the participant also has symptoms consistent with clinical hepatitis (for example, fatigue, nausea/vomiting, right upper quadrant [RUQ] abdominal pain or tenderness, fever, rash, or eosinophilia) without an alternative explanation for the event as judged by the site investigator.
- When the baseline values are ≥2 x ULN but <5 x ULN, and the ALT and/or AST increases to >3 x the baseline value (confirmed upon repeat testing).
- When the baseline values are ≥2 x ULN but <5 x ULN, and the ALT and/or AST increases to >2 x the baseline but ≤3 x baseline value (confirmed upon repeat testing) AND the increase is accompanied by total bilirubin >2 x ULN (in participants with Gilbert's syndrome use direct bilirubin >2 x baseline) AND/OR if the participant also has symptoms consistent with clinical hepatitis (e.g., fatigue, nausea/vomiting, RUQ abdominal pain or tenderness, fever, rash, eosinophilia) without an alternative explanation for the event as judged by the site investigator.
- When baseline values are ≥5 × ULN and ALT and/or AST increases to >2 × the baseline value (confirmed upon repeat testing).
- When the ALT and/or AST increases to >3 x ULN and >2 x baseline (confirmed upon repeat testing) AND the increase is accompanied by either total bilirubin increase to >2 x the baseline value OR INR increase by >0.3 from baseline to a value >1.5.

The participant must return to the CRS for re-evaluation within 5 days after the treatment-emergent AST and/or ALT elevation for confirmatory testing that will include an ALT or AST, AND total bilirubin or INR. A comprehensive clinical evaluation, including evaluations for causes other than study treatment, and close clinical monitoring must be performed. The A5415 CMC should be informed via email (actg.cmca5415@fstrf.org) within 48 hours of receipt of the treatment-emergent AST and/or ALT elevation.

After the confirmation that the ALT or AST elevations and other laboratory tests meet the criteria for suspected DILI, the A5415 CMC should be informed via email (actg.cmca5415@fstrf.org) within 48 hours. Study treatment should be interrupted upon confirmation. After consultation with the CMC, a decision regarding temporary or permanent discontinuation will be made. The participant should continue to be followed for close monitoring, which will include repeat liver enzyme and serum bilirubin tests at least once a week, and INR as clinically indicated, until abnormalities stabilize and the participant is asymptomatic. Refer to the A5415 MOPS for additional guidance on evaluating participants with suspected DILI.

Site investigators may involve the CMC in the clinical management of LFT abnormality or clinical hepatitis without other explanation whenever there is concern that the event is study treatment-related, regardless of whether specific DILI criteria are met, to discuss study drug management.

8.2.2 GFR

GFR will be monitored as scheduled in section 6.1.

A participant experiencing an estimated GFR <50 mL/min/1.73 m^2 should have the value confirmed within 14 days.

A participant who has confirmed two consecutive reductions in estimated GFR to <60 mL/min/1.73 m^2 may continue to participate, however the site investigator should consider dose adjustment or discontinuation of TDF and inform the participant's primary physician.

8.3 Adverse Event Related to FDG-PET/CT Imaging

Any Grade ≥3 AE that occurs due to or during the FDG-PET/CT imaging must be reported to the A5415 CMC (actg.cmca5415@fstrf.org) within 48-72 hours after the occurrence of the AE and monitored for resolution.

8.4 FDG-PET/CT Imaging Findings

Any incidental findings in the imaging must be reviewed by the site investigator, and consult with the local radiologist designated by the site to read for incidental findings should be considered. Refer to section 6.3.9 for the details regarding the requirement for a local radiologist to review all imaging. The site investigator should inform the participant and the participant's primary physician of any clinically relevant incidental finding and discuss the need for further evaluations.

8.5 Pregnancy

Participants who become pregnant after study entry must discontinue study treatment immediately. These participants should be seen for premature treatment discontinuation evaluations as per section 6.2.4. These participants will also be followed on study, off study treatment through completion of the study with evaluations per section 6.1, except they will not be required to fast and will not have the FDG-PET/CT imaging performed and PK samples drawn. The only safety laboratory tests that will be performed are hematology (except ANC) and LFTs. The A5415 CMC (actg.cmca5415@fstrf.org) must be notified of any pregnancies that occur in participants on study. Management of the background ART is at the discretion of the site investigator.

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy

Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052. (For studies conducted at sites outside the United States, report to The Antiretroviral Pregnancy Registry—Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.)

Pregnancy Outcomes and Reporting
If an individual chooses to discontinue from the study before the end of the pregnancy, site staff should request permission to contact them regarding pregnancy outcomes at the end of pregnancy. Once the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy and EAE reporting, if appropriate.

8.6 Breastfeeding

Breastfeeding is exclusionary and not allowed during the study. If a participant begins breastfeeding during the study, they will be discontinued from study treatment. The participant will continue to be followed on study, off study treatment through the end of the study period with evaluations per section 6.1, except they will not be required to fast and will not have the FDG-PET/CT imaging performed and PK samples drawn.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see sections 8.1 and 8.2).
- Requirement for prohibited concomitant medications (see section 5.4).
- Confirmed virologic failure (see section 6.2.3).
- Pregnancy or breast-feeding.
- Request by participant to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the Toxicity section of the protocol.

9.2 Premature Study Discontinuation

- Participant repeatedly noncompliant (missing eight consecutive doses or more) with study medications as prescribed.
- Failure to start study treatment.
- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/Ethics Committee, ACTG, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5415 is a double-blind, randomized, placebo-controlled, phase II trial to evaluate 24 weeks of CVC on TBR in the carotid arteries and aorta 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 total sample size will be 93 participants (62 in the CVC arm and 31 in the placebo arm).

10.2 Outcome Measures

Primary and secondary outcomes listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the primary statistical analysis report. This report will form the basis for the primary study manuscript(s) and results reporting to https://ClinicalTrials.gov. Outcomes of interest for secondary and exploratory objectives intended for subsequent publications are listed as other outcome measures.

10.2.1 Primary Outcome Measures

Change in arterial most diseased segment (MDS) 18-FDG-PET target-to-background ratio (TBR), measured in the carotid arteries and aorta, from baseline to week 24.

The standardized uptake value (SUV) of FDG will be measured in the carotid arteries, aortic root, and the left main coronary artery. The SUV is the decay-corrected tissue concentration of FDG (in kBq/mL) divided by the injected dose per body weight (kBq/g). TBR will be calculated for each vascular segment as the segment SUV divided by mean venous blood SUV.

NOTE: The MDS has been preferred as the primary outcome measure at the time of the study design. However, since this choice of endpoint is guided by studies in populations with chronic atherosclerotic disease that typically excluded individuals with active inflammatory diseases or HIV, the study team intends to re-evaluate this choice of primary outcome measure closer to the time of the analysis (prior to review of the arterial inflammation data) based on contemporary data at that time.

10.2.2 Secondary Outcome Measures

10.2.2.1 Change in aortic TBR (and other TBRs) from baseline to week 24

10.2.2.2 Change in SUV measured in the carotid arteries and aorta from baseline to week 24

10.2.2.3 Change in fasting glucose from baseline to week 24

10.2.2.4 Change in HOMA-IR from baseline to week 24

10.2.2.5 Change in biomarkers from baseline to week 22/24

10.2.3 Other Outcome Measures

10.2.3.1 Change in FDG uptake in visceral fat and lymph nodes from baseline to week 24

10.2.3.2 Change in adipocytokines (such as adiponectin) from baseline to week 24

10.2.3.3 Change in plasma CCR5 and CCL2 levels from baseline to week 22/24

10.2.3.4 Changes in myeloid derived suppressor cell (MDSC) frequencies as well as monocyte subsets (as defined by expression of CD14 AND CD16, expression of homing receptors: CX3CR1, CCR5, CCR2, and activation as determined by HLA-DR density and CD69 expression) from baseline to week 22/24

10.2.3.5 Changes in CD4 and CD8 T cell expression of CX3CR1, CCR2, CCR5, and activation as determined by expression of CD38 and HLA-DR from baseline to week 22/24

10.2.3.6 Change in fasting insulin from baseline to week 24

10.2.3.7 Change in fibrinogen and other coagulation markers from baseline to week 24

10.2.3.8 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 from baseline to week 24

10.3 Randomization and Stratification

At study entry, participants will be randomized at a 2:1 ratio (CVC arm: placebo arm), using permuted blocks stratified by statin use. Institutional balance will not be used at randomization.

While enrollment is ongoing, enrollment limits will be increased to replace participants who are randomized but do not start treatment.

10.4 Sample Size and Accrual

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, we plan to enroll 93 participants (62 in the CVC arm and 31 in the placebo arm) in this trial.

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 [46].
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).

If the variability in the change in MDS TBR is lower than assumed (smaller SD) or the total data loss is lower than assumed, the statistical power to detect the targeted effect size for our primary analysis will be higher (see Table 10.4-1).

Table 10.4-1: Sample Sizes and Power Corresponding to Various Total Data Loss and Assumed SD

Total sample size	Total data loss	Evaluable sample size	Power	Assumed SD for change in MDS TBR (in $\log_{10}$)
93 (62 + 31)	20%	75 (50 + 25)	80%	0.065
108 (72 + 36)	20%	87 (58 + 29)	80%	0.071
93 (62 + 31)	20%	75 (50 + 25)	85%	0.061
93 (62 + 31)	17%	78 (52 + 26)	83%	0.065

For secondary outcome measures (excluding the secondary imaging measures), the sample size of N=93 will provide 90% power to detect a 0.052 SD difference. This

assumes a 15% total data loss (lower since there will be no loss due to image scheduling or quality related issues).

