A5370

Safety and Immunotherapeutic Activity of an Anti-PD-1 Antibody (Cemiplimab) in HIV-1-infected Participants on Suppressive cART: A Phase I/II, Double-blind, Placebo-controlled, Ascending Multiple Dose Study

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

National Institute of Allergy and Infectious Diseases

Industry Support Provided by:

Regeneron Pharmaceuticals, Inc.

IND #137978

The ACTG HIV Reservoirs and Viral Eradication Transformative Science Group:	**Rajesh Gandhi, MD, Chair**
Protocol Co-Chairs:	**Cynthia Gay, MD** **W. David Hardy, MD**
Protocol Vice Chair:	**Joseph J. Eron, Jr., MD**
DAIDS Clinical Representative:	**Randall Tressler, MD**
Clinical Trials Specialist:	**Chanelle Houston, BS**

FINAL Version 1.0
November 16, 2018

A5370

Safety and Immunotherapeutic Activity of an Anti-PD-1 Antibody (Cemiplimab) in HIV-1-infected Participants on Suppressive cART: A Phase I/II, Double-blind, Placebo-controlled, Ascending Multiple Dose Study

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 U.S. 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: _____
Name/Title

TABLE OF CONTENTS

Page

CONTENTS (Cont'd)

Page

SITES PARTICIPATING IN THE STUDY

A5370 is a multicenter study open to all US clinical research sites (CRSs).

PROTOCOL TEAM ROSTER

Co-Chairs
Cynthia Gay, MD
Chapel Hill CRS
Bioinformatics Building
130 Mason Farm Road, Suite 2112
Chapel Hill, NC 27599-7030
Phone: 919-843-2726
Fax: 919-966-8928
Email: cynthia_gay@med.unc.edu

W. David Hardy, MD
Division of Infectious Diseases
Johns Hopkins University School of Medicine
4627 47th Street, NW
Washington, DC 20016
Phone: 310-709-3505
Email: wdavidhardymd@gmail.com

Vice Chair
Joseph J. Eron, Jr., MD
University of North Carolina Global HIV Prevention and Treatment CTU
Bioinformatics Building
130 Mason Farm Road, Suite 210
Chapel Hill, NC 27599-7215
Phone: 919-843-2722
Fax: 919-966-6714
Email: jeron@med.unc.edu

DAIDS Medical Officer
Randall Tressler, MD
HIV Research Branch
DAIDS, NIAID, NIH
5601 Fishers Lane
Room 9E49
Rockville, MD 20852
Phone: 240-627-3072
Fax: 301-435-9282
Email: Randall.tressler@nih.gov

Clinical Trials Specialist
Chanelle Houston, BS
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3367
Fax: 301-628-3302
Email: CHouston@s-3.com

Statisticians
Ronald Bosch, PhD
Statistical and Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building, Room 603
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-3024
Fax: 617-432-2843
Email: ronbosch@sdac.harvard.edu

Ashley McKhann, MS
Statistical and Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building, Room 604b
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-7986
Fax: 617-432-2843
Email: amckhann@sdac.harvard.edu

Data Manager
Bernadette M. Jarocki, BS
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 (Ext. 7263)
Fax: 716-834-8432
Email: jarocki@fstrf.org

DAIDS Pharmacist
Lynette Purdue, PharmD
Pharmaceutical Affairs Branch
DAIDS, NIAID, NIH
5601 Fishers Lane
Room 9E28
Rockville, MD 20852
Phone: 240-627-3061
Fax: 240-627-3112
Email: lpurdue@niaid.nih.gov

Immunologist
Bernard J.C. Macatangay, MD
University of Pittsburgh CRS
S827 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261
Phone: 412-383-1272
Fax: 412-648-8455
Email: macatangaybj@upmc.edu

Virologist
Daniel R. Kuritzkes, MD
Brigham and Women's Hospital
Therapeutics (BWHT) CRS
Section of Retroviral Therapeutics
Harvard Medical School
65 Landsdowne Street, Room 447
Cambridge, MA 02139
Phone: 617-768-8398
Fax: 617-768-8738
Email: dkuritzkes@partners.org

Pharmacologists
Gene Morse, PharmD
University of Rochester Adult HIV
Therapeutic Strategies Network CRS
Translational Pharmacology Research Core
NYS Center of Excellence in Bioinformatics
and Life Sciences
701 Ellicott Street
Buffalo, NY 14203
Phone: 716-881-7464
Email: emorse@buffalo.edu

Pharmacologists, cont'd
Raymond Cha, PharmD
University at Buffalo
SUNY Buffalo
212 Kapoor Hall
Buffalo, NY 14214
Phone: 716-645-4790
Email: rcha@buffalo.edu

Endocrinologist
Kendall Moseley, MD
Division of Endocrinology, Diabetes &
Metabolism
Johns Hopkins University School of
Medicine
5501 Hopkins Bayview Circle, 2A62 Asthma
and Allergy Center
Baltimore, Maryland 21224
Phone: 410-550-8720
Fax: 410-367-2042
Email: kmosele4@jhmi.edu

Oncologist
Thomas Uldrick, MD, MS
Deputy Head, Global Oncology
Associate Member, Vaccine and Infectious
Disease Division
Associate Member, Clinical Research
Division
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North
Seattle, WA 98109-1024
Phone: 206-667-7585
Fax: 206-667-1965
Email: tuldrick@fredhutch.org

Field Representatives
Susan Pedersen, RN, BSN
University of North Carolina Global HIV
Prevention and Treatment CTU
Bioinformatics Building, Suite 2100
130 Mason Farm Road
Chapel Hill, NC 27599-7215
Phone: 919-966-6713
Fax: 919-966-6712
Email: spederse@med.unc.edu

Field Representatives, cont'd
Amanda Tipton, LPN
Chapel Hill CRS
130 Mason Farm Road, 2nd Floor
Chapel Hill, NC 27599-7030
Phone: 919-843-2239
Fax: 919-966-6714
Email: tiptoe13@med.unc.edu

Laboratory Technologists
Cheryl Jennings, BS
Northwestern University CRS
Clinical Retrovirology Research Laboratory
1181 Jelke Building
1750 West Harrison Street
Chicago, IL 60612
Phone: 312-942-5954
Fax: 312-942-6787
Email: cheryl_jennings@rush.edu

Pamela Lankford-Turner, BS
The Ponce de Leon Center CRS
500 Irvin Court
Suite 100
Decatur, GA 30030
Phone: 404-727-3747
Fax: 404-499-9726
Email: pturn01@emory.edu

Community Scientific Subcommittee (CSS) Representative
Danielle Campbell, MPH
University of California, Los Angeles CARE Center CRS
8810 South Mary Avenue
Los Angeles, CA 90002
Phone: 310-910-8341
Email: danielle.m.campbell1@gmail.com

Industry Representative
Elizabeth Miller, MD
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road, 62-002
Tarrytown, NY 10591
Phone: 914-847-1290
Email: elizabeth.miller@regeneron.com

Laboratory Data Manager
Kyle Whitson, MA
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14221
Phone: 716-340-0900 (Ext. 7273)
Email: whitson@fstrf.org

Laboratory Specialists
Emmanuell Choueiry, MSc
IMPAACT Network Laboratory Center
University of California Los Angeles
11075 Santa Monica Blvd. Suite #200
Los Angeles, CA 90025
Phone: 310-794-9894
Email: echoueiry@impaactlabcenter.org

Sara Zabih
IMPAACT Network Laboratory Center
University of California Los Angeles
11075 Santa Monica Blvd. Suite #200
Los Angeles, CA 90025
Phone: 310-794-9052
Email: szabih@impaactlabcenter.org

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5370@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5370@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail 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.protA5370 e-mail group. Include the protocol number in the e-mail subject line.

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

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the core protocol team.

- Send an e-mail message to actg.coreA5370@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to immunologic, virologic, or pharmacologic laboratory tests, contact the protocol immunologist, virologist, or pharmacologist.

- Send an e-mail message to actg.teamA5370@fstrf.org (ATTENTION: [Beej Macatangay, immunologist; Dan Kuritzkes, virologist; Gene Morse, and Raymond Cha, pharmacologists]).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Bernie Jarocki, jarocki@fstrf.org, directly.
- For other questions, send an e-mail message to actg.teamA5370@fstrf.org (ATTENTION: Bernie Jarocki).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support:

- Send an e-mail 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 e-mail message to actg.teamA5370@fstrf.org (ATTENTION: Chanelle Houston).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@s-3.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

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

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation at US sites, contact the clinical trials specialist
- Send an e-mail message to actg.teamA5370@fstrf.org (ATTENTION: [Chanelle Houston]).

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Lynette Purdue, protocol pharmacist, at 240-627-3061.

Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
The IND number will be available on the protocol-specific web page (PSWP) within 30 days of the submission to the Food and Drug Administration (FDA). For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

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.

Telephone Calls
Sites are responsible for documenting telephone calls made to A5370 team members.
- Send an e-mail message to actg.teamA5370@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADLs	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibody
AST	aspartate transaminase
AUC_t	area under the concentration-time profile
$AUC_{6wk,ss}$	area under the concentration-time profile over 6 weeks at steady-state
AUC_t	AUC until the last detectable concentration
BLQ	below the limit of quantification
BSA	body surface area
BUN	blood urea nitrogen
C_{eoi}	concentration at end of infusion
C_{max}	maximum serum concentration of drug
C_{trough}	concentration at trough (pre-dose)
cART	combination antiretroviral therapy
CFSE	carboxyfluorescein diacetate succinimidyl ester
CL	clearance
CLIA	Clinical Laboratory Improvement Amendments
COPD	chronic obstructive pulmonary disease
CR	complete responses
CT	computed tomography
CTCAE	Common Terminology Criteria for AEs
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DAERS	DAIDS Adverse Experience Reporting System
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
ESR	erythrocyte sedimentation rate
FIH	first-in-human
FL	follicular lymphoma
FSH	follicle stimulating hormone-release factor

GAD65/GAD	glutamic acid decarboxylase 65
HBV	hepatitis B virus
HBsAg	hepatitis B virus surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HgbA1c	hemoglobin A1c
ICI	immune checkpoint inhibitors
IgG	immunoglobulin
IFN-γ	interferon gamma
IGRA	interferon-gamma release assay
INR	International Normalized Ratio
irAE	immune-related adverse event
IRIS	immune reconstitution syndrome
IU	international unit
IUD	intrauterine device
IV	intravenous
LDMS	laboratory data management system
LTR	long terminals repeats
LPC	Laboratory Processing Chart
mAb	monoclonal antibody
MedDRA	Medical Dictionary of Regulatory Activities System Organ Class
MOPS	Manual of Procedures
NHP	non-human primate
NSCLC	non-small cell lung carcinoma
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PD-1	programmed cell death 1
PK	pharmacokinetics
PPD	purified protein derivative
PR	partial responses
PSWP	Protocol-Specific Web Page
PVC	polyvinyl chloride
qHBsAg	quantitative HBV surface antigen
RO	receptor occupancy
SAE	Serious Adverse Event
SCA	single copy assay

SD	standard deviation
SMC	study monitoring committee
SOE	schedule of evaluations
$t_{1/2}$	elimination half-life
T4	free thyroxine
TEN	toxic epidermal necrolysis
TB	tuberculosis
TK	toxicokinetic
TPO	thyroid peroxidase
TNFα	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
TVR	total virus recovery
ULN	upper limit of normal
VL	viral load
WBC	white blood cell

SCHEMA

A5370

Safety and Immunotherapeutic Activity of an Anti-PD-1 Antibody (Cemiplimab) in HIV-1-infected Participants on Suppressive cART: A Phase I/II, Double-blind, Placebo-controlled, Ascending Multiple Dose Study

DESIGN	This trial is a phase I/II, double-blinded (within each cohort), dose-escalating, placebo-controlled study of the safety and immunotherapeutic activity of two infusions of anti-PD-1 (REGN2810/cemiplimab) monoclonal antibody in HIV-1-infected participants on combination antiretroviral therapy (cART) who have HIV-1 RNA below the limit of quantification and CD4+ T cell counts ≥350/mm^3. Cemiplimab (0.3 mg/kg [Cohort 1], 1 mg/kg [Cohort 2], and 3 mg/kg [Cohort 3]) or placebo will be given to 15 participants in each Cohort (12 active and 3 placebo). Participants will receive infusions of antibody or placebo at entry/day 0 and week 6, for a total of 2 infusions, with the primary safety endpoint through week 48 and the primary immunologic endpoint through week 12. The study will enroll sequential dose-rising cohorts with the second and third cohorts receiving the first infusion after all participants in the previous cohort have reached week 12 and an evaluation of safety outcomes is completed, which determines whether to dose escalate or not.
DURATION	Participants will be followed for 48 weeks
SAMPLE SIZE	45 participants (15 participants each in Cohorts 1-3).
POPULATION	HIV-1-infected men and women ages ≥18 and <65 years, on cART who have a CD4+ T cell count of ≥350 cells/mm^3 and a screening plasma HIV-1 RNA below the level of quantification by a FDA-approved HIV RNA assay.
INTERVENTION	Within each sequentially enrolled dose cohort, participants will be randomized 4:1 to receive REGN2810/cemiplimab or placebo infusion: Cohort 1: Two doses of REGN2810/cemiplimab 0.3 mg/kg or placebo (12 active: 3 placebo); one dose at entry/day 0 and one dose at week 6 Cohort 2: Two doses of REGN2810/cemiplimab 1 mg/kg or placebo (12 active: 3 placebo; one dose at entry/day 0 and one dose at week 6 Cohort 3: Two doses of REGN2810/cemiplimab 3 mg/kg or placebo (12 active: 3 placebo); one dose at entry/day 0 and one dose week 6

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Two doses of the anti-PD-1 (programmed cell death) monoclonal antibody (mAb), cemiplimab, will be safe in HIV-1-infected participants on cART with plasma HIV-1 RNA suppressed below the level of quantification on standard assays.

1.1.2 Blocking PD-1 interaction with its ligands (PD-L1 and PD-L2) with anti-PD-1 antibody will enhance HIV-1-specific immune responses that promote the clearance (CL) of HIV-1-expressing cells.