We expect to have slow accrual completed over a period of 2 years. Full details of the accrual plan will be outlined in the Study Progress, Data, and Safety Monitoring Plan (SPDSMP). Participants who do not start study treatment will be replaced unless enrollment has been completed.

10.5 Data and Safety Monitoring

The ACTG CTSG SMC will review study conduct and adverse events over time, broken by treatment arms. Efficacy review or treatment arm comparisons will not be included in the SMC interim reviews. There is no other formal stopping guideline for this study. See section 7.4 for study monitoring timelines and other details.

10.6 Analyses

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 all analyses unless stated otherwise.

Since the goal of the study is to determine the biological activity of CVC on vascular inflammation, the primary analytic approach will be per protocol and limited to participants who remain on study treatment without change in background ART drug class per the study design.

Baseline is defined as pre-entry for TBR and SUV, average of entry and pre-entry for immunology markers, and entry for all other outcome measures.

10.6.1 Analysis Sets

Per-protocol population is defined as all participants who receive study treatment over 22 weeks and remain on the same ART drug class during the entire study period.

Safety analysis population is defined as all participants who initiated study treatment.

10.6.2 Primary Analyses

The primary analysis of efficacy will be limited to the per-protocol population.

TBR will be transformed for analyses on the $\log_{10}$ scale and back transformed to percentage change for interpretation and presentation. Change in TBR will be summarized by mean and 95% confidence interval for percentage for each treatment arm and compared between the arms using a T-test, stratified by statin

use. A 95% confidence interval for the relative between-arm shift will also be estimated.

10.6.3 Secondary Analyses

A sensitivity analysis for the primary analysis will include participants in the per-protocol analysis described in the primary analysis above as well as participants with data available for evaluation completed at premature treatment or study discontinuation that is after week 12 as long as they are on treatment within 7 days of the evaluation.

Supplementary analyses for the primary analysis will exclude participants with confirmed HIV-1 RNA >200 copies/mL at any time during the course of the study and extensive periods of ART interruption (see SAP for more detail).

Key secondary endpoints (section 10.2.2) will be analyzed in the same manner (also per-protocol) as in the primary analysis.

For immunology markers, two blood draws will be performed at baseline (pre-entry and entry) and week 22/24 (week 22 and week 24) and the measurements will be the average of two values in order to reduce intra-participant variability. Outcome measurements may be transformed for analyses on the $\log_{10}$ scale, as appropriate.

Safety will be evaluated by summarizing the nature and rate of AEs (signs and symptoms, laboratory values, SAEs) for the safety analysis population.

10.6.4 Handling of Missing Data and Sensitivity Analyses

Multiple imputation will be used to account for missing data due to unreadable or missed scans.

A sensitivity analysis for the primary analysis will include a complete case analysis.

10.7 Unblinding

Planned Unblinding
Participants will be unblinded at completion of the study. Please refer to ACTG SOP-123 Unblinding Participants for details.

Sudden/Unplanned Unblinding

- The decision to unblind one or more arms of an ongoing study is made by the team in conjunction with the relevant Scientific Committee and the Executive Committee. This can occur based on a recommendation from the SMC or the results of another trial (also see the DAIDS SOP “Termination of a Trial or a Single Treatment Arm”).

- If the decision is made to unblind, participants should be unblinded as soon as possible. Unblinding is conducted through the DMC, which sends treatment assignments to the sites soon after the unblinding decision. Every effort should be made by the sites to contact participants who have completed follow-up in order to explain the study results.
- When a treatment comparison is unblinded based on an interim analysis, the results of that interim analysis must be reported in publications. Data from visits that occurred before the interim review but that were not in the database at the data cutoff date have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In unblinding due to both “interim analysis” and the “other trial results” situations, if analyses are reported on clinical data or samples taken after the unblinding date, the conditions under which these data were gathered must be made clear in any publication.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

11.1.1 To determine the impact of INSTI and NNRTI-based ART on CVC trough estimates.

11.1.2 To determine the impact of CVC treatment on the trough exposure of ART.

11.1.3 To determine the association between CVC trough exposure and the primary treatment outcome (i.e., reduced arterial inflammation).

11.2 Pharmacology Study Design

Participants will be enrolled who are stabilized on an NNRTI-based or unboosted INSTI-based ART regimen for ≥48 weeks prior to study entry. PK data available to date is specified in section 2.1 (“Supporting Pharmacokinetic Data from Allergan/AbbVie”). Appropriate dosage adjustments will be made for participants on EFV-based ART based on these prior data. Data for those on INSTI-based ART is limited to DTG where modest reduction in CVC exposure (28% and 29% reduction in CVC Cmax and AUC 0-24 hr, respectively) was detected. Therefore, to provide information for CVC PK in individuals living with HIV on these regimens and to provide ART PK in the context of CVC specifically in individuals living with HIV, a sparse PK design will be completed. Since CVC should be taken with meals, information about whether or not dosing is done with food will be collected.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

11.3.1 Outcome Measures

Blood for PK sampling will be collected at select study visits, and before the morning dose of CVC/placebo, as per protocol for CVC and ART. Trough ART levels will be determined for all participants at pre-entry and weeks 4, 8, 12, and 24. For those randomized to active drug, trough levels for CVC will be determined at weeks 4, 8, 12, and 24.

Only drug concentration levels determined from samples obtained at steady state (no missed doses within the preceding 4 days) and no more than 14 hours post last EFV-based ART or 26 hours post last non-EFV based ART and CVC/placebo for CVC dose will be used in analyses.

11.3.2 Data Analysis

Pharmacokinetics

CVC Exposure: An average steady-state CVC trough concentration will be estimated by ART regimen (INSTI- or NNRTI-based ART) and compared between ART regimens and with historical data for CVC.

ART exposure: An average steady-state ART trough concentration will be estimated pre- and post-CVC/placebo for CVC dosing. Average steady state ART trough concentrations during CVC/placebo for CVC co-administration will be compared a) between those on CVC and those on placebo for CVC (inter-participant comparison) and b) with pre-CVC levels (intra-participant comparison).

Analyses will use time-adjusted linear mixed effect models with measured concentration log-transformed.

Pharmacodynamics

Correlation of CVC exposure to outcomes: A composite time-adjusted CVC exposure estimate over the 24-week study period will be obtained for each participant from the mixed effect modelling based on their measured concentrations at weeks 4, 8, 12, and 24. Associations of these empirical Bayes estimates and the following arterial inflammation outcomes measured will be estimated via Spearman's rank-based correlation.

- Change in most diseased vessel TBR from baseline to week 24
- Change in aortic TBR from baseline to week 24
- Change in carotid artery TBR from baseline to week 24
- Week 24 aortic TBR
- Week 24 carotid artery TBR

11.4 Anticipated Outcomes

Average trough estimates for CVC and each ART will be calculated for comparisons outlined above. Trough estimates for CVC at weeks 4, 8, 12, and 24 will be time adjusted to provide a composite exposure estimate as described above.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to ensure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [47]. The site **must** make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. **The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage Sites to use the the DMC provided Medidata RSR platform but other potential** platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, **and** direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12.4 Reporting Protocol Deviations

The site principal investigator and staff are responsible for identifying and reporting deviations. If protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be reported to the IRB/EC per their guidelines.

Refer to the MOPS for the definition of protocol deviation and instructions for completing the study protocol deviation eCRF.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the Informed Consent document and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal guardian or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory authorities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other country-specific government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: RESULTS OF CENICRIVIROC MESYLATE (CVC) STUDIES

Appendix I Table 1

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-1-104 Phase 1	A phase 1 multiple-dose, cross-over study to assess the potential interaction between TBR-652 and RTV in healthy volunteers	20 healthy adults	50 mg CVC po × 10 days, then 50 mg CVC + 100 mg RTV po × 10 days (CVC administered as 2×25 mg tablets after a standardized meal) [Standardized meal contained approximately 500-700 kcal and <15-20 g fat]	DP3_25 formulation, manufactured by Emerson Resources	1. Plasma PK of CVC with/without RTV 2. Safety, tolerability
Noteworthy Findings: RTV significantly increased exposure to CVC (based on ratios of LS geometric means: 2.39-fold increase in Cmax and a 3.55-fold increase in AUC0-24) and reduced exposure to CVC metabolites. There were no clinically important safety findings.					
Allergan Study 652-1-105 Phase 1	A phase 1, open-label, single-dose, randomized, cross-over study to assess the potential interaction between TDF and TBR-652 in healthy volunteers	21 healthy adults	150 mg CVC po, 300 mg TDF, 150 mg CVC po + 300 mg TDF (CVC administered as 6×25 mg tablets after a standardized breakfast) [Standardized breakfast contained approximately 500-700 kcal and <15-20 g fat] 14-day washout between regimens	DP3_25 formulation, manufactured by Emerson Resources	1. Plasma PK of CVC with/without TDF 2. Plasma PK of TDF with/without CVC 3. Safety, tolerability
Noteworthy Findings: TDF had no effect on CVC exposure. Co-administration of CVC and TDF did not affect the AUC0-t and AUC0-∞ of TDF, based on the protocol-defined equivalence range of 0.70-1.43. However, co-administration with CVC increased the AUC and Cmax of TDF by approximately 28%-36%, with the 90% CI for the Cmax of TDF falling outside the 0.80-1.25 “no effect” range. There were no clinically important safety findings.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-1-107 Phase 1	A Phase 1, multiple-dose, open-label, crossover study in healthy participants to assess the effect of DRV/r on the PK of CVC	20 healthy adults	Period 1: CVC 50 mg QD po × 10 days after a standardized breakfast Period 2: CVC 50 mg QD po + DRV/r 800/100 mg QD po × 10 days after a standardized breakfast	DP6_50 formulation, manufactured by Bend Research	1. Plasma PK of CVC 2. Safety and tolerability
Noteworthy Findings: Co-administration of DRV/r 800/100 mg with CVC 50 mg daily for 10 days resulted in an approximately 2.17-fold increase in plasma CVC Cmax, a 4.17-fold increase in Cmin, and a 3.13-fold increase in AUC0–24.					
Allergan Study 652-1-108 Phase 1	A Phase 1, multiple-dose, open-label, crossover study in healthy participants to assess the effect of ATV/r on the PK of CVC	20 healthy adults	Period 1: CVC 50 mg QD po × 10 days after a standardized breakfast Period 2: CVC 50 mg QD po + ATV/r 300/100 mg QD po × 10 days after a standardized breakfast	DP6_50 formulation, manufactured by Bend Research	1. Plasma PK of CVC 2. Safety and tolerability
Noteworthy Findings: Co-administration of ATV/r 300/100 mg with CVC 50 mg daily for 10 days resulted in an approximately 2.55-fold increase in plasma CVC Cmax, a 5.75-fold increase in Cmin, and a 3.89-fold increase in AUC0-24.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-1-109 Phase 1	A Phase 1, multiple-dose, open-label, crossover study in healthy participants to assess the effect of EFV on the PK of CVC and to assess the effect of CVC on the PK of EFV	40 healthy adults (20 in Group 1 and 20 in Group 2)	Group 1 (effect of EFV on CVC): Period 1: CVC 200 mg QD po after dinner* × 10 days Period 2: CVC 200 mg QD po after dinner* + EFV 600 mg QD po at bedtime × 10 days Period 3: CVC 400 mg QD po after dinner* + EFV 600 mg QD po at bedtime × 10 days (14-day washout between Periods 2 and 3) Group 2 (effect of CVC on EFV): Period 1: EFV 600 mg QD po at bedtime × 10 days Period 2: EFV 600 mg QD po at bedtime + CVC 400 mg QD po after dinner* × 10 days [*Standardized dinner contained 725 kcal, 26 g fat, 89 g carbohydrates, 26 g protein]	DP6_50 formulation, manufactured by Bend Research	1. Plasma PK of CVC (Group 1) 2. Plasma PK of EFV (Group 2) 3. Safety and tolerability
Noteworthy Findings: In Group 1, co-administration of EFV 600 mg with CVC 200 mg daily for 10 days during Period 2 resulted in a significant decrease in CVC exposure compared to CVC alone, with Cmax, Cmin, and AUC0–24 being 23%, 48%, and 43% lower, respectively, for EFV + CVC co-administration compared to CVC alone. Dose adjustment of CVC to 400 mg daily in Period 3 offset the drug interacting effect of EFV 600 mg co-administration with CVC; for Cmax, Cmin, and AUC0–24, the ratios of the LS geometric means (90% CI) were 1.23 (1.12, 1.35), 0.85 (0.71, 1.01), and 0.98 (0.85, 1.12), respectively (i.e., with the 90% CIs including 1.00 for Cmin, and AUC0–24 and within the 0.80–1.25 “no-effect” range for AUC0–τ and within the 0.70–1.43 “equivalence” range for Cmax and Cmin). In Group 2, plasma EFV exposure remained essentially unchanged in the presence of CVC 400 mg daily.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-1-110 Phase 1	A Phase 1, multiple-dose, open-label, crossover study in healthy participants to assess the effect of DTG on the PK of CVC and the effect of CVC on the PK of DTG and on a single dose of midazolam	40 healthy participants (20 in Group 1 and 20 in Group 2)	Group 1: Period 1: Single dose of midazolam 5 mg po on Day –1 and Day 9 + CVC 150 mg QD po after a standardized breakfast × 10 days (Days 1 to 10) Period 2: CVC 150 mg QD po + DTG 50 mg po QD after a standardized breakfast × 10 days Group 2: Period 1: DTG 50 mg QD po after a standardized breakfast × 10 days Period 2: DTG 50 mg QD po + CVC 150 mg QD po after a standardized breakfast × 10 days	DP7_150 formulation, manufactured by QS Pharma	1. Plasma PK of CVC (Group 1) 2. Plasma PK of DTG administered with and without CVC 3. PK of midazolam and α-hydroxy midazolam 4. Safety and tolerability
Noteworthy Findings: In Group 1, co-administration of DTG 50 mg with CVC 150 mg once daily for 10 days during Period 2 resulted in a significant reduction in plasma CVC exposure (by 28% for Cmax, 23% for Cmin, and 29% for AUC0–24). In Group 2, co-administration of CVC 150 mg with DTG 50 mg once daily for 10 days during Period 2 had no effect on plasma DTG exposure. CVC increased plasma midazolam Cmax and AUC0-∞ by approximately 49% and 84%, respectively, indicating it is a mild inhibitor of CYP3A4. CVC did not result in a meaningful change in plasma α-hydroxymidazolam exposures: there was a 7% decrease in Cmax and an 18% increase in AUC0-∞.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-1-111 Phase 1	A Phase 1, open-label, single-dose, crossover study in healthy participants to assess the bioavailability of a new oral tablet formulation of CVC when administered fasting and after food relative to the current formulation	42 healthy adult participants (14 participants per group)	Group 1: 50 mg CVC: DP6 fed, DP7 fed, DP7 fasting Group 2: 150 mg CVC DP6 fed, DP7 fed, DP7 fasting Group 3: 200 mg CVC DP6 fed, DP7 bedtime Single oral dose of the current CVC formulation (DP6) or the new formulation (DP7) in each of 2 or 3 periods after a standardized breakfast (“fed”), fasting, or ≥3 h post dinner (“bedtime”), separated by a washout period of ≥10 days.	DP6_50 formulation, manufactured by Bend Research DP7 formulation (DP7_25, 150), manufactured by QS Pharma	1. Relative bioavailability of plasma CVC (current and new formulations) 2. Safety and tolerability 3. Effect of intragastric pH on PK of CVC
Noteworthy Findings: For comparison of the 50 mg CVC dose administered under fed conditions in the morning, the ratios of LS geometric means for plasma CVC Cmax, AUC0-t, and AUC0-∞ for the DP7 formulation (Treatment B) relative to the DP6 formulation (Treatment A) were 0.83, 0.72, and 0.79, respectively, with 90% CIs including 1.0. For comparison of the 150 mg CVC dose administered under fed conditions in the morning, the ratios of LS geometric means for plasma CVC Cmax, AUC0-t, and AUC0-∞ for the DP7 formulation (Treatment E) relative to the DP6 formulation (Treatment D) were 1.22, 0.98, and 1.05, respectively, with 90% CIs including 1.0. The DP7 formulation was significantly better absorbed in the fed than fasting state, particularly at the 150 mg dose. The DP7 formulation administered as a single oral dose of 200 mg at bedtime (Treatment H: DP7 200 mg HS) had an approximately 2-fold higher exposure compared to the DP6 formulation administered as a single oral dose of 200 mg in the morning following a standard breakfast (Treatment G: DP6 200 mg Fed AM); the ratios of LS geometric means for plasma CVC Cmax, AUC0-t, and AUC0-∞ for the DP7 formulation administered at bedtime (Treatment H) compared to the DP6 formulation after a standardized breakfast (Treatment G) were 1.49, 2.08 and 2.06, respectively.			