1.2 Primary Objective

1.2.1 To assess the safety of multiple dose levels (0.3, 1, and 3 mg/kg) of cemiplimab versus placebo in HIV-1-infected, cART-suppressed participants.

1.3 Secondary Objectives

1.3.1 To evaluate the change in magnitude of HIV-1 gag-specific CD8+ T cells by intracellular staining for both CD107a and interferon gamma (IFN-γ) from a pre-treatment baseline level (average of 2 measurements) to time points after one or two doses of cemiplimab (average of responses from weeks 2, 4, 6, 8, 10, and 12).

1.3.2 To evaluate the change in magnitude of HIV-1 gag-specific CD8+ T cell responses using both CD107a and IFN-γ expression from baseline to time points after the first dose of cemiplimab or placebo (average of responses from weeks 2, 4, and 6), and to time points after the second dose or placebo (average of responses from weeks 8, 10, and 12).

1.3.3 To evaluate the change in magnitude of HIV-1 gag-specific CD8+ T cells by intracellular staining for IFN-γ or CD107a alone, from baseline (pre-treatment average) to time points after one or two sequential doses of cemiplimab or placebo (average of responses from weeks 2, 4, 6, 8, 10, and 12) and explore difference following each dose.

1.3.4 To evaluate changes in polyfunctional response of HIV-1-gag-specific CD8+ T cells by intracellular staining for IFN-γ, CD107a, IL-2, and TNFα from baseline (pre-treatment average) to time points after one or two sequential doses of cemiplimab or placebo and explore difference following each dose.

1.3.5 To assess the durability of response to cemiplimab by evaluating the magnitude of HIV-1 gag-specific CD8+ T cell responses by intracellular staining of CD107a and IFN-γ and polyfunctional response through week 48.

1.3.6 To assess immunogenicity to cemiplimab after multi-dose administration to cART-treated HIV-1-infected participants.

1.4 Exploratory Objectives

1.4.1 To evaluate changes in total HIV-1 DNA, intact proviral HIV-1 genomes, plasma HIV RNA by single copy assay (SCA), cell-associated HIV-1 RNA, and HIV-1 RNA/DNA ratios in total CD4+ cells prior to and following cemiplimab administration.

1.4.2 To explore the human genetic and gene expression correlates of response to cemiplimab administration.

1.4.3 To explore relationships between serum cemiplimab exposure and changes in biomarkers of virologic and immune response.

1.4.4 To explore the proportion of total and HIV-1 gag-specific CD8+ and CD4+ T cells that express PD-1, PD-L1, and other exhaustion markers by multi-parameter flow cytometry. The expression profile of PD-L2 on dendritic cells and monocyte derived-macrophages will also be determined.

1.4.5 To explore changes in poly-functionality of HIV-1-specific CD4+ T cells by intracellular staining for two or more immune mediators using flow cytometry.

1.4.6 To explore changes in immune activation and cell cycling of CD8+ and CD4+ T cells by quantifying CD38+ HLA-DR+ and Ki 67 expression prior to and following anti-PD-1 administration by flow cytometry.

1.4.7 To evaluate the relationship between pre-therapy ex vivo HIV-specific T cell proliferation to HIV antigens following cemiplimab exposure and the in vivo HIV specific immune responses post cemiplimab administration.

1.4.8 To describe the pharmacokinetics (PK) and receptor occupancy (RO) of cemiplimab after administration to cART-treated HIV-1-infected participants.

2.0 INTRODUCTION

2.1 Background

In patients who are effectively treated with cART, HIV-1 persists in latently infected resting CD4+ T cells and possibly other tissues or cellular reservoirs. Elimination of latently infected cells with replication competent virus is necessary to cure HIV-1 infection. Although recent evidence suggests that the histone deacetylase inhibitors, such as vorinostat and romidepsin, can increase expression of HIV-1 RNA in resting CD4+ T cells and in plasma [1-3], additional steps may be necessary to kill HIV-1-expressing cells and reduce the resting CD4+ T cell reservoir [4]. Consequently, reduction or elimination of HIV-1 reservoirs that persist on suppressive cART may

require the combination of multiple therapeutic modalities including interventions that enhance the HIV-1-specific immune response. Hence, the testing of interventions that have the potential to impact persistent HIV-1, enhance HIV-specific immunity, and be combined with other interventions that may be additive or synergistic is a necessary step in a comprehensive strategy for cure research.

cART clearly has been effective at suppressing plasma HIV-1 RNA to well below the limits of detection by conventional tests in most treated HIV-infected patients [5]. However, despite effective cART, low-level HIV-1 viremia persists in most patients [6]. Why this persistent viremia and the resulting antigenemia fail to stimulate effective HIV-1-specific T cell responses and why virus-producing cells are ineffectively cleared is not completely understood. Chronic antigen stimulation results in marked down regulation of the antigen-specific cellular immune responses to HIV-1 and other chronic viral infections [7]. The resulting T cell "exhaustion" is characterized by reduced T cell proliferation, cytokine production, cytotoxic T lymphocyte (CTL) function, and cell survival [8]. The molecular mechanisms behind this "immune exhaustion" in the context of chronic infection are only recently coming to light [8, 9]. In individuals receiving suppressive ART, CD4+ T cells expressing PD-1 and other immune checkpoint molecules are enriched in HIV infection. In addition to reversing immune exhaustion, anti-PD-1 administration may target the latent cell pool [10, 11].

2.2 Rationale

T-cell Exhaustion in Chronic Viral Infections
During chronic viral infections, persistent antigenic stimulation leads to the T cell expression of inhibitory co-receptors (e.g., PD-1 and cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) which are associated with a downregulation of immune responses. [12, 13] This loss of T cell function occurs in several stages starting with loss in proliferative potential, cytotoxic responses (i.e., T cell ability to lyse target cells), and polyfunctionality, followed by defects in cytokine production such as IFN-γ [8, 14]. Indeed, an important factor underlying ineffective HIV-1-specific immune responses is previous evidence that chronic HIV-1 infection leads to up-regulation of these inhibitory co-receptors on T cells. The expression of PD-1 and CTLA-4, on CD4+ and/or CD8+ T cells is associated with disease progression in untreated HIV-1 infection [15-18]. PD-1 expression on HIV-1 specific CD8+ and CD4+ T cells is reduced by ART [15, 19], but in some studies expression remained elevated compared to that in uninfected persons [15, 20], especially in patients with less robust CD4+ T cell responses [21]. In a study evaluating PD-1 expression in HIV-infected individuals starting ART early (within 6-12 months of estimated infection) or later, PD-1 expression on total CD4+ and CD8+ T cells after several years of cART (median of 2.8 years and 2.3 years, respectively) was comparable to levels seen in the HIV-uninfected controls [22]. However, in this study median PD-1 mean fluorescent intensity remained elevated on the CD4+ effector memory T cells compared to uninfected controls, even in the early ART group (234 vs. 206, P=0.007). Expression of PD-L1, a ligand for PD-1, in addition to being inducible on antigen-presenting cells [23], is also up-regulated on both CD4+ and CD8+ HIV-1-specific T cells in response to HIV-1 infection. Levels of PD-L1 on T-cells in this context remain elevated despite suppression of HIV-1 by ART [20, 24]. Further, recently

published data with a single, low dose of anti-PD-L1 antibody (BMS-936559) in ACTG A5326 suggests that blockade of the PD-1/PD-L1 axis may improve HIV-specific immune responses, even in patients with durable viral suppression on ART [25]. In this study, two of six participants who received the anti-PD-L1 antibody demonstrated improvements in HIV-1-specific CD8+ responses, including improvement in the percentage of poly-functional HIV-1 gag-specific cells. In addition, CD8+ T cells obtained prior to study entry from these two apparent responders demonstrated proliferative responses to gag peptides after anti-PD-L1 exposure ex vivo compared to isotype antibody exposure. This proliferation corresponded to their in vivo response as assessed by IFN-γ, CD107a (a marker of T cell degranulation), and TNF and was not observed in non-responders. An additional rationale for evaluating anti-PD-1 in HIV-infected patients derives from the demonstration that CD8+ T cells from patients suppressed on ART were unable to kill infected resting CD4+ T cells after viral reactivation, suggesting diminished CTL function and residual dysfunction [26]. Whether blockade of the PD-1/PD-L1 axis can restore function, specifically cytotoxic function and cytokine production, in exhausted T cells in chronic HIV-1 is an important unanswered question.

Further, data suggest that CD4+ T cells expressing PD-1 are enriched for latent HIV infection, and thus, an antibody to PD-1 may provide a relevant strategy to target latently infected T cells [11].

We propose a study evaluating the safety of the anti-PD-1 antibody, cemiplimab (REGN2810), in HIV-infected participants on suppressive ART. Cemiplimab, is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD L1-mediated T cell inhibition. To characterize the pharmacological action of cemiplimab, in vitro cell-based assays were used to evaluate the binding of cemiplimab to PD-1, the blocking activity of cemiplimab on PD-1/PD-L1 interaction and its effect on T cell signaling. Also, the anti-tumor activity of cemiplimab was assessed in vivo using a MC38.Ova tumor model in mice genetically engineered to express human PD-1. To compare the activity of cemiplimab to the most clinically advanced anti-PD-1 antibodies, the above assays were also performed on two in-house generated PD-1 antibodies, REGN1672 (primary sequence identical to nivolumab) and REGN2626 (primary sequence identical to pembrolizumab), produced based on publicly available sequences. Results from these studies demonstrate that cemiplimab binds human and cynomolgus PD-1 with high affinity and blocks PD-1/PD-L1-driven inhibitory T cell signaling. Cemiplimab also displayed a robust, dose-dependent suppression of MC38.Ova tumors in the syngeneic mouse tumor model. Furthermore, the nonclinical activity of cemiplimab is similar to the two in-house generated anti-PD-1 comparator antibodies (Investigator Brochure [IB], Edition 6). As an IgG4 subtype antibody, cemiplimab is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity cells. In addition, incubation of cemiplimab in blood samples from healthy human donors ex vivo did not result in any significant cytokine secretion and is thus not expected to independently promote T cell activation.

As of 27 March 2018, 757 oncology patients with several different cancer types have been treated with cemiplimab either as monotherapy or in combination with radiotherapy and/or other cancer therapy in seven studies. The safety and efficacy information to date

for cemiplimab indicates that it is a clinically active inhibitor of the PD-1 pathway (IB, Edition 6). These preliminary clinical data suggest that the anti-tumor activity and safety profile of cemiplimab is similar with other anti-PD-1 agents, though no direct clinical comparisons exist between anti-PD-1 agents at this time. LIBTAYO (cemiplimab-rwlc) is approved in the United States for advanced cutaneous squamous cell carcinoma (CSCC).

PD-1 and PD-L1 Blockade in Animal Models of Chronic Infection
In a study of chronic hepatitis C (HCV) in chimpanzees, one of three animals treated with an anti-PD-1 antibody demonstrated a decline in viremia and improved HCV-specific CD4+ and CD8+ T cell responses [27].

Blocking the PD-1 pathway using multiple doses of an antibody to PD-1 in a macaque model of SIV infection resulted in rapid expansion of virus-specific CD8+ T cells with improved functional quality of antiviral CD8+ T cells in the blood and gut as demonstrated by the generation of polyfunctional cells capable of co-producing cytokines IFN-γ, TNF-α, and IL-2 [28]. These immune responses were associated with significant reductions in plasma SIV RNA and prolonged survival in the absence of ART [28], as well as reduction in markers of immune activation and microbial translocation [29]. In animal models of vaccination, blocking PD-1/PD-L1 axis led to improved anti-vaccine antibodies [30, 31]. However, the question of whether multiple doses of anti-PD-1 will result in increased immunologic effects cannot fully be answered in the non-human primate (NHP) model given the rapid CL of human antibodies due to development of anti-drug antibodies (ADA) in the primate model.

Clinical Data for PD-1 and PD-L1 Blockade in Humans: Malignancy, Hepatitis B and C, and HIV

Malignancy
The use of antibodies to the inhibitory receptors PD-1 and CTLA-4 have revolutionized immunotherapy for cancer [32] and become standard of care for several tumor types. Similar to HIV infection, PD-1 expression is increased on activated effector T cells in tumor tissues and results in an exhausted T cell phenotype with ineffective immune response to tumor antigens. Most recently, both anti-PD-1 and anti-PD-L1 antibodies given to patients with different types of cancer demonstrated substantial anti-tumor activity in a minority of patients [33, 34].

Efficacy data for cemiplimab from a phase I, first-in-human (FIH) dose escalation study in CSCC and non-small cell lung cancer (NSCLC), and from a phase II study in CSCC are available. In the phase I study, among 60 patients who received cemiplimab in dose-escalation cohorts (1 mg/kg, 3 mg/kg, or 10 mg/kg every 2 weeks), the investigator determined that the objective response rate was 18.3% (9 partial responses [PR], 2 complete responses [CR]). Among 21 patients with NSCLC (1 patient in dose escalation, 20 patients in expansion cohort 1 that studied cemiplimab 200 mg monotherapy every 2 weeks), the response rate according to independent central review was 29% (6 PR). Among 26 patients in the CSCC expansion cohorts of the phase I study (including patients with locally advanced disease and those with metastatic disease), the response

rate according to independent central review was 50% (13 PR). The phase II CSCC study enrolled 59 patients with metastatic CSCC, and the response rate per independent central review was 48% (4 CR, 24 PR) (IB Edition 6).

Clinical Data for PD-1 Blockade in HCV Infection
Cemiplimab has not been studied in hepatitis C, however nivolumab, a similar anti-PD-1 mAb has been studied in patients with HCV mono-infection using a wide range of single doses (0.03 to 10 mg/kg). An antiviral effect was demonstrated in a minority of participants. Five out of 45 treated patients had a confirmed 0.5 $\log_{10}$ decline in HCV RNA, which was similar to the proportion in placebo (1/9). However, at the 10 mg/kg dose, 3 of 20 participants had a greater than 4.0 $\log_{10}$ decline in HCV RNA; 2 had levels fall below the limit of quantification. No response of this magnitude was observed in any placebo recipient. One patient treated with 10 mg/kg had an undetectable HCV RNA 1 year following a single infusion of the anti-PD-1 antibody [35].