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-1-112 Phase 1	A Phase 1, multiple-dose, open-label, crossover study in healthy participants to assess the effect of CVC on the PK of ATV and RTV	20 healthy adults	Period 1: ATV/r 300/100 mg QD po after a standardized breakfast × 10 days (Days 1-10) Period 2: ATV/r 300/100 mg QD po + CVC 50 mg QD po after a standardized breakfast × 10 days (Days 11-20) Period 1 was immediately followed by Period 2 without washout.	DP6_50 formulation, manufactured by Bend Research	1. PK of ATV and RTV with/without CVC 2. Safety and tolerability of CVC with ATV and RTV
Noteworthy Findings: CVC had no effect on RTV Cmax or AUC0–24, although significantly increased exposure to ATV (1.2-fold increase in Cmax, 1.6-fold increase in Cmin, and a 1.3-fold increase in AUC0–24) and RTV Cmin (1.5-fold increase in RTV Cmin).					
Allergan Study 652-1-113 Phase 1	A Phase 1, multiple-dose, open-label, crossover study in healthy participants to assess the effect of CVC on the PK of DRV and RTV	20 healthy adults	Period 1: DRV/r 800/100 mg QD po after a standardized breakfast × 10 days Period 2: DRV/r 800/100 mg QD po + CVC 50 mg QD po after a standardized breakfast × 10 days Period 1 was immediately followed by Period 2 without washout.	DP6_50 formulation, manufactured by Bend Research	1. PK of DRV and RTV with/without CVC 2. Safety and tolerability of CVC with DRV and RTV
Noteworthy Findings: Co-administration of CVC 50 mg with DRV/r 800/100 mg daily for 10 days during Period 2 resulted in no meaningful effects of CVC on plasma DRV or RTV exposure. The ratios of LS geometric means for DRV Cmax, Cmin, and AUC0–24 for CVC+DRV/r co-administration compared to DRV alone were 1.02, 0.94, and 0.98, respectively, with 90% CIs including 1.0 and being well within the 0.80–1.25 “no effect” range for all 3 plasma DRV PK parameters.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-2-201 Phase 2a	A double-blind, randomized, placebo-controlled, proof of concept, multiple dose-escalating study to evaluate the antiviral activity, safety, and PK of the CCR5 antagonist CVC in HIV-1-infected, antiretroviral treatment-experienced, CCR5 antagonist-naïve participants	54 adults with R5-tropic HIV-1 8/dose level on CVC 2/dose level on placebo	25 mg (1×25 mg DP3 tablet) 50 mg (2×25 mg DP3 tablets) 75 mg (3×25 mg DP3 tablets) 100 mg (1×100 mg DP4 tablet) 150 mg (6×25 mg DP3 tablets) All administered orally once daily and all provided with a meal. Participants knew to which dose group they were assigned, but were blind to treatment assignment (CVC or placebo)	DP3_25 formulation, manufactured by Emerson Resources DP4_100 formulation, manufactured by Emerson Resources	1. Antiviral activity 2. Safety, tolerability 3. Plasma PK 4. PD 5. Biomarkers of inflammation
Noteworthy Findings: CVC significantly reduced HIV-1 RNA. The median nadir changes from Baseline for the 25, 50, 75, and 150 mg dose groups were −0.7, −1.6, −1.8, and −1.7 log10 copies/mL, respectively (note that the efficacy and PK results with CVC 100 mg [administered as an alternative formulation] are not shown). CVC significantly increased MCP-1 by up to 340 pg/mL at the 150 mg dose level. Treatment was well tolerated with no dose-limiting AEs.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-2-202 Phase 2b	A Phase 2b randomized, double-blind, double-dummy trial of 100 or 200 mg once-daily doses of CVC or once-daily EFV, each with open-label FTC/TDF, in HIV-1-infected, antiretroviral treatment-naïve, adult participants with only CCR5-tropic virus	143 adults living with HIV, treatment-naïve participants with CCR5-tropic virus Participants were randomized in a 2:2:1 ratio to: CVC 100 mg, CVC 200 mg, or EFV 600 mg (all administered orally QD, but not at the same time, in combination with FTC/TDF).	CVC 100 mg (Phase 2b formulation; administered as 2×50 mg tablets + 2× CVC matching placebo tablets) and EFV placebo CVC 200 mg (Phase 2b formulation; administered as 4×50 mg tablets) and EFV placebo EFV 600 mg and 4 × CVC matching placebo tablets CVC/placebo administered following a low-fat breakfast; EFV/placebo on an empty stomach at bedtime	DP6_50 formulation, manufactured by Bend Research	1. Efficacy 2. Safety, tolerability 3. Plasma PK 4. PD 5. Biomarkers of inflammation and immune function 6. Metabolic parameters

Noteworthy Findings:

CVC when administered as either 100 mg + FTC/TDF or 200 mg + FTC/TDF was effective and well tolerated over 48 weeks in participants living with HIV, antiretroviral treatment-naïve adult participants with only CCR5-tropic virus. A greater proportion of CVC- than EFV-treated participants completed the study, 42 (71%), 41 (73%), and 17 (61%) for the CVC 100 mg, CVC 200 mg, and EFV treatment arm, respectively. The percentage of participants with virologic success, defined as HIV-1 RNA <50 copies/mL (using the FDA Snapshot analysis and the ITT population), was comparable among the 3 treatment arms at Week 24 (the primary efficacy endpoint: 76% with CVC 100 mg, 73% with CVC 200 mg, and 71% with EFV) and higher in the CVC arms than in the EFV arm at Week 48 (68% with CVC 100 mg, 64% with CVC 200 mg, and 50% with EFV).

A dose-response was observed with CVC in increases over time of MCP-1, the ligand of CCR2, which is a chemokine receptor found on monocytes, suggesting potent CCR2 blockade. Additionally, a decrease over the first 48 weeks was observed for sCD14, an established biomarker of monocyte activation, in both CVC treatment arms, while an increase was observed for sCD14 in the EFV arm during the same observation period.

CVC showed a favorable safety profile with fewer treatment-related AEs, fewer AEs of at least Grade 3 in severity, and fewer AEs leading to discontinuations compared to EFV. Both doses of CVC (100 mg and 200 mg) were well tolerated and no apparent dose-relationship based on safety data or dose-limiting toxicities were observed.

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Allergan Study 652-2-203 Phase 2b	CENTAUR: Efficacy and Safety Study of Cenicriviroc for the Treatment of Nonalcoholic Steatohepatitis (NASH) in Adult Participants with Liver Fibrosis	289 adults with NASH with liver fibrosis (biopsy-diagnosed NASH with NAS ≥4 and liver fibrosis (Stage 1 to 3 [NASH CRN system]), who are at increased risk of disease progression. Randomization 1:1 stratified by NAS at Screening (4 or ≥5) and fibrosis stage (≤2 or >2).	150 mg tablets and matching placebo tablets	DP7_150 formulation Manufactured by QS Pharma	The primary efficacy endpoint: Hepatic histological improvement as measured by the NAFLD Activity Score (NAS) at Year 1 relative to the Screening biopsy.

Noteworthy Findings:

Year 1: Twenty-three (15.9%) participants in the CVC group met the primary efficacy endpoint compared to 27 (18.8%) participants in the placebo group. The difference between the treatment groups was not statistically significant in the ITT population (p=0.5194).

In the ITT population, 11 participants (7.6%) in the CVC group compared with 8 participants (5.6%) in the placebo group had complete resolution of steatohepatitis and no concurrent worsening of fibrosis stage at Year 1 relative to the Screening biopsy (p=0.4941). These results did not change after prespecified sensitivity analyses. Importantly, in the Year 1 analysis, 29 participants (20.0%) in the CVC group compared with 15 participants (10.4%) in the placebo group had improvement in fibrosis by at least 1 stage and no worsening of steatohepatitis at Year 1 relative to the Screening biopsy in the ITT population set (p=0.0234). A higher proportion of participants in the CVC group (29%) compared with the combined placebo group (19%) had an improvement of at least 1 stage at Year 1 per the NASH CRN staging system. Furthermore, at Year 1, the proportion of participants achieving the more stringent endpoint of ≥2-stage improvement in fibrosis AND no worsening of steatohepatitis for CVC or placebo = 8.2% (8/98) and 3.1% (3/96), respectively, in the ITT population excluding participants with baseline NASH CRN fibrosis Stage 1.

Year 2: At the end of the first year of treatment, a total of 242 participants remained in the study and entered Year 2 according to their treatment assignment at randomization (121, 61, and 60 participants in the CVC/CVC, placebo/CVC, and placebo/placebo groups, respectively). Given the lack of apparent effect of CVC treatment on the NAS or resolution of steatohepatitis at Year 1, the results presented below describe findings from prespecified analyses focused on the endpoint of improvement in fibrosis stage (by ≥1 stage or by ≥2 stages) AND no worsening of steatohepatitis in the ITT population.

Overall, the results from the final Year 2 analysis confirmed the clinically meaningful antifibrotic effect of CVC treatment observed in the Year 1 primary analysis. Twice as many CVC-treated participants achieving ≥1-stage improvement in fibrosis at Year 1 (CVC/CVC group) maintained this benefit at Year 2 compared to placebo (60% vs 30%, respectively). A higher proportion of Year 1 placebo nonresponder participants who received CVC (placebo/CVC group) experienced an improvement in fibrosis by ≥1 stage AND no worsening of steatohepatitis compared with participants who remained on placebo (placebo/placebo group) from Year 1 to Year 2 (24.4% vs 17.1%, respectively). In this analysis, improvement in fibrosis by ≥1 stage regardless of effect on steatohepatitis was reported in 39.0% of placebo/CVC participants versus 28.6% of placebo/placebo participants.

A similar and consistent antifibrotic response was observed in the pooled analysis of participants treated with CVC for 1 year (participants in the CVC/CVC group who received CVC during Year 1 and the placebo/CVC group who received CVC during Year 2) compared with participants treated with placebo for 1 year (placebo/placebo

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
group; data from Year 1): improvement in fibrosis by ≥1 stage AND no worsening of steatohepatitis (19.9% vs 11.1%); improvement in fibrosis by ≥1 stage regardless of effect on steatohepatitis (27.7% vs 16.7%). Furthermore, consistent with observation at Year 1, a higher proportion of participants receiving CVC relative to participants receiving placebo (9.3% [7/75] in the CVC/CVC group versus 2.7% [1/37] in the placebo/placebo group) achieved ≥2-stage improvement in fibrosis AND no worsening of steatohepatitis at Year 2.					
Tobira Study 652-2-204- Phase 2a	ORION: Effect of CCR2 and CCR5 Antagonism by Cenicriviroc on Peripheral and Adipose Tissue Insulin Sensitivity in Adult Obese Participants with Prediabetes or Type 2 Diabetes Mellitus and Suspected Non-Alcoholic Fatty Liver Disease (NAFLD)	45 adult obese participants (BMI ≥ 30 kg/m^2) with prediabetes or T2DM and suspected NAFLD; randomized 1:1 to active drug or placebo (50 participants planned, 45 enrolled)	150 mg tablets and matching placebo tablets once daily for 24 weeks	DP7_150 formulation Manufactured by QS Pharma	1. Efficacy 2. Safety, tolerability 3. Plasma PK 4. PD 5. Biomarkers of inflammation and immune function Metabolic parameters
Noteworthy Findings: There was no observed therapeutic effect of CVC on peripheral and adipose tissue insulin sensitivity as compared to placebo. CVC was well tolerated and resulted in a lower incidence of AEs compared with placebo. No new safety signals were observed.					
Tobira Study 652-205 Phase 2	PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Participants with Primary Sclerosing Cholangitis (PSC)	24 adult participants with PSC	150 mg tablets once daily for 24 weeks	DP7_150 formulation Manufactured by QS Pharma	1. Efficacy 3. Safety, tolerability
Noteworthy findings: In adults with PSC, treatment with CVC 150 mg QD for 24 weeks resulted in a modest (median of 18%) decrease in the surrogate endpoint of ALP. No new safety signals were observed					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
3152-201-002 Rollover Phase 2	Open-label Rollover Study of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis (NASH	167 Adult participants with NASH enrolled in the study who completed both Treatment Period 1 and Treatment Period 2 in the CENTAUR study, or who completed the AURORA study because of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study; all 167 received CVC	Cenicriviroc mesylate 150 mg immediate release oral tablet daily for duration of trial	The CVC drug product was formulated with fumaric acid (160 mg) and other excipients, including microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and Opadry® II yellow (film coating). The CVC drug product was provided as 150-mg yellow-coated, immediate release tablets for oral administration.	Safety; incidence of adverse events
Noteworthy findings: CVC 150 mg once daily was well tolerated in this study. No clinically significant safety findings were identified. The study was terminated early for administrative reasons					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
3152-301-002 Phase 3	AURORA: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis	Part 1: A total of 1288 participants with NASH were analyzed in Part 1 (859 participants in Arm A; and 429 participants in Arm B) [1293 participants were randomized (861 to the CVC group and 432 to the placebo group)] Part 2: A total of 1769 participants with NASH were analyzed in the full study cohort (1180 participants in Arm A, and 589 participants in Arm B) [A total of 1778 participants were enrolled in the full study cohort. Of these, 1185 participants were randomized to the CVC group and 593 participants were randomized to the placebo group.]	Cenicriviroc mesylate 150 mg immediate release oral tablet (Arm A) or placebo (Arm B) once daily (2:1)	Cenicriviroc mesylate 150 mg immediate release oral tablet (Arm A) or placebo (Arm B) once daily (2:1)	Part 1: Proportion of participants with improvement in fibrosis by at least 1 stage (NASH CRN system) AND no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade) Safety and tolerability Part 2: Composite endpoint of histopathologic progression to cirrhosis (defined by NASH CRN Fibrosis Stage 4), liver-related clinical outcomes, and all-cause mortality, as measured by the time to first occurrence of any of the listed adjudicated events (clinical outcomes composite endpoint) Safety and tolerability

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
Noteworthy findings: The primary endpoint was not met for Part 1, leading to early termination of the study. No meaningful numerical or statistical difference was observed between CVC 150 mg once daily and placebo with respect to the key efficacy endpoints regarding liver histology at Month 12 relative to the screening biopsy in adult participants with a liver biopsy diagnosis of NASH and Stage 2 or 3 liver fibrosis (by NASH CRN system). CVC 150 mg once daily was, in general, well tolerated in this study, and there were no treatment-related AEs that were fatal or life-threatening.					
CLJC242A2201J Phase 2	TANDEM: A randomized, double-blind multicenter study to assess the safety, tolerability, and efficacy of CVC with tropifexor in adults with NASH and LF	40 healthy participants (20 in Group 1 and 20 in Group 2)	193 adults with NSH and LF	150mg tablets immediate release	Occurrence of AEs, SAEs and AESIs. AEs resulting in d/c. Effect on vital signs over 48w. Proportion of patients with at least 1 point improvement in fibrosis and proportion with resolution of steatohepatitis
Noteworthy findings: Neither of the combination therapies, tropifexor 140 mcg + CVC 150 mg or tropifexor 90 mcg + CVC 150 mg, increased the likelihood of response compared with either tropifexor 140 mcg alone or CVC 150 mg alone. The safety profiles of the combination therapies of tropifexor 140 mcg + CVC 150 mg and tropifexor 90 mcg + CVC 150 mg were similar to those of each monotherapy, with no additional emergent safety signals compared to those identified and reported in previous monotherapy studies. Overall, pruritus, nausea, and fatigue were the most frequently experienced AEs. The proportion of participants who experienced pruritus was highest in the tropifexor 140 mcg alone group and notably lower with tropifexor 140 mcg + CVC 150 mg combination treatment. Similar patterns are noted for fatigue and urinary tract infection, and this pattern may be explained by the DDI by which CVC treatment reduces tropifexor levels. No deaths were reported in the study. Most SAEs were single occurrences. There were few AESI of liver injury. Elevations in ALT and AST were higher in the tropifexor-containing groups, with most elevations transient and reversible. There was no drug-induced serious hepatotoxicity detected, and no participant met Hy's law criteria (total bilirubin >2 × ULN and ALT ≥ 3 × ULN) at any time after start of study treatment.					

Study Number/Phase	Study Title	Participant Description	Dose & Administration	CVC Formulation	Endpoints
CLJC242A2101 Phase 1	A randomized, parallel group, 3-arm, double-blind, double-dummy study to investigate the drug-drug interaction potential between tropifexor (LJN452) and cenicriviroc (CVC) in healthy and healthy but overweight to obese subjects	42 healthy and healthy but overweight to obese participants with BMI of up to 32 kg/m^2	Arm 1: 60 µg tropifexor + CVC placebo daily (n=14) Arm 2: 150 mg CVC + tropifexor placebo daily (n=14) Arm 3: 60 µg tropifexor + 150 mg CVC daily (n=14)	CVC is available as 150 mg yellow-coated immediate-release tablets for oral admin.	PK of tropifexor, CVC, and their metabolites Safety assessments and measurements (including physical examination, vital signs, ECG, clinical laboratory evaluations and AEs) up to and including the end of study visit
Noteworthy findings: When tropifexor is used in combination with CVC, an increase in the dose of tropifexor may be considered to compensate for the lower exposure seen when co-administered with CVC. Overall, administration of tropifexor alone, CVC alone, and tropifexor + CVC was considered to be well tolerated by the participants in the study. Co-administration of tropifexor and CVC did not increase the safety and tolerability profiles when compared to administration of each drug independently. All reported TEAEs were of mild severity. There were no deaths reported during this study, and 1 SAE (unrelated ovarian torsion) was reported after the clinical database cut-off date. One participant who received tropifexor + CVC discontinued from the study due to a TEAE (rash), which was suspected to be definitely related to the study drugs. No clinically significant changes were noted in laboratory parameters, vital signs, or ECG parameters.					

INFORMED CONSENT AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

SHORT TITLE FOR THE STUDY: Cenicriviroc for Arterial Inflammation in HIV

Sponsor / Study Title:	National Institute of Allergy and Infectious Diseases (NIAID / "A Limited-Center, Prospective, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Cenicriviroc Mesylate on Arterial Inflammation in People Living with HIV"
Protocol Number:	A5415
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Address:	«PiLocations»

SUMMARY

PURPOSE
The purpose of this study is to see if cenicriviroc mesylate (or CVC) can reduce inflammation of the arteries (the blood vessels that carry blood from the heart through the body) in people living with HIV (human immunodeficiency virus) (the virus that causes acquired immune deficiency syndrome [AIDS]). This study will also look at how safe CVC is when it is taken by people living with HIV who are taking anti-HIV medications. You are being asked to participate in this study because you are a person living with HIV and have one or more cardiovascular (heart and/or blood vessel) risk factors.

NUMBER OF PARTICIPANTS
There will be **at least** 93 participants in this study**.**

LENGTH OF STUDY
This study will last about 24 weeks (about 6 months). You will have about 7 visits (including the entry visit) over this time period. If needed, you may have to be in this study longer to complete all the required tests.

STUDY TREATMENT
Study drug and placebo (inactive substance) provided and required in this study.

- You will be randomly assigned (as if by flipping a coin) to receive study drug or placebo, and you will have twice the chance of getting CVC versus placebo. Study drug that will be provided is CVC, a drug that reduces inflammation (a reaction of the body to injury or infection) and fibrosis (thickening or scarring of tissue, usually as a result of injury). It is

taken by mouth. It is an experimental drug that is not yet approved by the United States (U.S.) Food and Drug Administration (FDA). This study will also provide a placebo, a pill that looks like the study treatment (CVC) but does not have any active drug in it.
- This study also requires you to continue the anti-HIV medications that you are currently taking. However, this study will not provide you with the anti-HIV medications.

REQUIRED ACTIVITIES

Blood and urine collections

At most visits, some blood will be collected from a vein in your arm. If you are able to become pregnant, you may also be asked to provide a urine sample for a pregnancy test.