Clinical Data for PD-1 Blockade in Hepatitis B Virus (HBV) Infection
A study evaluating PD-L1 blockade ex vivo in chronically infected patients with hepatitis B infection demonstrated increased HBV-specific CD8+ T cell responses, and notably, CD8+ responses in this study did not correlate with the percentage of PD-1+ cells or PD-1 median fluorescence intensity [36]. Nivolumab was studied in 51 HBV-infected patients with hepatocellular carcinoma (HCC) in the Checkmate 040 study. In this study, 3 of 51 patients with chronic HBV demonstrated a 1 log decline in hepatitis B virus surface antigen (HBsAg) during anti-PD-1 inhibition [37]. Nivolumab was also studied with and without a therapeutic HBV vaccine (GS-4774) in hepatitis B e antigen-negative virally suppressed HBV-infected participants in a single-dose study of 0.1 mg/kg and 0.3 mg/kg [38]. Participants who received 0.3 mg/kg nivolumab had a mean and median decline of quantitative HBsAg (qHBsAg) at 12 weeks from baseline of -0.3 and -0.13 IU/ml, respectively. HBsAg declined persisted through week 24 with mean and median declines of -0.47 and -0.14 IU/ml, respectively [38]. Nine (2/22) and 14% (3/22) of participants had a greater than 0.5 log reduction in HBsAg. Notably, there was no added benefit to qHBsAg decline with the addition of the HBV therapeutic vaccine GS-4774. One participant experienced HBsAb seroconversion and has been maintained off of HBV antiviral therapy. Of note, in this study, RO of nivolumab given at 0.3 mg/kg persisted at high levels for at least 6 weeks.

Clinical Data for PD-L1 Blockade in HIV Infection
There are data to suggest that improved immune function seen in cancer trials may translate to HIV infection. A recent case study demonstrated a decline in plasma HIV-1 viremia as measured by a single-copy HIV RNA assay following CTLA-4 blockade with ipilimumab for metastatic melanoma in an HIV-infected individual suppressed on ART [39]. In addition and as noted above, in a study of HIV-infected participants suppressed on cART, a single, low dose (0.3 mg/kg) infusion of an anti-PD-L1 mAb (BMS-936559) appeared to enhance HIV-1-specific immunity in two of six participants, with improvements in HIV-1-specific CD8+ responses and the percentage of poly-functional HIV-1 gag-specific cells [25]. Both of the two potential responders had durable viral

suppression for 5.2 years. This response correlated with pre-treatment ex vivo proliferative responses of HIV-1-specific CD8+ T cells to gag and was not observed in non-responders.

Ipilimumab administered to 24 viremic HIV-infected participants as 2 or 4 doses of 0.1, 1, 3, or 5 mg/kg every 28 days was well tolerated overall; 83% had ≥1 AEs but all were Grade 1 or 2 except for grade 3 neutropenia in a participant with mild neutropenia at baseline. Eight (33%) of these untreated HIV-infected participants had a potential immune-related adverse events (irAE) (seven with Grade 1 diarrhea not requiring corticosteroids; one with diarrhea and transient detectable antinuclear antibody (ANA); one with Grade 2 facial palsy requiring corticosteroids) [40]. In addition, an ongoing study of multiple doses of pembrolizumab administered to HIV-infected participants with relapsed/refractory malignancy will evaluate the safety and tolerability of every-3-weeks infusions in this study population (ClinicalTrials.gov Identifier NCT02595866). Notably, immunologic responses among healthy HIV-infected participants compared with participants in oncology studies may differ given that participants in oncology studies likely have impaired immune responses related to their underlying malignancy. Accordingly, evaluation of cemiplimab in healthy HIV-infected participants may be more likely to demonstrate an effect on immune responses.

PK and Toxicology in Non-Human Primates (NHPs)
Cemiplimab has similar binding affinities to monkey and human PD-1, therefore the cynomolgus monkey *(Macaca fascicularis)* was used for the preclinical assessment of PK and toxicology. The use of the cynomolgus monkey allows for a robust evaluation of cardiovascular and respiratory safety pharmacology endpoints, and provides clinically relevant PK and toxicokinetic (TK) evaluations of cemiplimab. The PK and TK of cemiplimab in cynomolgus monkeys were characterized by non-linear kinetics and predominance of target-mediated CL at low concentrations and linear kinetics at high concentrations, when the target was likely saturated. The prevalence of immunogenicity (anti-drug antibodies; ADA) was high; however, continuous drug exposure was maintained for 80% and 50% of animals throughout the 4-week and 26-week toxicology studies, respectively. As cemiplimab is a human antibody, the presence of ADA following cemiplimab administration to cynomolgus monkeys was not unexpected. However, the observed immunogenicity in monkeys is not necessarily predictive of immunogenicity in humans. The presence of ADA did not affect the ability to characterize the PK or safety profiles of cemiplimab in these studies (IB Edition 6).

In the monkey model, cemiplimab was well-tolerated. There were no unscheduled deaths and no drug-related effects on morbidity and mortality, body weights, food consumption, ophthalmology, cardiovascular hemodynamics, including blood pressure and heart rate, body temperature, respiration rate and pulse oximetry, neurological examination, or any clinical pathology parameters evaluated. Cemiplimab administered once weekly for 4 weeks by intravenous (IV) infusion to male and female cynomolgus monkeys, at dose levels of 2, 10, and 50 mg/kg, resulted in a number of findings that were considered directly attributable to cemiplimab, and additional findings that were interpreted to be due to ADA production and subsequent ADA/drug complex (circulating immune complex) formation. Findings directly attributable to cemiplimab were limited to

dose-independent reversible increases in the frequency and absolute counts of proliferating T-lymphocytes, and increased T-cell-dependent antibody secondary responses. Given the tolerability of cemiplimab in the monkeys and that most findings were associated with immune complexes and/or ADA responses due to administration of a human IgG protein to monkeys, the no-observable-adverse-effect-level (NOAEL) is considered to be 50 mg/kg, the highest dose evaluated (IB Edition 6).

PK of Cemiplimab in Humans
In a FIH study of cemiplimab as monotherapy, or combined with radiation and/or cyclophosphamide, after the first dose cemiplimab was shown to have fairly dose proportional increases in C_{max} (maximum concentration) and AUC (area under the concentration time curve) over the dosing interval, when administered at 1 mg/kg, 3 mg/kg, or 10 mg/kg every 2 weeks. Target mediated drug disposition (non-linear PK) likely occurs at lower concentrations, i.e. at lower doses and/or at later time points than those observed in the FIH study. Based on a population PK analysis, the mean elimination half-life of cemiplimab at steady-state in patients with solid tumors is 19.2 days. To date, there is no available data on RO with cemiplimab. Steady-state exposure appears to be reached by ~120 days (after eight doses, administered every 2 weeks).

Human Safety Data with anti-PD-1 Antibodies
There are considerable safety data on the use of immune checkpoint inhibitors (ICI) in oncology patients, given approval for their use in melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer and squamous cell carcinoma of the head and neck, with expanding approvals for additional tumor types expected. Cemiplimab, along with other checkpoint blockers (e.g., anti-PD-1, anti-CTLA-4), are associated with a unique set of toxicities termed irAE. Immune-related adverse events are thought to be caused by unrestrained cellular immune responses directed at normal host tissues. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Increasing use and experience has resulted in clinical algorithms addressing the management of more common irAEs and the recognition that a high suspicion and prompt management of new symptoms which could be due to irAEs is critical [41, 42].

A meta-analysis with 21 randomized controlled trials with ICIs included data with ipilimumab, nivolumab, pembrolizumab, and atezolizumab found a higher risk of specific irAEs in those receiving an ICI versus chemotherapy including colitis, AST elevation, rash, hypothyroidism, and pneumonitis [43]. In another meta-analysis of clinical trials with ICIs, the most common irAEs associated with PD-1 inhibitors included skin rash, diarrhea and/or colitis, pneumonitis, arthralgia, endocrine disorders (thyroid dysfunction most common), hepatic dysfunction, and neurologic dysfunction [41].

Safety of nivolumab (similar PD-1 inhibitor): Most recently, an open-label phase III study randomly assigned 423 patients with untreated stage IV or recurrent NSCLC to a similar anti-PD-1 antibody, nivolumab, versus chemotherapy in a 1:1 ratio [44]. Patients in the nivolumab arm received 3 mg/kg every 2 weeks with a 3.7-month median duration of treatment in the nivolumab group. Nivolumab had similar, but not longer, progression-free survival among patients with PD-L1 expression of 5% or more. Treatment-related AEs Grade ≥3 were more common in the chemotherapy arm (51%) versus the

nivolumab arm (18%) and rates of treatment-related serious adverse events (SAEs) were similar in the two treatment groups. The most common AEs with a possible immunologic cause in the nivolumab group were skin-related AEs (24%). Hypothyroidism occurred in 17 (6.4%) patients in the nivolumab arm compared with 1 (0.4%) in the chemotherapy arm. There were seven (2.6%) reported pneumonitis AEs of any grade, with four (1.5%) Grade ≥3. There were two deaths in the nivolumab group attributed to study treatment, one due to multi-organ failure and one due to pneumonitis.

Safety Data with Cemiplimab in Oncology Patients
Overall, toxicities observed to date with cemiplimab in oncology patients/study participants are similar to those noted for FDA-approved anti-PD-1 mAbs (nivolumab and pembrolizumab), and include fatigue, pyrexia, chills, infusion reactions, skin rash, diarrhea/colitis, endocrine toxicities, hepatic toxicities (mainly asymptomatic elevations in aspartate transaminase [AST] and alanine transaminase [ALT] levels), pneumonitis, uveitis, interstitial nephritis, pancreatitis, and neurologic syndromes.

Cemiplimab is being evaluated in more than 20 phase I through phase III clinical studies. The safety profile of cemiplimab appears to be consistent across tumor types and dose of cemiplimab. Safety was obtained and assessed primarily from a pooled analysis of patients treated in non-randomized studies with cemiplimab monotherapy or cemiplimab in combination with standard chemotherapies and/or radiation therapy.

As of 27 March 2018, 757 oncology patients have been treated with cemiplimab either as monotherapy or in combination with radiotherapy and/or other cancer therapy in 7 of the ongoing studies. A total of 512 patients (67.6%) experienced at least 1 treatment-related adverse event (AE) of which 96 patients (12.7%) experienced Grade 3 or higher treatment-related AEs. Sixty-four patients (8.5%) experienced investigator-attributed treatment-related SAEs. Seven patients (0.9%) experienced fatal treatment-related AEs: two patients with hepatic failure (one patient with HCC and one patient with diffuse large B-cell lymphoma), paraneoplastic encephalomyelitis (one patient with soft tissue sarcoma), toxic epidermal necrolysis (TEN) (one patient with follicular lymphoma [FL]), nosocomial pneumonia secondary to Grade 4 mucositis (one patient with FL), and pneumonitis (two patients: one with NSCLC and one with cervical cancer) (IB Edition 6). The one patient who died due to TEN had previously received PI3K inhibitor treatment prior to enrollment on this study of cemiplimab.

In the pooled analysis, cemiplimab-related AEs occur at similar frequency in patients on cemiplimab monotherapy compared to cemiplimab combination therapy, with a few exceptions such as nausea and pruritus. The most common (>5%) treatment-related treatment emergent AEs were fatigue (17.2% patients), nausea (9.2%), diarrhea (8.2%), arthralgia (6.3%), pruritus (6.2%), rash maculo-papular (5.9%), rash (5.8%), and hypothyroidism (5.2%). Amongst the most common treatment-related AEs, nausea occurred twice as frequently in combination therapy patients, whereas pruritus occurred twice as commonly in monotherapy patients.

The most common Grade 3/4/5 treatment-related AEs for the total pooled population were pneumonitis (1.2% of patients), AST increased and autoimmune hepatitis (0.8%

each), and ALT increased and anemia (0.5% each).

Immune-related Adverse Events (IrAEs) Attributed to Study Treatment
Treatment-related AEs were characterized as potential irAEs based on a three-level approach that included a Regeneron-provided Medical Dictionary of Regulatory Activities System Organ Class (MedDRA) terms list (using known irAEs from previous studies in this class), AEs assessed as immune related by investigators (including those not on the MedDRA list), and review of these additional AEs by an independent four physician panel. A subset of potential irAEs categorized as identified irAEs were defined as potential irAEs requiring treatment with corticosteroid or events that were immune-related endocrinopathies.

A total of 339 patients (44.8%) experienced potential irAEs including 123 patients (16.2%) with identified irAEs. The majority of potential irAEs were mild to moderate. Sixty-three patients (8.3%) experienced potential irAEs of Grade 3 or higher including 53 (7.0%) with identified irAEs. Forty-nine patients (6.5%) experienced serious potential irAEs including 41 patients (5.4%) with serious identified irAEs. Thirty-three (4.4%) patients discontinued study treatment due to potential irAEs. Six patients (0.8%) experienced fatal irAEs including hepatic failure, TEN, pneumonitis, and paraneoplastic encephalomyelitis.

Potential irAEs
The most common potential irAE preferred terms and composite terms were:
- Immune-related skin adverse reactions in 123 (16.2%) patients including 13 (1.7%) patients with Grade 3-5 events;
- Immune-related colitis (including diarrhea) in 67 (8.9%) patients including 5 (0.7%) patients with Grade 3-5 events;
- Pruritus in 49 (6.5%) patients including 1 (0.1%) patient with a grade 3 event
- Arthralgia in 48 (6.3%) patients (no Grade 3-5 events);
- Immune-related hepatitis in 44 (5.8%) patients including 17 (2.2%) patients with Grade 3-5 events; and
- Hypothyroidism in 39 (5.2%) patients including 1 (0.1%) patient with a Grade 3 event.

The most common Grade 3-5 potential irAEs were:
- Immune-related hepatitis (17 [2.2%] patients);
- Immune-related skin adverse reactions (13 [1.7%] patients); and
- Immune-related pneumonitis (9 [1.2%] patients).

Identified irAEs
As of 27 March 2018, for the total pooled population, 123/757 (16.2%) of patients experienced an identified irAE including 53 (7.0%) that were Grades 3-5. The most common identified irAE composite terms were hypothyroidism (39 [5.2%] patients), immune-related pneumonitis (20 [1.2%] patients), immune-related hepatitis and immune-related skin adverse reactions (14 [1.8%] patients each), and hyperthyroidism (12 [1.6%] patients). The most common Grade 3-5 identified irAEs were immune-related hepatitis

(13 [1.7%] patients), immune-related pneumonitis (9 [1.2%] patients), and immune-related skin adverse reactions (8 [1.1%] patients). See Table 2.2-1 below for more details regarding identified irAEs attributed to cemiplimab in oncology patients (IB Edition 6).