Special procedures

You will have a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan and computed tomography (CT) scan of your head, neck, chest, and abdomen. A PET scan is a medical imaging technique that produces a 3-D image of processes in the body. A small amount of radiotracer (a drug that emits radioactivity), called fluorodeoxyglucose or FDG, will be injected into a vein to show differences between healthy tissue and diseased tissue. A CT scan or computerized axial tomography (CAT) scan is a diagnostic medical test that produces multiple images or pictures of the inside of the body. You will be asked to lie down for about 2 hours after the FDG injection before the scans are performed. The scans will take about 45 minutes.

RISKS

Because CVC is an investigational drug (an experimental drug being tested in a research study that involves people), all of its possible side effects may not be known. The most common side effects reported in studies of CVC were the following:
- Diarrhea (watery stools)
- Nausea (feeling of sickness with an urge to vomit)
- Joint pain
- Rash
- Itchy skin
- Vomiting
- Flatulence (passing gas) and abdominal distension (abdominal bloating due to gas in the intestine)
- Fever
- Joint swelling
- Asthenia (abnormal physical weakness or lack of energy)
- Contact dermatitis (skin irritation or rash caused by touching something)
- Headache
- Urinary tract infection
- Pain in extremity (limbs, such as arms or legs)

You may also experience an increase in liver enzymes, a blood test that can be a sign of liver damage. If you have liver disease, there is a chance that you may develop autoimmune hepatitis, a disease in which the body’s immune system attacks liver cells, but this is very rare.

You will also be exposed to radiation from the FDG-PET and CT scans. The total amount of radiation exposure you will receive from participation in this research study is about the same as you would normally receive in approximately 5.4 years from background radiation sources. A possible effect that could occur at the exposure associated with this study is a slight increase in the risk of developing cancer later in life. If you have taken part in other studies or tests in the past 12 months that have involved radiation exposure, please inform the study doctor or study staff.

There is a rare risk of a major allergic reaction to FDG, the radioactive substance that is used for the FDG-PET scan. FDG may also expose the fetus of a pregnant individual or the infant of an individual who is breastfeeding to radiation. Because of this, pregnant people and people breastfeeding cannot join this study.

BENEFITS
No direct benefits should be expected from participating in this study. Taking medication to reduce inflammation in arteries is not part of standard of care, even for individuals with HIV and with cardiovascular risk factors; however, it is being evaluated to see if it may provide benefit in this study.

OTHER CHOICES
This project is research with voluntary participation. Instead of being in this study, you have the following options:

- Receiving treatment to reduce cardiovascular risk with a prescription medication under the care of your regular doctor or other health care provider
- Starting a new treatment with another investigational drug, if you qualify for a research study
- No treatment

INTRODUCTION

You are being asked to take part in this research study because you are living with human immunodeficiency virus (HIV), the virus that causes AIDS, your HIV viral load (the amount of HIV in your blood) is under control on your anti-HIV medicines for at least 48 weeks (almost 1 year), and you are at risk for cardiovascular disease. This study is sponsored by the National Institutes of Health (NIH). The study doctor is in charge of this study at this site. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign and date this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Cardiovascular disease or heart disease, is a disease of the heart and blood vessels, which can include heart attacks, strokes, coronary artery disease (when arteries that supply blood to heart muscle become hardened and narrowed), congestive heart failure (when the heart muscle doesn't

pump blood as well as it should), and hypertension (high blood pressure). Studies have shown that individuals living with HIV are more likely to develop heart disease than individuals without HIV because HIV itself and some anti-HIV medications increase the risk for heart disease. Also, the traditional risk factors for heart disease, such as abnormally elevated cholesterol or fats in the blood, diabetes, excessive abdominal fat, and smoking, are very common in people living with HIV. HIV is also associated with increased arterial inflammation (inflammation of the blood vessels), which may also contribute to the increased risk for heart disease.

The study drug being evaluated in this study is oral cenicriviroc mesylate (or CVC), which is a drug that reduces inflammation (a reaction of the body to injury or infection) and fibrosis (thickening or scarring of tissue, usually as a result of injury). CVC is still being studied for this and other purposes but is not approved by the U.S. Food and Drug Administration (FDA) for any purpose.

We are doing this study to see if CVC can reduce inflammation of the arteries (the blood vessels that carry blood from the heart through the body) in people with HIV. We will also evaluate how safe CVC is when it is taken by people with HIV who are taking anti-HIV medications.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to join this study, you will be asked to sign and date this consent form. After you have signed and dated the form, you will be asked some questions and will undergo some tests at the screening visit to see if it is safe for you to join the study. You may have as little as ¼ tablespoon (around 3.5 mL) to as much as 8 tablespoons (around 118 mL) of blood collected at any one visit. Over the course of the study, the amount of blood collected from you will be within approved limits.

During the study, you will receive results, when they are available, from any routine tests, blood sugar tests, HIV tests, tests to evaluate risk of heart disease, and pregnancy tests that are done during the study. Any important medical problems on the FDG-PET scan and CT scan of your head, neck, chest, and abdomen will be shared with your regular doctor when the results of the scans are available.

Information Collected at Screening

There is some information that we collect on everyone who is screened for an ACTG (AIDS Clinical Trials Group) study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Screening Visit

The screening visit will take about 1-2 hours. You will be asked to come to clinic having fasted (no food or drink, except water and your medicines, for the 8 to 10 hours just before the visit).

- You will be asked about your medical history, including your HIV history, and any conditions or habits that raise your risk of coronary artery disease.
- An HIV test may be required to document your HIV status. The study doctor may be required by law to report the result of the test to the local health authority.
- You will also be asked about any medicines you have ever taken and are taking, including any anti-HIV drugs.
- You will have a brief physical exam. The study staff will check your vital signs, such as temperature, blood pressure, breathing, and pulse. Your height, weight, and waist circumference will also be measured.
- You will have blood drawn for routine blood tests, blood sugar, insulin (a hormone that helps keep your blood sugar from getting too high or too low), average blood sugar level over the last 2-3 months, HIV viral load, and tests to evaluate risk of heart disease.
- If you are able to become pregnant, you will have a pregnancy test. Pregnant individuals cannot enter the study. If you plan to become pregnant any time during the length of the study and three months after completing the study, which is a period of about 9 months, you also cannot enter the study.

Pre-entry Visit

If you are eligible for this study, based on the screening visit, you will come in for a pre-entry visit. The visit will take about 3-4 hours.

- Within 7 days of the FDG-PET scan and CT scan, you will complete the Perceived Stress Scale-10. The scale asks 10 questions about stress.
- You will have blood drawn to measure your red and white blood cell counts and $CD4^+$/$CD8^+$ count (infection-fighting cells in the blood). Some of the blood will also be stored for future tests that will evaluate metabolism (processes in the body that turn food into energy) and inflammation and measure the levels of anti-HIV drugs you are taking.
- You will be given a food diary to record everything that you eat and drink for a 4-day period. The study staff will tell you when to start and stop recording in the food diary.
- You will have an FDG-PET scan and CT scan of your head, neck, chest, and abdomen. A PET scan is a type of medical imaging technique that produces a 3-D image of processes in the body. A small amount of radiotracer (a drug that emits radioactivity) called fluorodeoxyglucose or FDG will be used to show differences between healthy tissue and diseased tissue. FDG is injected into a vein. A CT scan or CAT scan is a diagnostic medical test that, like traditional x-rays, produces multiple images or pictures of the inside of the body. The FDG-PET and CT scans are being done to evaluate the effects of CVC on inflammation of the arteries. The image will also be used to assess physical appearance and tracer accumulation. The scans at the pre-entry visit will be used to confirm that you can join this study. You may not be able to join this study based on the findings of the scans. If you enter the study, the scans at pre-entry will also be compared with the scans at week 24 to evaluate the effects of CVC on inflammation of the arteries.
    - You will be asked to follow a low-carbohydrate diet for your meal the night before the scan. The study staff will provide you with dietary instructions to follow for this meal.

  - You will be asked not to exercise for 24 hours before the scan.
  - If your scan is scheduled in the morning, you will be asked to come to clinic fasting (no food or drink, except water, for at least 8 to 10 hours just before the visit).
  - If your scan is scheduled in the afternoon, you will be asked to fast (no food or drink, except water) for at least 8 to 10 hours the previous night. You may have a low-carbohydrate meal for breakfast. The study staff will provide you with dietary instructions for your breakfast. However, you will have to come to the clinic fasting for at least 4 hours before your scheduled scan in the afternoon.
  - If you are able to become pregnant, you may have a pregnancy test before the scans are performed if it is required by the Institutional Review Board (IRB; a committee that protects the rights and safety of participants in research) of this study site.
  - Your blood sugar level will be measured before the FDG injection following the local imaging center procedure.
  - You will be asked to lie down for about 2 hours after the FDG injection so the drug can distribute throughout your body. You will have the scans after this time. The scans will take about 30-45 minutes to complete.
  - The study staff and study doctor will give you detailed instructions on how to prepare for the scans and can answer any questions you have.
- The FDG-PET and CT scans will be reviewed to confirm that you qualify for this study.

Entry Visit

Within 90 days after your screening visit, you will come to clinic for entry evaluations. This visit will last about 1-2 hours. You will be asked to come to clinic having fasted (no food or drink, except water and your medicines, for the 8 to 10 hours just before the visit).