Five (0.7%) patients presented with Type I diabetes, three with diabetic ketoacidosis, and all with ≥Grade 3 events requiring treatment.

Table 2.2-1: Summary of Most Common Treatment-Emergent irAEs

	Cemiplimab Monotherapy (N=489)		Cemiplimab Combination Therapy (N=268)		Total (N=757)	
Composite*/Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of treatment-emergent sponsor identified irAEs	121	44	51	22	172	66
Number of Patients with any treatment-emergent sponsor identified irAE, n (%)	85 (17.4%)	34 (7.0%)	38 (14.2%)	19 (7.1%)	123 (16.2%)	53 (7.0%)
Hypothyroidism*	25 (5.1%)	0	14 (5.2%)	1 (0.4%)	39 (5.2%)	1 (0.1%)
Immune related Pneumonitis*	14 (2.9%)	5 (1.0%)	6 (2.2%)	4 (1.5%)	20 (2.6%)	9 (1.2%)
Immune related hepatitis*	10 (2.0%)	9 (1.8%)	4 (1.5%)	4 (1.5%)	14 (1.8%)	13 (1.7%)
Immune related skin adverse reaction*	8 (1.6%)	5 (1.0%)	6 (2.2%)	3 (1.1%)	14 (1.8%)	8 (1.1%)
Hyperthyroidism*	7 (1.4%)	0	5 (1.9%)	1 (0.4%)	12 (1.6%)	1 (0.1%)
Arthralgia	5 (1.0%)	0	2 (0.7%)	0	7 (0.9%)	0
Immune related colitis*	6 (1.2%)	2 (0.4%)	1 (0.4%)	1 (0.4%)	7 (0.9%)	3 (0.4%)
Type 1 diabetes mellitus*	2 (0.4%)	2 (0.4%)	3 (1.1%)	3 (1.1%)	5 (0.7%)	5 (0.7%)
Adrenal insufficiency*	1 (0.2%)	1 (0.2%)	2 (0.7%)	0	3 (0.4%)	1 (0.1%)
Immune related nephritis*	2 (0.4%)	1 (0.2%)	1 (0.4%)	1 (0.4%)	3 (0.4%)	2 (0.3%)

Table 2.2-1 (*continued)*: Summary of Most Common Treatment-Emergent irAEs

Composite*/Preferred Term, n (%)	Cemiplimab Monotherapy (N=489)		Cemiplimab Combination Therapy (N=268)		Total (N=757)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Stomatitis	3 (0.6%)	1 (0.2%)	0	0	3 (0.4%)	1 (0.1%)
Arthritis*	2 (0.4%)	1 (0.2%)	0	0	2 (0.3%)	1 (0.1%)
Encephalitis*	1 (0.2%)	1 (0.2%)	1 (0.4%)	1 (0.4%)	2 (0.3%)	2 (0.3%)
Hypophysitis	2 (0.4%)	2 (0.4%)	0	0	2 (0.3%)	2 (0.3%)
Meningitis*	1 (0.2%)	1 (0.2%)	1 (0.4%)	1 (0.4%)	2 (0.3%)	2 (0.3%)
Muscular weakness	2 (0.4%)	0	0	0	2 (0.3%)	0
Myalgia*	2 (0.4%)	1 (0.2%)	0	0	2 (0.3%)	1 (0.1%)
Pruritus*	2 (0.4%)	1 (0.2%)	0	0	2 (0.3%)	1 (0.1%)
Autoimmune myocarditis*	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Blood creatine phosphokinase increased	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.2%)	0	0	0	1 (0.1%)	0
Immune thrombocytopenic purpura	1 (0.2%)	0	0	0	1 (0.1%)	0
Myasthenia gravis*	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Myositis*	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Neuropathy peripheral*	1 (0.2%)	0	0	0	1 (0.1%)	0
Pancreatitis*	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Paraneoplastic encephalomyelitis	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Sjogren's syndrome	1 (0.2%)	0	0	0	1 (0.1%)	0
Vasculitis	0	0	1 (0.4%)	0	1 (0.1%)	0

Data cut-off as of Mar 27, 2018.

Safety Data of Anti-PD-1 Antibodies in HIV-infected Patients with Cancer
There is limited available safety data of anti-PD-1 treatment in HIV-infected patients receiving treatment for cancer. In the previously described study of an anti-PD-L1 mAb in six healthy, HIV-infected participants, viral rebound was not observed following a single dose. There was one potential irAE of hypophysitis without MRI changes, which occurred 36 weeks following a single dose, and for which relatedness to study treatment could not be ruled out [25].

In a small study (N=12) HIV-infected participants received multiple doses as second line treatment with nivolumab for NSCLC (n=11) and melanoma (n=1) [45]. Partial tumor responses or stability was observed in 6/12 (50%) participants. HIV viral rebound was not observed when measured with an HIV-1 RNA ultra-sensitive quantification, with only one viral blip to 101 copies/mL in one participant, and there were no significant changes in CD4+ or CD8+ T cells counts. HIV-specific IFNγ+CD8+ cells increased from 0.1% at baseline to 0.4% (gag) at day 30 in one participant and from 0.31 to 1.31% (RT+nef) of CD8+ T cells at day 120 in another participant.

Finally, among six cART-treated HIV-infected patients who have received cemiplimab for cancer, treatment has been well-tolerated to date. We are not aware of any increase in HIV viremia during treatment, although this was not followed as an outcome measure in this study.

The Role of PD-1 and PD-L1 in Fetomaternal Tolerance
In pregnancy, maternal tolerance of the developing fetus has been shown to depend on negative signals from the PD-1/PD-L1 co-stimulatory pathway. Early work demonstrated the expression of PD-L1 in human placenta by villous syncytiotrophoblasts and cytotrophoblasts, the fetal cells which lie adjacent to maternal blood and tissue [46]. As these are the only fetal cells exposed to maternal blood and tissues, the location of PD-L1 in these cells suggests it may play a critical role in protecting the fetus against activated maternal leukocytes. Other studies have demonstrated that blockade of PD-1 [47] and PD-L1 [48] during murine pregnancy increases abortion rates, possibly related to the finding that blockade or deficiency in PD-L1 increases expansion of alloreactive T cells and diminished Treg function at the fetal-maternal interface [49]. Additional studies have implicated PD-1 in the induction of apoptosis of paternal-antigen specific T-cells at the fetal-maternal interface during pregnancy [50], and shown that PD-L1 blockade inhibits antigen-specific alloreactive T-cell apoptosis and induces apoptosis of Tregs and a shift toward higher frequency of Th17 cells, breaking fetomaternal tolerance [51]. Based on these data, strict criteria for pregnancy prevention are warranted in the study given the lack of a proven benefit of anti-PD-1 mAb in HIV+ individuals and a potential risk to the fetus.

Dose Rationale
The doses selected for this study were guided primarily by the primary objective of evaluating the safety of cemiplimab in this first study with an anti-PD-1 in otherwise healthy, HIV-infected patients. In the oncology studies with cemiplimab described above with multiple IV administrations, doses have ranged from 1.0 mg/kg to 10 mg/kg. In clinical oncology studies with both anti-PD-1 and anti-PD-L1 mAbs, efficacy of multiple doses has been shown across several dose cohorts, and in particular, in the cohorts that received 1 mg/kg and 3 mg/kg.

Multiple data sets support the dose panels selected for examination in this study. First, cemiplimab is an IgG4 subtype antibody and therefore is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity cells. In addition, incubation of cemiplimab in blood samples from healthy human donors ex vivo did not result in any significant cytokine secretion and is thus not expected to independently promote T-cell activation. Given the need to establish safety in a different patient population from those patients previously tested (advanced malignancies), an initial dose of 0.3 mg/kg was selected with dose escalation to a top dose of 3 mg/kg based on interim review of safety during the protocol.

The initial dose selected to assess safety in this population is 0.3 mg/kg dose of cemiplimab, which is lower than that commonly administered in oncology studies. A dose lower than that with confirmed efficacy related to tumor stabilization or response in the oncology studies with cemiplimab was felt to be warranted, given this is the first study of an anti-PD-1 mAb in otherwise healthy, HIV-infected participants. Further, the 0.3 mg/kg cohort is important to help clearly define PK and RO in HIV-infected individuals, in addition to safety.

The dose of 1 mg/kg was selected based on prior use in the oncology studies described above with multiple doses of cemiplimab. As immunologic and virologic responses might be anticipated at the 1 mg/kg dose, data in this cohort will provide critical information for the lower dose response curve and the safety profile in the study population. The 1 mg/kg dose also provides a conservative margin of safety with a dose escalation of 3.3-fold (0.3 to 1 mg/kg).

The highest dose of 3 mg/kg was selected given the primary objective of confirming safety in the proposed study population, and as the vast majority of patients in the oncology studies with multiple doses of cemiplimab have received the 3 mg/kg dose. Very few oncology patients have received the 10 mg/kg dose of cemiplimab, there is no clear evidence of a dose response at higher doses (>1 mg/kg) with cemiplimab and efficacy has been confirmed in oncology patients at the 3 mg/kg dose. Further, in other clinical oncology studies with both anti-PD-1 and anti-PD-L1 mAbs, efficacy of *multiple* doses has been shown primarily with 3mg/kg or the 350 mg every three weeks, fixed doses. Although there is no data on RO with cemiplimab in humans, mean peak RO of 85% at 4-24 hours and average plateau occupancy of 72% (range 59% to 81%) at 57 days and beyond was observed following one infusion of 0.3, 1.0, 3.0 or 10.0 mg/kg of nivolumab [52], suggesting sufficient binding is likely with the proposed 3 mg/kg cemiplimab dose. Given no dose-limiting toxicities were observed in pre-clinical studies in cynomolgus monkeys, dose escalation is not designed to determine a maximum tolerated dose in this study population, as unlikely to improve efficacy and to minimize risk.

Rationale for Multi-dose Study
This is a multiple dose escalation study with two doses administered 6 weeks apart. The interval of 6 weeks is designed to provide for prolonged safety assessment prior to subsequent dosing (versus every 2 week dosing in oncology patients/participants), as well as the opportunity to evaluate the kinetics of immune and viral parameters post-dosing and is supported by the observation of prolonged RO in the recent study of nivolumab in participants with HBV [36]. Importantly, the second dose will permit evaluation of a potential additive benefit on these immune and viral parameters. As above, studies of SIV in the NHP that demonstrated immune enhancement and anti-viral activity have utilized multiple dosing strategies [28].

In oncology studies there are no data on immune responses following multiple doses of cemiplimab, as oncology studies with ICIs primarily follow radiographic anti-tumor responses at approximately 6-8-week intervals following several doses, and antigen specific tumor responses are not readily identifiable in these patients. Accordingly, there are very limited data on immunologic effects following single doses or multiple doses of anti-PD-1 in oncology studies, and, to date, no data on the immunologic effect of single doses of cemiplimab. However, data suggest a potential benefit of multiple doses of anti-PD-1. In a dose escalation study of nivolumab, patients with advanced malignancies received 0.3, 1, 3, or 10 mg/kg, and patients with tumor responses at 3 months could receive additional doses. In this study, 12 patients with stable or tumor regression at the first assessment at week 8 received multiple doses, and several had improvement in tumor response following additional multiple doses [52]. Accordingly, we propose 2

doses of cemiplimab to allow evaluation of an additive benefit, but separated by 6 weeks, a longer duration than the every-2-weeks dosing schedule used in the oncology studies described above.

Rationale for Placebo
The proposed study is the first to evaluate cemiplimab in cART-suppressed individuals living with HIV. As a primary objective of the study is to evaluate the safety of cemiplimab in this study population, a placebo arm for each dose cohort is felt to be warranted and critical in the assessment of AEs, and particularly common events such as low grade diarrhea or respiratory illnesses.

Rationale for PK Sampling
For this study, a strategy will be implemented that aims to characterize cemiplimab concentrations with corresponding peripheral RO at similar time points, including maximal concentrations and throughout the elimination phase of cemiplimab, possibly including the target-mediated component of the elimination. No RO data are available for cemiplimab, and elimination data for two widely spaced doses are not available.

In the current study, cemiplimab and RO sampling time points will occur over the course of the 48-week study to define the PK and RO profile in HIV-infected participants. RO data may be useful if prolonged responses or delayed AEs are observed.

Risks versus Benefits of the Proposed Research
Given that most HIV-1-infected patients on effective ART have persistent low level viremia and despite this viremia have blunted HIV-1-specific immune responses, interventions with the potential to improve HIV-specific immunity and limit viremia should be tested. Therapies which improve HIV-1-specific immune responses will likely be a necessary component of any HIV remission or eradication strategy. Based on the data outlined above there is sufficient expectation that the proposed study will show an improvement in HIV-specific immune responses and the potential for latency reversal such that this result would advance the field. Although participants in this early phase study will receive no direct benefit for their participation in this study, there remains a strong desire among HIV-infected individuals, and the HIV community at-large, to pursue an HIV cure and remission strategies. The potential adverse effects, stigmatization and financial costs encountered by HIV-infected persons receiving life-long antiretroviral therapy along with the potential harm of persistent immune activation/inflammation are strong reasons to pursue HIV cure and remission research. In short, an HIV cure or sustained remission off therapy remain desirable goals that would have substantial benefits for many individuals if achieved.

In recognizing the risk of irAEs with the use of ICIs in the proposed study population and no immediate clinical benefit as previously seen in the setting of cancer treatment, we have attempted to mitigate risk to potential participants to the greatest degree possible. The proposed study will enroll HIV-infected participants with well-controlled HIV-1 viremia on ART and high CD4+ T cell counts without acute illness or malignancy, following a thoughtfully designed and supported dose escalation protocol with close clinical and laboratory monitoring. Risk mitigation related to study drug includes: dose

escalation starting with a dose lower than normally used in the oncology dose escalation studies; and limiting treatment to only two doses of cemiplimab versus placebo separated by 6 weeks to allow for extended safety monitoring prior to the second dose, compared with ongoing every-2-weeks dosing in cancer studies. Eligibility criteria exclude individuals with an increased risk for an irAE including but not limited to: history of an autoimmune disorder, pneumonitis, asthma, diabetes or pre-existing conditions that could make detection or attribution of a potential irAE difficult (e.g., chronic obstructive pulmonary disease [COPD]), the presence of select pre-existing auto-antibodies, or current or history of endocrine disorders. Building upon substantial experience in the cancer studies, we have adapted guidelines for toxicity management of irAEs to ensure prompt detection, appropriate management, and discontinuation of study drug in the event of an irAE.

Summary
The primary goal of this study is: 1) to test the safety of two doses of cemiplimab versus placebo in a dose rising fashion in participants on suppressive cART, and 2) to determine whether cemiplimab can improve HIV-1-specific cellular immune responses. In addition, we will evaluate the PK of cemiplimab in serum, and examine the time course of RO in whole blood. We plan to simultaneously measure and assess the impact of cemiplimab on: 1) HIV-1-specific T cell magnitude and function, 2) persistent viremia by SCA, and 3) additional measures of HIV-1 persistence in total CD4+ T cells from peripheral blood. Given that only a subset of cancer patients have responded to blockade of the PD-1/PD-L1 pathway in previous clinical trials, we will also explore whether ex vivo response to gag peptides in the presence of cemiplimab pre-treatment is associated with an in vivo response, to identify biomarker(s) predictive of a response to cemiplimab that could inform patient stratification in future studies [33].

If the goals of the study are achieved, the potential next steps would be a larger phase II multiple-dose study of cemiplimab, to further assess safety, HIV specific immune responses, and the impact on HIV reservoirs in blood and tissue, or studies in combination with latency reversing agents or HIV vaccines.

3.0 STUDY DESIGN

This trial is a phase I/II, double-blinded (within each cohort), dose-escalating, placebo-controlled study of the safety and immunotherapeutic activity of two infusions of anti-PD-1 (cemiplimab) or placebo in HIV-1-infected participants on cART who have HIV-1 RNA below the limit of quantification and CD4+ T-cell counts ≥350/mm^3. Cemiplimab (0.3 mg/kg [Cohort 1], 1 mg/kg [Cohort 2], and 3 mg/kg [Cohort 3]) or placebo will be given to 15 participants in each Cohort (12 active and 3 placebo). Participants will receive infusions of antibody or placebo at entry/day 0 and week 6, for a total of two infusions, with the primary safety endpoint through week 48 and the primary immunologic endpoint through week 12. The study will enroll sequential dose-escalating cohorts with the second and third cohorts receiving the first infusion after all participants in the previous cohort have reached week 12 and an evaluation of safety outcomes by the study team and the study monitoring committee (SMC) is completed, which determines whether to

dose escalate or not. Participants will be followed for 48 weeks with frequent safety evaluations.

Cemiplimab/placebo infusion will occur over 30 minutes via IV infusion. Safety data from Cohort 1 (first dose level) will be reviewed by the core team (blinded to treatment assignment) and an SMC, before higher doses are administered. Guidance criteria for the SMC with respect to dose escalation are described in section 10.4.1. If the first dose level is well tolerated and the core team and SMC note no safety concerns, Cohort 2 will be enrolled after Cohort 1 reaches week 12. If the second dose level is well tolerated and the core team and SMC note no safety concerns, Cohort 3 will be enrolled after Cohort 2 reaches week 12. Immunologic and virologic response data from lower dose cohort(s) may not be available prior to the enrollment of the subsequent dose cohort(s).

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 a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral assay.

NOTE: The term “licensed” refers to a US FDA-approved kit, which is required for all 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 (VL).

4.1.2 On ART for at least 24 months prior to screening.

4.1.3 Receiving a stable cART regimen (defined as no changes of the components of ART agents within 90 days prior to study entry) containing:

1) at least three ART agents (not counting ritonavir if not more than 200 mg total daily dose or cobicistat as one of the agents).

NOTE: One of the agents must include an integrase inhibitor, NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitors), or a boosted-PI (protease inhibitor).

OR

2) two ART agents in which one of the agents is either a boosted protease inhibitor or an integrase inhibitor and the 2-drug regimen is listed as an acceptable alternative regimen in the Department of Health and Human Services guidelines (https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.)

NOTE: Changes within treatment class, in drug formulation or dose are allowed >30 days prior to study entry (e.g., dolutegravir or elvitegravir to bictegravir, TDF to TAF, ritonavir to cobicistat, or separate ART agent dosing to fixed-dose combination).

4.1.4 CD4+ T cell count ≥350 cells/mm^3 obtained within 90 days prior to study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.

4.1.5 At least two documented plasma HIV-1 RNA below quantifiable limit on cART obtained by FDA-approved assays by any US laboratory that has a CLIA certification or its equivalent within 18 months prior to screening HIV RNA (section 4.1.6).

NOTE: A single unconfirmed plasma HIV-1 RNA ≥limit of quantification but <1000 copies/mL is allowed if followed by HIV-1 RNA below quantifiable limits.

4.1.6 Plasma HIV-1 RNA level that is less than the quantification limit of an FDA-approved HIV RNA assay within 90 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent.

4.1.7 The following laboratory values obtained within 90 days prior to entry by any US laboratory that has a CLIA certification or its equivalent.

- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Hemoglobin ≥14.0 g/dL for men and ≥12.0 g/dL for women
- Platelet count ≥150,000/mm^3
- Creatinine clearance ≥60 mL/min estimated by the Cockcroft-Gault equation

NOTE: A program for calculating creatinine clearance by the Cockcroft-Gault method is available on www.frontierscience.org.

- Alanine aminotransferase (ALT) (SGPT) ≤upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (SGOT) ≤ULN
- AM cortisol >10 mcg/dL and <ULN

NOTE A: Female participants on estrogen-containing oral contraception or other exogenous estrogen treatment may repeat the AM cortisol as part of screening to determine eligibility. AM cortisol should be drawn as early as possible before 9:00AM, and should not be drawn later than 10:00 AM.

NOTE B: Participants with a low cortisol level that was drawn after 10:00 AM may repeat the AM cortisol as part of screening to determine eligibility.

- Thyroid stimulating hormone (TSH) within normal limits
- Free thyroxine (T4) level within normal limits
- Hemoglobin A1c (HgbA1c) <5.7%
- Fasting blood glucose <110 mg/dL
- Total bilirubin ≤1.6 x ULN

NOTE: If the participant is on an atazanavir-containing therapy then a direct bilirubin should be measured instead of the total bilirubin and must be ≤1.0 mg/dL.

4.1.8 Interferon-gamma release assay (IGRA) for tuberculosis (TB) with negative results within 90 days prior to study entry, OR

Prior positive TB IGRA or positive purified protein derivative (PPD) skin test with documented evidence of completed prophylaxis treatment (NOTE: IGRA does not need to be repeated at screening). These potential participants cannot have had TB exposure or have traveled to a TB-endemic area since completing prophylaxis treatment. A list of countries with high TB burden is accessible via the following link: http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf.

4.1.9 HCV antibody negative result within 60 days prior to study entry or, if the participant is HCV antibody positive, undetectable HCV RNA result within 60 days prior to study entry.

4.1.10 Negative HBsAg result obtained within 60 days prior to study entry.

4.1.11 Negative results for all of the following antibody tests at screening: thyroid peroxidase (TPO), glutamic acid decarboxylase 65 (GAD65/GAD), and islet cell antigen.

4.1.12 Antinuclear antibody (ANA) <1:80 at screening.

4.1.13 Men and women age ≥18 years and <65 years.

4.1.14 Documentation of the availability of the stored pre-entry plasma specimens for virology assays and stored pre-entry peripheral blood mononuclear cell (PBMC) specimens for CD8+ T-cell assays. Sites must receive confirmation from the processing lab via phone, e-mail, or fax, that specimens have been entered into the ACTG's Laboratory Data Management System (LDMS).

4.1.15 Ability and willingness of participant to provide informed consent.

4.1.16 Ability and willingness of participant to continue cART throughout the study.

4.1.17 In the opinion of the site investigator, the ability to construct a fully active alternative cART regimen in the event of virologic failure on the current ART regimen.

4.1.18 Female participants of reproductive potential (defined as women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy or bilateral salpingectomy) must have a negative serum pregnancy test with a sensitivity of at least 25 mIU/mL performed at screening, and a serum or urine pregnancy test within 48 hours prior to study entry.

4.1.19 All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization, egg donation) during the study.

4.1.20 When participating in sexual activity that could lead to pregnancy, all participants must agree to use at least two reliable forms of contraception simultaneously during the study (i.e., entry through week 48). Such methods include:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptive

4.1.21 Participants who are not of reproductive potential (women who have been post-menopausal for at least 24 consecutive months or have undergone hysterectomy and/or bilateral oophorectomy or salpingectomy or men who have documented azoospermia or undergone vasectomy) are eligible without requiring the use of contraceptives. Acceptable documentation of sterilization and menopause is specified below.

Written or oral documentation communicated by clinician or clinician's staff of one of the following:

- Physician report/letter
- Operative report or other source documentation in the patient record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary
- Follicle stimulating hormone-release factor (FSH) measurement elevated into the menopausal range as established by the reporting laboratory

4.1.22 Weight ≥50 kg

4.2 Exclusion Criteria

4.2.1 History of malignancy within the last 5 years.

NOTE: A history of non-melanoma skin cancer (e.g., basal cell carcinoma or squamous cell skin cancer) is not exclusionary with documentation of complete resection at least 3 months prior to enrollment).

4.2.2 History of HIV-related opportunistic infections within the last 5 years prior to study entry.

NOTE: The CDC classifications are available on the A5370 PSWP.

4.2.3 Prior history of immune reconstitution syndrome (IRIS), including a clinical diagnosis of IRIS and/or IRIS requiring intervention (e.g., steroids).

4.2.4 Current chronic, acute, or recurrent bacterial, fungal or viral (other than HIV) infections that are serious, in the opinion of the site investigator, and required systemic therapy within 30 days prior to entry.

4.2.5 History of COPD.

4.2.6 History of prior radiation therapy.

4.2.7 Active or previously treated active TB.

4.2.8 Active asthma requiring any treatment in the prior 2 years, including "as needed" inhaler use prior to study entry.

4.2.9 Type I or type II diabetes mellitus.

4.2.10 History of or active autoimmune disorders including but not limited to inflammatory bowel diseases, scleroderma, severe psoriasis, myocarditis, uveitis, pneumonitis, systemic lupus erythematosus, rheumatoid arthritis, optic neuritis,

myasthenia gravis, adrenal insufficiency, hypothyroidism and/or hyperthyroidism, autoimmune thyroiditis, hypophysitis, or sarcoidosis.

NOTE: For questions related to the definition of autoimmune disorders, sites should contact the team per the Study Management section.

4.2.11 Immune deficiency other than that caused by HIV infection.

4.2.12 Currently breastfeeding or pregnant.

4.2.13 Known allergy/sensitivity or any hypersensitivity to mAb-based biologics, cemiplimab (anti-PD-1) or its formulation.

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

4.2.15 Received investigational drug or device within 6 months prior to study entry.

4.2.16 Use of immunomodulators (e.g., interleukins, interferons, cyclosporine, systemic corticosteroids exceeding physiologic doses), HIV vaccine, or systemic cytotoxic chemotherapy within 60 days prior to study entry.

NOTE: Participants receiving stable physiologic glucocorticoid doses, defined as prednisone ≤10 mg/day or the equivalent, will not be excluded. Stable physiologic glucocorticoid doses should not be discontinued for the duration of the study. In addition, participants receiving topical corticosteroids will not be excluded.

4.2.17 Intent to use immunomodulators (e.g., IL-2, IL-12, interferons, systemic corticosteroids exceeding physiologic doses, or TNF modifiers) during the course of the study.

4.2.18 Any vaccination within 30 days prior to pre-entry or entry.

NOTE: Individuals who require vaccination will delay screening for the study until 30 days after receiving the last injection.

4.2.19 HCV treatment within 6 months prior to study entry.

4.2.20 Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the participant ineligible for participation.

4.2.21 History of solid organ transplant.

NOTE: Participants with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the study medical officer.

4.2.22 History of previous treatment with a phosphoinositide 3-kinase inhibitor, including idelalisib.

4.2.23 History of prior checkpoint inhibitor treatment including anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies (including ipilimumab).

4.2.24 History of prior immunoglobulin (IgG) therapy.

4.2.25 Current use or intent to use biotin ≥5 mg/day, including within dietary supplements during the study.

NOTE: Please see section 5.4 for a list of other names used for biotin that should be looked for on the labels of dietary supplements.

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 their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). 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 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 required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO, and 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 with the participant. 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.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the DMC Subject 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 initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

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

4.4 Co-enrollment Guidelines

Sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5370 protocol chairs.

Co-enrollment with A5332 (REPRIEVE) and substudies of REPRIEVE- A5333s and A5361s- will be permitted as long as A5332 participants have reached the 1 year visit for that study.

For specific questions and approval for co-enrollment in other studies, sites should first check the A5370 PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY INTERVENTION

Study treatment is defined as two infusions of REGN2810 (cemiplimab) or placebo. cART will not be provided by the study.

5.1 Intervention, Administration, and Duration

5.1.1 Regimens

Forty-five HIV-1-infected participants will be sequentially assigned to one of three cohorts, beginning with the lowest dose cohort:

Cohort 1: Participants will receive 0.3 mg/kg of REGN2810 (cemiplimab) or placebo, administered at entry/day 0 and week 6 for a total of two infusions.

Cohort 2: Participants will receive 1 mg/kg of REGN2810 (cemiplimab) or placebo, administered at entry/day 0 and week 6 for a total of two infusions.

Cohort 3: Participants will receive 3 mg/kg of REGN2810 (cemiplimab) or placebo, administered at entry/day 0 and week 6 for a total of two infusions.

5.1.2 Administration

REGN2810 (cemiplimab)/placebo infusion will occur over 30 minutes via intravenous (IV) infusion.