- You will have a brief physical exam and will be asked questions about your health and about any medicine changes you have had since your screening visit.
- You will have blood drawn for routine blood tests, blood sugar test, $CD4^+/CD8^+$ count, and HIV viral load. Some of the blood will also be stored for future tests that will evaluate metabolism, inflammation, and coagulation (the process by which blood changes from liquid to a gel to form a clot to stop bleeding).
- If you are able to become pregnant, you will have a pregnancy test. You cannot enter the study if you are pregnant.
- You will be asked to fill out a questionnaire to see how well you are taking your anti-HIV drugs.
- You will be asked to bring your food diary with a record of everything that you ate and drank during a 4-day period before your entry visit.

If you qualify to participate in this study, you will be randomly assigned (like “flipping a coin”) to one of two groups (Group A or Group B). However, because of the way the study is designed, there will be twice the chance of your being assigned in Group A, compared to Group B.

- Group A: CVC (one pill once a day; the dose of CVC will depend on the HIV medications you are taking)
- Group B: placebo for CVC (one pill once a day) – A placebo is a pill that looks exactly like the experimental drug but contains no active study drug.

This study is a double-blind study. This means that you, the study staff, and the study doctor will not know which group you are assigned to. You will not be able to choose which group you will be in. However, your study doctor can find out which group you are in if there is an emergency. Upon completion of the study, participants will be unblinded.

You will continue taking the anti-HIV drugs that you are currently taking. You will also be given the study drug based on the group that you are randomly assigned to. You must start the study drug within 72 hours after you are randomized.

On Study Visits after Entry

Regardless of which group you are assigned to, you will come to clinic every 4 weeks for 16 weeks (at weeks 4, 8, 12, and 16, about 4 months) and then at week 22 (about 5 months) and week 24 (about 6 months). The visits will take about 1 hour except week 24, which will take about 3-4 hours. You will be asked to come to clinic fasting (no food or drink, except water and your medicines, for the 8 to 10 hours just before the visit) for the week 12 and week 24 visits. During these visits:

- You will have a brief physical exam, and will be asked questions about your health and about any medicine changes you have had, at every visit.
- Your weight and waist circumference will be measured at weeks 12 and 24.
- You will have blood drawn for:
  - Routine blood tests at weeks 4, 12, 22, and 24
  - HIV viral load at weeks 4, 12, and 24
  - Measurement of $CD4^+/CD8^+$ count and storage for future tests that will evaluate metabolism, inflammation, and coagulation at weeks 12, 22, and 24
  - Blood sugar test at weeks 12 and 24
  - Average blood sugar level over the last 2-3 months at week 24
  - A test to evaluate risk of heart disease
  - Levels of study drug and/or anti-HIV drugs at weeks 4, 8, 12, and 24
- If you are able to become pregnant, you will have a pregnancy test if it is suspected that you may be pregnant.
- You will be asked to fill out a questionnaire to see how well you are taking your anti-HIV drugs and the study drug. You will also be asked to bring the bottle of your study drug so the number of pills you took between visits can be counted.
- You will be given a food diary at your week 22 visit and will be asked to record everything that you eat and drink for a 4-day period before your week 24 visit. You will be asked to bring your food diary at your week 24 visit.
- Within 7 days of the FDG-PET scan and CT scan, you will complete the Perceived Stress Scale-10. You will have an FDG-PET scan and CT scan of your head, neck, chest, and abdomen at week 24. You will be asked to follow the same instructions to prepare for the scans and you will have the same tests that were done for the scans before you entered the study. If you are able to become pregnant, you may have a pregnancy test before the scans are performed if it is required by the IRB of this study site. Your blood sugar level will be measured before the FDG injection following the local imaging center procedure. You will be asked to lie down for about 2 hours after the FDG injection so the drug can distribute throughout your body. You will have the scans after this time and the scans will take about

30-45 minutes to complete. The study staff and study doctor will give you the detailed instructions on how to prepare for the scans and can answer any questions you have.

Virologic Failure

Virologic failure is when your anti-HIV drugs are not keeping HIV at a very low level. If the study staff sees that your HIV viral load has gone up, you will be asked to have another test done within 2 weeks. You will have blood drawn for the HIV viral load test. If your viral load is still up and you are still taking study drug, you will be asked to stop the study drug and come to the clinic within 7 days to have the evaluations for stopping the study early.

Confirming Toxicity

You may develop a side effect (such as a new symptom you report to the study staff, an abnormality found during physical examination, or an abnormal laboratory result) while participating in this study. If this occurs, you will be asked to return to the clinic within 5 days for evaluation. You will have a brief physical exam. You may also have blood drawn for a repeat test and any other test that may be required to confirm the abnormal laboratory result. The study staff and study doctor will explain to you the side effects that have to be checked, the evaluations that will be done, and answer any questions you may have.

If You Have to Stop Taking the Study Drug Early

If you have to stop taking the study drug early, you will come to the clinic for an additional visit. This visit will last about 1-4 hours. If you are not pregnant, you will be asked to come to clinic fasting (no food or drink, except water and your medicines, for the 8 to 10 hours just before the visit). If you are pregnant, you will not be asked to fast. At this visit:

- You will have a brief physical exam, and will be asked questions about your health and about any medicine changes you have had. Your weight and waist circumference will also be measured.
- You will have blood drawn for routine blood tests, blood sugar, average blood sugar level over the last 2-3 months, test to evaluate risk of heart disease, $CD4^+/CD8^+$ count, HIV viral load, and storage for future tests that will evaluate metabolism, inflammation, and coagulation.
- You will be asked to fill out a questionnaire to see how well you are taking your anti-HIV drugs and the study drug. You will also be asked to bring the bottle of your study drug so the number of pills you took since your last visit can be counted.
- If you stop taking the study drug at, or after you complete, the week 12 visit but before week 24, you will have an FDG-PET scan and CT scan of your head, neck, chest, and abdomen within 7 days after stopping the study drug. You will be asked to follow the same instructions to prepare for the scans and you will have the same tests that were done for the scans before you entered the study. If you are able to become pregnant, you may have a pregnancy test before the scans are performed. Your blood sugar level will be measured before the FDG injection following the local imaging center procedure. You will be asked to lie down for about 2 hours after the FDG injection so the drug can distribute throughout your body. You will have the scans after this time and the scans will take about 30-45 minutes to complete. The study staff and study doctor will give you detailed instructions on how to prepare for the scans and can answer any questions you have.

- If you stop taking the study drug before you complete the week 12 visit, or because you become pregnant, you will not have the FDG-PET scan and CT scan.
- You may be asked to continue to be part of the study and return for some study visits and procedures until you complete the rest of the study visits.

If You Stop Taking the Study Drug and Stop the Study Early
If you stop taking the study drug early, and at the same time you also stop the study, you will not have any more study visits unless you developed a side effect that is still ongoing. The study staff and study doctor will explain to you if you need an additional visit and the side effect that has to be checked, the evaluations that will be done, and answer any questions you may have.

If You Have to Stop the Study Before You Complete All the Study Visits
If you continued in the study after stopping the study drug early, and then later stop the study before completing the rest of the study visits, you may need to have an additional visit if you developed a side effect that is not yet resolved at the time you stop. The study staff and study doctor will explain to you if you need an additional visit and the side effect that has to be checked, the evaluations that will be done, and answer any questions you may have.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required (metabolic, inflammatory, and coagulation) testing.

Your samples and any private information that is collected about you will be coded. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

More information about the storage of extra samples and use in other studies are provided in Attachment A.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

At least 93 people (age 45 years and older) will take part in this study. **On October 27, 2023, the study closed to screening, and participants who were in screening prior to that point were allowed to enroll, if eligible. All screenings that were ongoing at the time of screening closure were completed on January 5, 2024, and the study closed to accrual. This resulted in over-enrollment of 110/93 participants.**

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 24 weeks (about 6 months). It is possible that you will have to be in this study longer so that all the required tests can be completed. You will be informed if this occurs.

WHY WOULD THE STUDY DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- You are unable to follow the requirements of the study
- You request to stop participating
- Your study doctor or regular doctor believes that remaining on the study is no longer what is best for you
- The study is stopped or cancelled
- You never start study treatment

The study doctor may also need to take you off the study drug without your permission if:
- Continuing the study drug may be harmful to you
- You need a treatment that you may not take while on the study
- Your HIV viral load tests show that the anti-HIV drugs you are taking are no longer working well for you; this is known as having virologic failure
- You become pregnant or are breastfeeding
- You are not able to take the study drug as required by the study

If you must stop taking the study drug before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

<u>If I have to permanently stop taking study-provided CVC, or once I leave the study, how would CVC be provided?</u>
During the study:
If you must permanently stop taking study-provided CVC before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:
After you have completed you study participation, the study will not be able to continue to provide you with CVC. If continuing to take this or a similar drug would be of benefit to you, the study staff will discuss how you may be able to obtain it.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this study drug. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the study staff at your study site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or study nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or study nurse before enrolling in any other clinical trials while on this study.

Because CVC is an investigational drug (an experimental drug being tested in a research study that involves people), all of its possible side effects may not be known. There may be rare and unknown side effects. Some of these may be life-threatening. You must tell the study doctor or study staff about all side effects that you have. Please see below the list of reported adverse events (medical conditions occurring during participation in clinical studies that may or may not be side effects) seen to date.