REGN2810 (cemiplimab) or diluent for REGN2810 (placebo) will be administered as an intravenous infusion mini-bag piggybacked onto a primary line of 0.9% sodium chloride for injection, USP. After infusing the REGN2810 (cemiplimab) or placebo for REGN2810 (cemiplimab) (diluent for REGN2810), flush the IV tubing with 0.9% sodium chloride for injection, USP.

Administration of intravenous REGN2810 (cemiplimab) or diluent for REGN2810 (cemiplimab) must include the use of a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter is required for dosing. The total volume of the infusion will vary with the dose and participant weight. The infusion rate will vary based on the total volume needed to administer the full dose. Infusion access should be maintained and the participant observed for a minimum of 2 hours following completion of the first infusion and for a minimum of 30 minutes following the second infusion (see section 8.0 for further detail).

5.1.3 Duration

Participants will be followed for a total of 48 weeks after the first infusion of study drug.

5.2 Study Product Formulation and Preparation

REGN2810 (cemiplimab) (50 mg/mL) is formulated in an aqueous buffered solution at pH 6.0 containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L proline, and 0.2% (w/v) polysorbate 80. REGN2810 drug product is supplied as a sterile liquid solution of 5.5 mL in a 20 mL glass vial for IV administration. A volume of 5.0 mL can be withdrawn from each vial. Vials are for single use only.

Diluent for REGN2810 (cemiplimab) is an aqueous buffered solution at pH 6.0 containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L proline, and 0.2% (w/v) polysorbate 80. Diluent for REGN2810 (cemiplimab) will be used for 0.3 mg/kg cohort to prevent REGN2810 (cemiplimab) from binding to the bags and tubing when the REGN2810 (cemiplimab) is at low concentrations. Diluent for REGN2810 (cemiplimab) will also be used for the placebo for REGN2810 (cemiplimab) in all dose cohorts.

Store REGN2810 (cemiplimab) vials and diluent for REGN2810 (cemiplimab) vials at 2°C to 8°C.

Any unused portion of a REGN2810 (cemiplimab) vial will not be used for another participant.
The nurse responsible for administration and another clinician will each check the bag label and confirm that the identifier is correct and that the correct total milligrams to be administered is shown based on participant weight and the assigned mg/kg dose before beginning the IV administration.

5.2.1 REGN2810 (cemiplimab) 0.3 mg/kg Dose Cohort: Preparation for Intravenous Administration

The REGN2810 (cemiplimab) 0.3 mg/kg dose cohort requires the use of the diluent for REGN2810 (cemiplimab). REGN2810 (cemiplimab) must NOT be diluted lower than 1.0 mg/mL without adding diluent.

Preparation of REGN2810 (cemiplimab) for IV administration will require either sterile empty IV bags made of polyvinyl chloride (PVC) or polyolefin (polyethylene and polypropylene) or 25 mL bags of 0.9% sodium chloride for injection, USP (normal saline), REGN2810 (cemiplimab) and diluent for REGN2810 (cemiplimab).

For each IV infusion order, the participant's weight and assigned treatment dose will be included in the pharmacy order.

1. Remove the vial(s) of REGN2810 (cemiplimab) and diluent from the refrigerator.
2. Observe vial(s) for damages, discoloration or particles.
3. Using aseptic technique in compliance with USP <797>

a. Add 25 mL of 0.9% sodium chloride for injection, USP to the empty sterile IV bag (or start with a pre-made, commercially available 25 mL bag of 0.9% sodium chloride for injection, USP).
b. Add 1 mL of diluent for REGN2810 (cemiplimab) to the bag. Invert the bag 10 times to mix thoroughly.
c. Using a 1 mL polypropylene syringe for volumes less than 0.8 mL or a 3 mL polypropylene syringe for larger volumes, withdraw the correct volume of REGN2810 (cemiplimab) from the REGN2810 (cemiplimab) vial for the participant's weight based on Table 5.2.2-1 below.
d. Add the appropriate volume of REGN2810 (cemiplimab) to the IV bag then invert the IV bag 10 times to ensure that the investigational product and 0.9% sodium chloride are well mixed.

4. Label the IV bag with patient identifier, protocol number, REGN2810 (cemiplimab) x (mg) or placebo for REGN2810 (cemiplimab) in 0.9% sodium chloride Injection, USP, the final volume of the bag, final concentration, directions to infuse intravenously over 30 minutes the entire contents of the infusion bag plus sufficient volume of 0.9%. sodium chloride Injection, USP to flush the tubing, preparation date and time, expiration time of 8 hours after dilution if stored at controlled room temperature (15°C to 25°C) or 24 hours if refrigerated at 2°C to 8°C, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

If using a commercially available 25 mL mini-bag of 0.9% sodium chloride, USP then the final concentration must be calculated based on the best estimate of the total volume.

Expiration time includes the duration of infusion.

5.2.2 Placebo for REGN2810 (cemiplimab) 0.3 mg/kg Dose Cohort: Preparation for Intravenous Administration

Placebo for REGN2810 (cemiplimab) 0.3 mg/kg requires the use of two volumes of the diluent for REGN2810 (cemiplimab), the first as the diluent (1 mL per bag) and the second as placebo for REGN2810 (cemiplimab) calculated volume based on the participant's weight (0.006 mL/kg).

Preparation of placebo REGN2810 (cemiplimab) for IV administration will require either sterile empty IV bags made of PVC or polyolefin (polyethylene and polypropylene) or 25 mL bags of 0.9% sodium chloride for injection, USP (normal saline), and diluent for REGN2810 (cemiplimab).

For each IV infusion order, the participant's weight and assigned treatment dose will be included in the pharmacy order.

1. Remove the vial of diluent for REGN2810 (cemiplimab) from the refrigerator.
2. Observe vial for damages, discoloration or particles.
3. Using aseptic technique in compliance with USP <797>

a. Add 25 mL of 0.9% sodium chloride for injection, USP to the empty sterile IV bag (or start with a pre-made, commercially available 25 mL bag of 0.9% sodium chloride for injection, USP)
b. Add to the bag the:
   i. 1 mL of diluent for REGN2810 (cemiplimab) plus
   ii. Correct volume of diluent for REGN2810 (cemiplimab) for the participant's weight based on Table 5.2.2-1 below.

4. Invert the bag 10 times to mix thoroughly to ensure the investigational product and 0.9% sodium chloride are well mixed.
5. Label the IV bag with patient identifier, protocol number, REGN2810 (cemiplimab) x (mg) or placebo for REGN2810 (cemiplimab) in 0.9% sodium chloride Injection, USP, the final volume of the bag, final concentration, directions to infuse intravenously over 30 minutes the entire contents of the infusion bag plus sufficient volume of 0.9% sodium chloride Injection, USP to flush the tubing, preparation date and time, expiration time of 6 hours after dilution if stored at controlled room temperature (15°C to 25°C) or 24 hours if refrigerated at 2°C to 8°C, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

   If using a commercially available 25 mL mini-bag of 0.9% sodium chloride, USP then the final concentration must be calculated based on the best estimate of the total volume.

   Expiration time includes the duration of infusion.

Table 5.2.2-1: 0.3 mg/kg REGN2810 (Cemiplimab) Dose Calculation Table with Volumes to Add to Sterile Empty IV Bag

Weight Band in kg Based on Entry Weight	Volume of 0.9% Sodium Chloride for Injection	Volume of Diluent to Add	Dose in mg	Drug Volume of REGN2810/ Cemiplimab or Diluent to Add to Bag	Total Volume in Bag	Concentration
50 kg to <60 kg	25 mL	1 mL	16 mg	0.32 mL	26.32 mL	0.61 mg/ mL
60 kg to <70 kg	25 mL	1 mL	19 mg	0.38 mL	26.38 mL	0.72 mg/ mL
70 kg to <80 kg	25 mL	1 mL	22 mg	0.44 mL	26.44 mL	0.83 mg/ mL
80 kg to <90 kg	25 mL	1 mL	25 mg	0.5 mL	26.5 mL	0.94 mg/ mL
90 kg to <100 kg	25 mL	1 mL	28 mg	0.56 mL	26.56 mL	1.05 mg/ mL
100 kg to <110 kg	25 mL	1 mL	31 mg	0.62 mL	26.62 mL	1.16 mg/mL
110 kg to <120 kg	25 mL	1 mL	34 mg	0.68 mL	26.68 mL	1.27 mg/ mL
120 kg to <130 kg	25 mL	1 mL	37 mg	0.74 mL	26.72 mL	1.38 mg/ mL
130 kg to <140 kg	25 mL	1 mL	40 mg	0.8 mL	26.8 mL	1.49 mg/ mL
140 kg to <150 kg	25 mL	1 mL	43 mg	0.86 mL	26.86 mL	1.6 mg/ mL
150 kg to <160 kg	25 mL	1 mL	46 mg	0.92 mL	29.91 mL	1.71 mg/ mL

160 kg to <170 kg	25 mL	1 mL	49 mg	0.98 mL	29.98 mL	1.82 mg/ mL
170 kg to <180 kg	25 mL	1 mL	52 mg	1.04 mL	27.04 mL	1.92 mg/ mL
180 kg to <190 kg	25 mL	1 mL	55 mg	1.1 mL	27.1 mL	2.03 mg/ mL
190 kg to <200 kg	25 mL	1 mL	58 mg	1.16 mL	27.16mL	2.14 mg/ mL

5.2.3 REGN2810 (cemiplimab) 1 mg/kg Dose Cohort: Preparation for Intravenous Administration

Preparation of REGN2810 (cemiplimab) for IV administration will require either sterile empty IV bags made of PVC or polyolefin (polyethylene and polypropylene) or 25 mL bags of 0.9% sodium chloride for injection, USP (normal saline), and REGN2810 (cemiplimab).

For each IV infusion order, the participant's weight and assigned treatment dose will be included in the pharmacy order.

1. Remove the vial of REGN2810 (cemiplimab) from the refrigerator.
2. Observe vial for damages, discoloration or particles.
3. Using aseptic technique in compliance with USP <797>
   a. Add 25 mL of 0.9% sodium chloride for injection, USP to the empty sterile IV bag (or start with a pre-made, commercially available 25 mL bag of 0.9% sodium chloride for injection, USP).
   b. Using a 3 mL or 5 mL polypropylene syringe withdraw the correct volume of REGN2810 (cemiplimab) from the REGN2810 (cemiplimab) vial for the participant's weight based on Table 5.2.4-1 below.
   c. Add the appropriate volume of REGN2810 (cemiplimab) to the IV bag then invert the IV bag 10 times to ensure that the investigational product and 0.9% sodium chloride are well mixed.
4. Label the IV bag with patient identifier, protocol number, REGN2810 (cemiplimab) x(mg) or placebo for REGN2810 (cemiplimab) in 0.9% sodium chloride Injection, USP, the final volume of the bag, final concentration, directions to infuse intravenously over 30 minutes the entire contents of the infusion bag plus sufficient volume of 0.9% sodium chloride Injection, USP to flush the tubing, preparation date and time, expiration time of 6 hours after dilution if stored at controlled room temperature (15°C to 25°C) or 24 hours if refrigerated at 2°C to 8°C, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

   If using a commercially available 25 mL mini-bag of 0.9% sodium chloride, USP than the final concentration must be calculated based on the best estimate of the total volume.

   Expiration time includes the duration of infusion.

5.2.4 Placebo for REGN2810 (cemiplimab) 1 mg/kg Dose Cohort: Preparation for Intravenous Administration

Preparation of placebo for REGN2810 (cemiplimab) for IV administration will require either sterile empty IV bags made of PVC or polyolefin (polyethylene and polypropylene) or 25 mL bags of 0.9% sodium chloride for injection, USP (normal saline) and diluent for REGN2810 (cemiplimab).

For each IV infusion order, the participant's weight and assigned treatment dose will be included in the pharmacy order.

1. Remove the vial of diluent for REGN2810 (cemiplimab) from the refrigerator.
2. Observe vial for damages, discoloration or particles
3. Using aseptic technique in compliance with USP <797>
   a. Add 25 mL of 0.9% sodium chloride for injection, USP to the empty sterile IV bag (or start with a pre-made, commercially available 25 mL bag of 0.9% sodium chloride for injection, USP).
   b. Using a 3 mL or 5 mL polypropylene syringe withdraw the correct volume of diluent for REGN2810 (cemiplimab) from the diluent for REGN2810 vial for the participant's weight based on Table 5.2.4-1 below.
   c. Add the appropriate volume of diluent for REGN2810 (cemiplimab) to the IV bag then invert the IV bag 10 times to ensure that the investigational product and 0.9% sodium chloride are well mixed.
4. Label the IV bag with patient identifier, protocol number, REGN2810 (cemiplimab) x (mg) or placebo for REGN2810 (cemiplimab) in 0.9% sodium chloride Injection, USP, the final volume of the bag, final concentration, directions to infuse intravenously over 30 minutes the entire contents of the infusion bag plus sufficient volume of 0.9% sodium chloride Injection, USP to flush the tubing, preparation date and time, expiration time of 6 hours after dilution if stored at controlled room temperature (15°C to 25°C) or 24 hours if refrigerated at 2°C to 8°C, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

   If using a commercially available 25 mL mini-bag of 0.9% sodium chloride, USP then the final concentration must be calculated based on the best estimate of the total volume.

   Expiration time includes the duration of infusion.

Table 5.2.4-1: 1 mg/kg REGN2810 (Cemiplimab) Dose Calculation Table with Volumes to Add to Sterile Empty IV Bag

Weight Band in KG Based on Entry Weight	Volume of 0.9% Sodium Chloride for Injection	Dose in mg	Drug Volume of REGN2810/ Cemiplimab or Diluent to Add to Bag	Total Volume in Bag	Concentration
50 kg to <55 kg	25 mL	50 mg	1 mL	26 mL	1.92 mg/mL
55 kg to <60 kg	25 mL	55 mg	1.1 mL	26.1 mL	2.11 mg/mL
60 kg to <65 kg	25 mL	60 mg	1.2 mL	26.2 mL	2.29 mg/mL
65 kg to <70 kg	25 mL	65 mg	1.3 mL	26.3mL	2.47 mg/mL
70 kg to <75 kg	25 mL	70 mg	1.4 mL	26.4 mL	2.65 mg/mL
75 kg to <80 kg	25 mL	75 mg	1.5 mL	26.5 mL	2.83 mg/mL
80 kg to <85 kg	25 mL	80 mg	1.6 mL	26.6 mL	3.01 mg/mL
85 kg to <90 kg	25 mL	85 mg	1.7 mL	26.7 mL	3.18 mg/mL
90 kg to <95 kg	25 mL	90 mg	1.8 mL	26.8 mL	3.36 mg/mL
95 kg to <100 kg	25 mL	95 mg	1.9 mL	26.9 mL	3.53 mg/mL
100 kg to <105 kg	25 mL	100 mg	2 mL	27 mL	3.7 mg/mL
105 kg to <110 kg	25 mL	105 mg	2.1 mL	27.1 mL	3.87 mg/mL
110 kg to <115 kg	25 mL	110 mg	2.2 mL	27.2 mL	4.04 mg/mL
115 kg to <120 kg	25 mL	115 mg	2.3 mL	27.3 mL	4.21 mg/mL
120 kg to <125 kg	25 mL	120 mg	2.4 mL	27.4 mL	4.38 mg/mL
125 kg to <130 kg	25 mL	125 mg	2.5 mL	27.5 mL	4.55 mg/mL
130 kg to <135 kg	25 mL	130 mg	2.6 mL	27.6 mL	4.71 mg/mL
135 kg to <140 kg	25 mL	135 mg	2.7 mL	27.7 mL	4.87 mg/mL
140 kg to <145 kg	25 mL	140 mg	2.8 mL	27.8 mL	5.04 mg/mL
145 kg to <150 kg	25 mL	145 mg	2.9 mL	27.9 mL	5.20 mg/mL
150 kg to <155 kg	25 mL	150 mg	3 mL	28 mL	5.36 mg/mL
155 kg to <160 kg	25 mL	155 mg	3.1 mL	28.1 mL	5.52 mg/mL
160 kg to <165 kg	25 mL	160 mg	3.2 mL	28.2 mL	5.67 mg/mL
165 kg to <170 kg	25 mL	165 mg	3.3 mL	28.3 mL	5.83 mg/mL
170 kg to <175 kg	25 mL	170 mg	3.4 mL	28.4 mL	5.99 mg/mL
175 kg to <180 kg	25 mL	175 mg	3.5 mL	28.5 mL	6.14 mg/mL
180 kg to <185 kg	25 mL	180 mg	3.6 mL	28.6 mL	6.29 mg/mL
185 kg to <190 kg	25 mL	185 mg	3.7 mL	28.7 mL	6.45 mg/mL
190 kg to <195 kg	25 mL	190 mg	3.8 mL	28.8 mL	6.6 mg/mL
195 kg to <200 kg	25 mL	195 mg	3.9 mL	28.9 mL	6.75 mg/mL

5.2.5 REGN2810 (cemiplimab) 3 mg/kg Dose Cohort: Preparation for Intravenous Administration

Preparation of REGN2810 (cemiplimab) for IV administration will require either sterile empty IV bags made of PVC or polyolefin (polyethylene and polypropylene) or 25 mL bags of 0.9% sodium chloride for injection, USP (normal saline) and REGN2810 (cemiplimab).

For each IV infusion order, the participant's weight and assigned treatment dose will be included in the pharmacy order.

1. Remove the vial(s) of REGN2810 (cemiplimab) from the refrigerator.
2. Observe vial(s) for damages, discoloration or particles.
3. Using aseptic technique in compliance with USP <797>
   a. Add 25 mL of 0.9% sodium chloride for injection, USP to the empty sterile IV bag (or start with a pre-made, commercially available 25 mL bag of 0.9% sodium chloride for injection, USP).
   b. Using a 3 mL, 5 mL, or 10 mL polypropylene syringe withdraw the correct volume of REGN2810 from the REGN2810 (cemiplimab) vial for the participant's weight based on Table 5.2.6-1 below.
   c. Add the appropriate volume of REGN2810 (cemiplimab) to the IV bag then invert the IV bag 10 times to ensure that the investigational product and 0.9% sodium chloride are well mixed.
4. Label the IV bag with patient identifier, protocol number, REGN2810 (cemiplimab) x (mg), or placebo for REGN2810 (cemiplimab) in 0.9% sodium chloride Injection, USP, the final volume of the bag, final concentration, directions to infuse intravenously over 30 minutes the entire contents of the infusion bag plus sufficient volume of 0.9% sodium chloride Injection, USP to flush the tubing, preparation date and time, expiration time of 6 hours after dilution if stored at controlled room temperature (15°C to 25°C) or 24 hours if refrigerated at 2°C to 8°C, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.
   If using a commercially available 25 mL mini-bag of 0.9% sodium chloride, USP then the final concentration must be calculated based on the best estimate of the total volume.

   Expiration time includes the duration of infusion.

5.2.6 Placebo for REGN2810 (cemiplimab) 3 mg/kg Dose Cohort: Preparation for Intravenous Administration

Preparation of placebo for IV administration will require either sterile empty IV bags made of PVC or polyolefin (polyethylene and polypropylene) or 25 mL bags of 0.9% sodium chloride for injection, USP (normal saline) and diluent for REGN2810 (cemiplimab).

For each IV infusion order, the participant's weight and assigned treatment dose will be included in the pharmacy order.

1. Remove the vial(s) of diluent for REGN2810 (cemiplimab) from the refrigerator.
2. Observe vial(s) for damages, discoloration or particles.
3. Using aseptic technique in compliance with USP <797>
   a. Add 25 mL of 0.9% sodium chloride for injection, USP, to the empty sterile IV bag (or start with a pre-made, commercially available 25 mL bag of 0.9% sodium chloride for injection, USP).
   b. Using a 3 mL, 5 mL, or 10 mL polypropylene syringe withdraw the correct volume of diluent for REGN2810 (cemiplimab) from the diluent for REGN2810 (cemiplimab) vial for the participant's weight based on Table 5.2.6-1 below.
   c. Add the appropriate volume of diluent for REGN2810 (cemiplimab) to the IV bag then invert the IV bag 10 times to ensure that the investigational product and 0.9% sodium chloride are well mixed.
4. Label the IV bag with patient identifier, protocol number, REGN2810 (cemiplimab) x(mg) or placebo for REGN2810 (cemiplimab) in 0.9% sodium chloride Injection, USP, the final volume of the bag, final concentration, directions to infuse intravenously over 30 minutes the entire contents of the infusion bag plus sufficient volume of 0.9% sodium chloride Injection, USP to flush the tubing, preparation date and time, expiration time of 6 hours after dilution if stored at controlled room temperature (15°C to 25°C) or 24 hours if refrigerated at 2°C to 8°C, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

   If using a commercially available 25 mL mini-bag of 0.9% sodium chloride, USP, then the final concentration must be calculated based on the best estimate of the total volume.

   Expiration time includes the duration of infusion.

Table 5.2.6-1: 3 mg/kg REGN2810 (Cemiplimab) Dose Calculation Table with Volumes to Add to Sterile Empty IV Bag

Weight Band in KG Based on Entry Weight	Volume of 0.9% Sodium Chloride for Injection	Dose in mg	Drug volume of REGN2810/ Cemiplimab or Diluent to Add to Bag	Total Volume in Bag	Concentration
50 kg to <55 kg	25 mL	150 mg	3 mL	28 mL	5.36 mg/mL
55 kg to <60 kg	25 mL	165 mg	3.3 mL	28.3 mL	5.83 mg/mL
60 kg to <65 kg	25 mL	180 mg	3.6 mL	28.6 mL	6.29 mg/mL
65 kg to <70 kg	25 mL	195 mg	3.9 mL	28.9 mL	6.75 mg/mL
70 kg to <75 kg	25 mL	210 mg	4.2 mL	29.2 mL	7.19 mg/mL
75 kg to <80 kg	25 mL	225 mg	4.5 mL	29.5 mL	7.63 mg/mL
80 kg to <85 kg	25 mL	240 mg	4.8 mL	29.8 mL	8.05 mg/mL
85 kg to <90 kg	25 mL	255 mg	5.1 mL	30.1 mL	8.47 mg/mL

Weight Band in KG Based on Entry Weight	Volume of 0.9% Sodium Chloride for Injection	Dose in mg	Drug volume of REGN2810/ Cemiplimab or Diluent to Add to Bag	Total Volume in Bag	Concentration
90 kg to <95 kg	25 mL	270 mg	5.4 mL	30.4 mL	8.88 mg/mL
95 kg to <100 kg	25 mL	285 mg	5.7 mL	30.7 mL	9.28 mg/mL
100 kg to <105 kg	25 mL	300 mg	6 mL	31 mL	9.68 mg/mL
105 kg to <110 kg	25 mL	315 mg	6.3 mL	31.3 mL	10.06 mg/mL
110 kg to <115 kg	25 mL	330 mg	6.6 mL	31.6 mL	10.44 mg/mL
115 kg to <120 kg	25 mL	345 mg	6.9 mL	31.9 mL	10.82 mg/mL
120 kg to <125 kg	25 mL	360 mg	7.2 mL	32.2 mL	11.18 mg/mL
125 kg to <130 kg	25 mL	375 mg	7.5 mL	32.5 mL	11.54 mg/mL
130 kg to <135 kg	25 mL	390 mg	7.8 mL	32.8 mL	11.89 mg/mL
135 kg to <140 kg	25 mL	405 mg	8.1 mL	33.1 mL	12.24 mg/mL
140 kg to <145 kg	25 mL	420 mg	8.4 mL	33.4 mL	12.57 mg/mL
145 kg to <150 kg	25 mL	435 mg	8.7 mL	33.7 mL	12.91 mg/mL
150 kg to <155 kg	25 mL	450 mg	9 mL	34 mL	13.24 mg/mL
155 kg to <160 kg	25 mL	465 mg	9.3 mL	34.3 mL	13.56 mg/mL
160 kg to <165 kg	25 mL	480 mg	9.6 mL	34.6 mL	13.87 mg/mL
165 kg to <170 kg	25 mL	495 mg	9.9 mL	34.9 mL	14.18 mg/mL
170 kg to <175 kg	25 mL	510 mg	10.2 mL	35.2 mL	14.49 mg/mL
175 kg to <180 kg	25 mL	525 mg	10.5 mL	35.5 mL	14.79 mg/mL
180 kg to <185 kg	25 mL	540 mg	10.8 mL	35.8 mL	15.08 mg/mL
185 kg to <190 kg	25 mL	555 mg	11.1 mL	36.1 mL	15.37 mg/mL
190 kg to <195 kg	25 mL	570 mg	11.4 mL	36.4 mL	15.66 mg/mL
195 kg to <200 kg	25 mL	585 mg	11.7 mL	36.7 mL	15.94 mg/mL

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

REGN2810 (cemiplimab) and diluent for REGN2810 (cemiplimab) provided by Regeneron Pharmaceuticals, Inc., will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the United States in NIAID (DAIDS)-supported and/or -sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf.

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. All unused study products in US CRSs 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 in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

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.

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

5.4.1 Required Medications

Participants must be on ART (not provided by the study) as specified in the inclusion criteria (section 4.1.3).

5.4.2 Prohibited Medications

Vaccinations are not allowed 30 days prior to any study visit.

- Cytotoxic chemotherapy
- Systemic immunosuppression (e.g. cyclosporin), except:
  - If indicated for treatment of toxicity or a life-threatening emergency.
- Systemic corticosteroids, except:
  - Topical corticosteroids
  - Physiologic prednisone doses ≤10 mg/day (or prednisone equivalent)
  - If indicated for treatment of toxicity or a life-threatening emergency
  - Brief course for prophylaxis (e.g., contrast dye allergy)
  - Brief treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen)
- Inhaled steroids for reactive airway disease (e.g., asthma) (see section 4.2.8), except:
  - If indicated for treatment of toxicity or a life-threatening emergency.
- Immunomodulators (e.g., IL-2 or IL-12)
- HIV vaccine
- Investigational drug
- IgG antibody therapy
- Checkpoint inhibitors including anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies (including ipilimumab).

- Phosphoinositide 3-kinase inhibitors, including idelalisib
- Biotin ≥5 mg/day

  NOTE: Biotin may also be listed as an ingredient in products (by itself or in supplements with multiple ingredients) by one of the following names: Factor S, vitamin B7, vitamin B complex, vitamin H, Biotina, Biotine, Biotine-D, Coenzyme R, D-Biotin, W Factor.

5.4.3 Precautionary Medications

- Biotin >1 mg/day and <5 mg/day

NOTE A: Biotin may also be listed as an ingredient in products (by itself or in supplements with multiple ingredients) by one of the following names: Factor S, vitamin B7, vitamin B complex, vitamin H, Biotina, Biotine, Biotine-D, Coenzyme R, D-Biotin, W Factor.