The common side effects reported in studies, after unique and multiple doses of CVC were the following:

- Diarrhea (watery stools)
- Nausea (feeling of sickness with an urge to vomit)
- Joint pain
- Rash
- Itchy skin
- Vomiting
- Flatulence (passing gas) and abdominal distension (abdominal bloating due to gas in the intestine)
- Fever
- Joint swelling
- Asthenia (abnormal physical weakness or lack of energy)
- Contact dermatitis (skin irritation or rash caused by touching something)
- Headaches
- Urinary tract infection
- Pain in extremity

Because in previous studies some participants experienced increases in enzymes that are found in the liver, you will be monitored for this throughout this study. Such elevation in liver function tests in the blood can be early signs of liver injury. Because of this possibility, some of the blood drawn while you are in the study will be used to measure liver tests. You will be asked to return for confirmatory tests, and additional blood draws may be required within 3-5 days after your laboratory data are available that show abnormality requiring close monitoring.

To date, rare cases of possible autoimmune hepatitis have been observed in clinical studies of CVC. Autoimmune Hepatitis is a serious condition involving inflammation of the liver that occurs when your body's immune system turns against liver cells. Possible cases of autoimmune hepatitis have been observed in people with liver disease treated with both CVC and placebo in previous studies. Signs and symptoms of autoimmune hepatitis can range from minor to severe, may come on suddenly and may include:

- Fatigue (tiredness)
- Abdominal discomfort
- Yellowing of the skin and whites of the eyes (jaundice)
- Enlarged liver
- Abnormal blood vessels on the skin (spider angiomas)
- Skin rashes
- Joint pains
- Loss of menstruation

Contact your study doctor or study staff if you experience any of these or if you experience:

- Loss of appetite for food
- Nausea
- Rash
- Vomiting
- Diarrhea
- Itchiness
- Fever

It is unknown whether these reported side effects are directly related to study drug, CVC. Because CVC is still being studied, information on possible side effects of the drug is not complete.

It is unknown whether reported adverse events are directly related to the study drug, CVC.

Risks of Radiation

As a result of your participation in this study, you will be exposed to radiation from FDG-PET/CT scans at the pre-entry and week 24 visits. There is also a very small possibility that the scan may be repeated if one of these two scans could not be evaluated. At most the scan will only be repeated one extra time. Please note that this radiation is not necessary for your medical care and is for research purposes only.

The total amount of radiation exposure you will receive from participation in this study is equal to a whole body exposure of up to approximately 19 to 21 milliSieverts (mSv) from two scans and up to 28 to 32 mSv if an extra scan is needed. The dose that you will receive from participation in this research study is about the same as you would normally receive in approximately 5.4 years from background radiation sources.

Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

Since the effects of radiation can be cumulative, it is important to know of your past radiation exposure. If you have taken part in other studies or tests in the past 12 months, which have involved radiation exposure, please inform the study doctor or study staff. If it is determined that your past radiation exposure exceeds this study's guidelines, it is possible that you will not be allowed to take part in this study.

Potential Risks with Fluorodeoxyglucose (FDG)
FDG is a radioactive drug with glucose (a type of sugar) that shows differences between healthy tissue and diseased tissue. This radioactive substance is taken up by your cells and remains in your body for a short time. This radioactive substance may expose the fetus of a pregnant individual or the infant of an individual who is breastfeeding to radiation. Pregnant and breastfeeding individuals cannot participate in this study. There is a rare risk of a major allergic reaction to FDG.

Risk of Findings on Non-Clinical Radiological Procedures
We are doing the FDG-PET/CT scan in this study to answer research questions, not as part of your medical care. The information created by this study will not usually become part of your hospital record. This FDG-PET/CT scan is not the same as one that your own doctor would order. It may or may not show problems that would be found on a standard FDG-PET/CT scan.

If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in x-rays/scans/test results of this sort) to review the results.

If the radiologist thinks there might be a problem, we will tell you and help you get follow-up care. If the radiologist thinks that you might have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Other Risks with the Radiological Procedures
- Pain at the site of injection/IV catheter – You may have pain or discomfort where we place the IV catheter and give you the injection of FDG. You may also get a bruise, have an allergic reaction, or get an infection.
- Discomfort during the scan – During the FDG-PET/CT scan, you will be asked to lie on your back for about 60 minutes. You may experience back pain, fatigue, and/or anxiety while the scan is taking place.

Risks of Fasting
You will be asked to not eat or drink anything for a number of hours before some study visits because of the FDG-PET scan or some blood tests that will be done at those visits. Fasting may cause hunger, weakness, fatigue (tiredness), anxiety, difficulty concentrating, and/or dizziness.

Risks of Blood Draws
A needle will be used to take blood from a vein in your arm. This may lead to brief pain from the needle stick, bruising, and rarely, infection. Some people become light-headed. The risk of taking blood includes low red blood cell counts, which can make you feel tired, weak, and dizzy. If the study staff feel you are at risk for low blood counts, the amount of blood taken will be lowered and your blood counts will be checked.

Allergic Reaction Risks
All drugs have a possible risk of an allergic reaction, which, if not treated right away, could become life-threatening. If you have a serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat, or eyes
- A fast pulse
- Sweating

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms.

Unknown Risks
Other side effects that are not known at this time could happen during the study. During the study, you will be told about any new information that may affect your decision to stay in the study. If you decide to stay in the study, you will be asked to sign and date an updated consent form. If you decide to leave the study early, the study staff will talk with you about your treatment options.

ARE THERE RISKS RELATED TO PREGNANCY?

The effects of CVC on an embryo/fetus are unknown at this time. It is also unknown if CVC passes through breast milk and whether it can produce adverse effects in the infant. If you are breastfeeding, pregnant, think you may be pregnant, or are trying to get pregnant, you may not join this study.

If you are having sex that could lead to pregnancy, you must agree not to become pregnant. Because of the risk involved, you and your partner must use at least two methods of birth control. You must continue to use birth control until 3 months after stopping CVC. You must choose two of the birth control methods listed below:

- A condom (male or female) with or without a spermicide
- Diaphragm or cervical cap with spermicide
- Hormone-based contraceptive
- An intrauterine device

If you become pregnant while on study, you will stay on study but come off the study drug, CVC. When you come off the study drug, study staff will get blood tests required for all participants who stop study drugs. After that, you will have minimal blood draws for safety tests only. The study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in individuals taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Since there is limited information about the effect of CVC in people with HIV, it is not known if there is a direct benefit from this study drug. It is also possible that you could be assigned to placebo. It is possible that you may receive no benefit from being in this study: your condition may not get better, and it may even get worse. Information learned from this study may help others who have HIV and are at higher risk for heart disease.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- Treatment with prescription drugs available to you
- Treatment with other experimental drugs, if you qualify
- No treatment

Please talk to your study doctor about these and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

<u>For sites in the US</u>
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, U.S., and international regulatory entities as part of their duties, Advarra IRB (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, the drug company supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on https://ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Identifiers might be removed from your identifiable private information or identifiable biospecimens collected during this study and could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent.

For sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations and policies of your country and research site.

A description of this clinical trial will be available on https://ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drugs, the study visits, physical examinations, laboratory tests or other tests required by the study. You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study.

Taking part in this study may lead to added costs to you and your insurance company if we learn of any medical problems that need extra testing or follow-up. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

«Compensation»

Your biospecimens collected during this study will never be used for commercial profit (even if identifiers are removed).

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment could be charged to you or your insurance company.

- *There is no program for compensation through the NIH, but this site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*
  OR
- *There is no program for compensation either through this institution or the NIH.*

You will not be giving up any of your legal rights by signing and dating this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research participant;
- Eligibility to participate in the study;
- The study doctor’s or study site’s decision to exclude you from participation;
- Results of tests and/or procedures;

Please contact the study doctor at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- Or call toll free: 877-992-4724
- Or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00065562.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name
- Address
- Phone number
- Date of birth
- Medical history
- Information from your study visits, including all test results

Health data may come from your study records or from existing records kept by your regular doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of National Institute of Allergy and Infectious Diseases (NIAID)
- Representatives of the AIDS Clinical Trials Group (ACTG)
- Representatives of AbbVie (the industry sponsor)
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study)
- The Food and Drug Administration (FDA) and other US federal and state agencies
- Government agencies to whom certain diseases (such as HIV, hepatitis, and STDs) must be reported
- Governmental agencies of other countries
- Other local, US, and international regulatory entities
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study
- Other research doctors and medical centers participating in this study, if applicable
- A data and safety monitoring board that oversees this study, if applicable

Your health data will be used to conduct and oversee the research, including, for instance:

- To see if the study drug works and is safe
- To compare the study drug to other drugs
- For other research activities related to the study drug

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here. Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do

this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form, and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use, and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

ATTACHMENT A: OPTIONAL CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called “extra samples”. The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Your samples and any private information that is collected about you will be coded. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored.

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the study staff may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

You may withdraw your consent for research on your extra samples at any time, and the **samples** will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the study staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples

OR
____ (initials) I understand but I do not agree to this storage and possible use of my samples

Research with Human Genetic Testing
The ACTG has **a study that collects** samples for genetic testing.

This study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

Your site might ask you if you would like to participate in **this** study if it is being done where you live. If you would like to participate, you will sign and date a separate consent form.

Your extra samples will not be used for human genetic testing unless you sign and date a consent form for A5128.