NOTE B: If a participant is taking a biotin dose within this range, the site-specific laboratory where the participant will have laboratory tests performed will need to be contacted by the core team. Any immunoassays that may be subject to biotin interference will need to have their package insert reviewed to supply the team with the manufacturer's recommendation for use of the assay with participants receiving biotin supplementation.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: SOE: Screening through Week 48

Evaluation	Screening	Pre-Entry	Entry/Day 0	Post-entry Evaluations (Weeks)														Premature Study Discontinuation (D/C) Visit	Confirm Virologic Failure (if needed)
				1	2	4	6	7	8	10	12	16	20	24	28	36	48		
Window	Between 60-90 days prior to entry	Between 30 and 50 days prior to entry	≤24 hours post-randomization	±2 days	-2/+7 days		±2 days		-2/+7 days										
Documentation of HIV-1 Infection	X																		
Medical History	X		X																
Medication History	X		X																
Clinical Assessments (see section 6.3.4)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cemiplimab/Placebo Administration (see section 6.3.5)			X				X												
Assessment Prior to Week 6 Cemiplimab/Placebo Administration (see section 6.3.5)							X												

Evaluation	Screening	Pre-Entry	Entry/Day 0	Post-entry Evaluations (Weeks)													Premature Study Discontinuation (D/C) Visit	Confirm Virologic Failure (if needed)
				1	2	4	6	7	8	10	12	16	20	24	28	36	48	
Window	Between 60-90 days prior to entry	Between 30 and 50 days prior to entry	≤24 hours post-randomization	±2 days	-2/+7 days		±2 days		-2/+7 days									
Telephone Contact			2-3 days post infusion				2-3 days post infu-sion												
Electrocardiogram (ECG)		X																	
Hematology	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Liver Function Tests	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Blood Chemistries	X	X	X		X	X	X					X	X	X	X	X	X	X	
Autoimmune Studies (TPO, GAD65, islet cells [ANA only at screening])	X (see section 6.3.7)					X					X						X	X	
Stored Autoimmune Studies (see section 6.3.7)			X				X					X	X	X	X	X			
Hepatitis Screen		X																	
TB Screen	X																		

Evaluation	Screening	Pre-Entry	Entry/Day 0	Post-entry Evaluations (Weeks)														Premature Study Discontinuation (D/C) Visit	Confirm Virologic Failure (if needed)
				1	2	4	6	7	8	10	12	16	20	24	28	36	48		
Window	Between 60-90 days prior to entry	Between 30 and 50 days prior to entry	≤24 hours post-randomization	±2 days	-2/+7 days		±2 days		-2/+7 days										
FSH	X																		
Free Testosterone (male participants only)		X				X					X						X	X	
Urinalysis			X				X				X			X			X	X	
Pregnancy Testing	X		X	If suspected			X	If suspected			X	If suspected		X	If suspected		X	X	If suspected
Metabolic Studies (see section 6.3.8)	X	X				X	X				X	X	X	X	X	X	X	X	
Adherence Assessment			X (see section 6.3.9)	X			X (see section 6.3.9)	X			X	X	X	X	X	X	X		X
CD4+/CD8+	X		X				X				X			X			X	X	
Stored Plasma/PBMCs for Immunologic Studies		X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Advanced Flow Analysis		X	X		X	X	X		X	X	X	X	X	X		X	X		
Standard Plasma HIV-1 RNA	X		X	X			X	X			X			X			X	X	X

Evaluation	Screening	Pre-Entry	Entry/Day 0	Post-entry Evaluations (Weeks)													Premature Study Discontinuation (D/C) Visit	Confirm Virologic Failure (if needed)
				1	2	4	6	7	8	10	12	16	20	24	28	36	48	
Window	Between 60-90 days prior to entry	Between 30 and 50 days prior to entry	≤24 hours post-randomization	±2 days	-2/+7 days		±2 days		-2/+7 days									
Stored Plasma for HIV-1 RNA Single-Copy Assay		X	X	X			X	X			X			X			X	X	
CD4+ T cell-associated HIV-1 RNA, DNA, RNA:DNA ratio, and Quantification of Intact Proviral Genomes		X	X				X				X			X			X	X	
HIV-1 Drug Resistance Genotype																			X

Table 6.1-2: SOE for PK Evaluations - Pre-Entry through Week 48

Evaluation	Pre-Entry	Entry/Day 0		Week 1	Week 2	Week 4	Week 6		Week 7	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 48	Premature Study Discontinuation	Confirm Virologic Failure (if needed)
							±2 days													
		Prior to infusion	Following infusion				Prior to infusion	Following infusion												
Window	Between 30 and 50 days prior to entry	Within 15 min prior to infusion	Within 15 min following infusion	±2 days	-2/+7 days		Within 15 min prior to infusion	Within 15 min following infusion	±2 days	-2/+7 days										
Cemiplimab Serum Concentrations[1]	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stored Blood for Gene Expression Assays[2]		X		X		X	X		X		X	X	X		X				X	
Stored PBMCs for RO Studies[1,3]	X			X	X		X		X	X	X	X	X	X	X	X	X	X	X	
Stored Plasma for ARV PK Assays[4]		X			X	X	X			X	X									
Anti-drug Antibody Detection Assays		X										X			X			X	X	

[1]For participants who do not complete cemiplimab infusion, the necessity for these studies will be determined on a case-by-case basis in discussion with the core team. The actual date, and start and stop times of the infusion, and rate of infusion should be recorded.
[2]The need to assay each of these timepoints will be based on changes observed from baseline.
[3]For RO: A determination of the need to assay certain/all stored samples will be based on the serum cemiplimab concentration seen.
[4]The date and time of the previous 3 doses of each antiretroviral medication(s) - must be documented in the eCRF with each sample.

6.2 Timing of Evaluations

6.2.1 Informed Consent

The study physician investigator will directly participate in the informed consent process. The informed consent process will include completion of the A5370-specific Assessment of Understanding tool to evaluate participants' comprehension of the risks and lack of direct benefits of study participation. See assessment in Appendix II.

6.2.2 Screening and Pre-Entry Evaluations

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

Screening
In order to optimally manage blood volume limits, screening evaluations to determine eligibility must be completed between 60-90 days prior to study entry as outlined in the SOE, unless otherwise specified.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in an electronic case report form (eCRF) and entered into the ACTG database.

Pre-Entry
Pre-entry evaluations must be completed 30-50 days prior to entry evaluations unless otherwise specified.

6.2.3 Entry Evaluations

Entry/Day 0 evaluations and administration of treatment/placebo must occur within 24 hours after randomization unless otherwise specified. The entry laboratory values and plasma for HIV-1 RNA SCA must be obtained prior to initiating cemiplimab/placebo infusion.

6.2.4 Post-Entry Evaluations

Post-Treatment/Placebo Evaluations
All evaluations and study visits occur in reference to the date and time for which the participant was administered cemiplimab/placebo. Study visits at weeks 1, 6, and 7 must be done ±2 days. Study visits at weeks 2, 4, 8, 10, 12, 16, 20, 24, 28, and 36 must be done -2/+7 days.

The cemiplimab/placebo infusion should be completed in 30 minutes. The date and time of start and end of infusion sample times will be recorded. All other cemiplimab/placebo and RO samples are collected as planned, the date and time of actual sample collection must be documented in the eCRF (see section 6.3.12 for further details of pharmacokinetic sample collection).

In the event that the infusion requires additional time, all subsequent time-points are calculated from the completion of the infusion (see section 6.3.5).

All other evaluations should be completed per SOE:

NOTE: The core team must be notified by email at actg.corea5370@fstrf.org for visits outside the window period for any visit through week 12.

For stored samples, all sites must have established procedures for regular reconciliation and verification of specimens, which must be followed throughout the study per the Laboratory Processing Chart (LPC). Collection of sample aliquots is of particular importance for all time points from the screening visit through week 12. In the event of a missed visit or that the required volume or number of sample aliquots is not obtained at any time point, designated site clinic and/or laboratory staff must immediately inform the study core team, who will provide guidance on how to respond to the problem.

In addition to following this guidance from the study team, designated site clinic and laboratory staff will work together to document the problem, take appropriate corrective and preventive action, and document all action taken. Reconciliation must be performed for all specimen types that are received by the laboratory and stored in the LDMS.

For other evaluations, if an evaluation is not completed at a scheduled visit, effort should be made to obtain the evaluation as soon as possible. If unsuccessful, complete the evaluation at the next study visit if not already included as part of the regularly scheduled visit.

Study Completion Evaluations
Week 48 evaluations will serve as the study completion evaluations for participants and must occur -2/+7 days.

Event-Driven Evaluations
Participants who experience a Grade ≥3 AE or clinical event on study that is not resolved by week 48 will be followed until resolution or clinical stabilization as defined by the site investigator (see section 8.1).

Participants who experience any grade of irAE on study that is not resolved by week 48 will be followed until resolution or stabilization as defined by the study team and DAIDS medical officer.

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

Participants with plasma HIV-1 RNA ≥200 copies/mL should have a confirmatory VL and a plasma sample for real-time genotyping obtained as soon as possible unless there is clear evidence of non-adherence to ART and have evaluations performed per the SOE. If ART non-adherence is confirmed, then HIV-1 RNA should be retested at least 2 weeks after ART is resumed. If HIV-1 RNA is confirmed ≥200 copies/mL then see section 8.7 for additional information regarding virologic failure management.

6.2.5 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
Participants who withdraw from the study prior to starting study treatment/placebo should have entry/day 0 and off-study forms completed and keyed. No further evaluations or follow-up are required for these participants. Participants will be replaced. All eCRFs must be completed for the period up to and including entry/day 0.

Premature Treatment/Placebo Discontinuation Evaluations
Participants who begin but do not complete of both infusions of cemiplimab/placebo, but receive some of the investigational product, and are willing to stay on the study, will be followed for safety by completing all study visits and evaluations as outlined in the SOE. If one or both cemiplimab/placebo infusions have been administered, samples for serum cemiplimab, RO, and ADA will be collected per the SOE (duration of sampling in participants that do not receive or complete the second infusion will be decided on a case-by-case basis with the core team). Whether virologic, immunologic, and stored ARV plasma samples will be stored or performed following premature discontinuation of cemiplimab/placebo infusions will be determined on a case-by-case basis in discussion with the core team. The duration of the infusion (including actual start and stop times) and the volume of each cemiplimab/placebo infusion should be recorded. Participants who do not complete ≥90% of both infusions of cemiplimab/placebo will be replaced unless the participant has reached a protocol-defined safety endpoint. Participants who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Discontinuation of Antiretroviral Therapy
Participants who discontinue cART for any reason will be followed for safety by completing all study visits and evaluations as outlined in the SOE. If ART is discontinued prior to completion of cemiplimab/placebo infusions, then no further infusions should be given. Whether cemiplimab serum concentrations or RO assays will be collected following discontinuation of ART will be determined on a case-by-case basis in discussion with the core team. Stored plasma/PBMC for

immunologic studies, stored plasma for SCA and samples for CD4+ T cell associated HIV-1 RNA, DNA, and 2-long terminals repeats (2-LTRs) do not need to be obtained for time points after the participant has discontinued ART.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue study participation after completing one or more of the cemiplimab/placebo infusions will have the premature study discontinuation (D/C visit) evaluations performed per the SOE. Participants who discontinue the study prior to week 12 without having met the primary safety outcome measure will be replaced.

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/daids-sourcedocpolicy.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 AE reporting of adverse events requirements.

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 must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Asthma
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B

Any allergies to any medications and their formulations must also be documented.

Document the pre-ART HIV-1 RNA level and nadir CD4 count if available. If pre-ART nadir CD4 count documentation or pre-ART HIV RNA level is not available, then collect and record participant recall. Document date of first undetectable HIV-1 RNA level prior to sustained VL suppression (may be estimated if exact date not available) and the date(s) of any previous virologic failure on ART.

The medical history evaluation will be assessed at the screening and entry visit and recorded on the eCRFs at the study entry visit.

6.3.3 Medication History

A medication history must be obtained at screening and updated at entry, 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	Start date of the current ART regimen, ART history over the prior 5 years and date of 1st use of ART
Immune-based therapy	Complete history
Blinded study treatment	Complete history
HIV-1-related vaccines	Complete history
All prescription drugs	Current use
All over-the-counter drugs	Current use
Dietary and herbal supplements	Current use
Sex-hormone medications or sex-hormone analogues or antagonists*	Last 12 months except as noted below
Prescription drugs for treatment of opportunistic infections	Current use
Prescription drugs for prophylaxis of opportunistic infections	Current use
Alternative therapies	Current use

*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; emergency contraception (current use only); anabolic steroids; gonadotropins.

6.3.4 Clinical Assessments

Complete Physical Examination
A complete physical examination is to be done at screening and should include at a minimum an examination of the skin, head, mouth, and neck (including thyroid exam); auscultation of the chest; cardiac examination; abdominal examination; gonadal exam in males, and examination of the lower extremities for edema. The complete physical examination will also include signs and symptoms, diagnoses, and vital signs (height, weight, temperature, pulse, respiration rate, and blood pressure).

The complete physical examination at screening should also include a nondilated funduscopic eye exam by a physician or appropriately trained clinician and must be documented in source documents.

Targeted Physical Examination
A targeted physical examination is to be done at entry, and weeks 1, 2, 4, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48, and should include vital signs (temperature, pulse, respiration rate, and blood pressure), and is to be driven by any previously identified or new AE/targeted event (as described in below bullets), that the participant has experienced since the last visit.

Height
Height (cm) will be recorded on the eCRF at screening or pre-entry.

Weight
Weight in kilograms (kg) should be assessed at screening, entry, weeks 6, 12, and 48. Weight should be documented prior to dosing, and the first infusion dose will be based on weight from entry. Week 6 dosing should also be based on weight from the entry visit unless there is a >10% change in body weight, in which case the dose should be adjusted accordingly.

Post entry, see section 8.8 for collection requirements for pregnancy.

Post entry, record the following targeted event(s) regardless of grade:
- Uterine pregnancy
- Autoimmune diseases
- Immune deficiency syndromes
- All potential irAEs including but not limited to pneumonitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, diabetes, hypophysitis, allergic skin reaction.
- Cancers
- Tuberculosis
- AIDS-defining conditions

Refer to section 7.2 for AE collection requirements.

Concomitant Medications Including Antiretroviral Drugs
At entry and all subsequent visits, the following new and discontinued concomitant medications must be recorded on the eCRFs since the last visit:

- Prescription medications
- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.3 for examples).
- Antiretroviral drugs
- Dietary and herbal supplements
- Over-the-counter medications
- Endocrine therapies
- Immunomodulatory agents (e.g., steroid injections/infusions/oral, inhalations, physiologic replacement)
- Alternative therapies

NOTE: Ongoing medications, other than antiretrovirals, do not have to be recorded at each visit. Once they have been captured, only changes in dosing, or discontinuation are to be recorded.

6.3.5 Study Treatment Administration and Evaluation

Study Treatment Administration
Record the cemiplimab infusion/placebo, including dose administered, the total volume contained in the infusion bag, the concentration of the cemiplimab infusion preparation (e.g., mg/mL), the rate of infusion (e.g., mL/min), whether the rate of the infusion changed, and what the rate changed to. Record whether administration was temporarily halted for any reason (record the time it was halted and the time if restarted). Record the start and stop infusion times, the time a change in infusion rate occurs, and whether the full dose was administered. If the full dose was not administered, the amount of cemiplimab/placebo (the volume and concentration) that was administered should be recorded and the core team should be notified.

NOTE A: The maximum time of infusion should not exceed 3 hours (180 minutes) (see sections 8.2.2 and 8.2.1).

NOTE B: If the second infusion is delayed for any reason, participants should complete all evaluations for the week 6 study visit per the SOE without the second infusion of cemiplimab/placebo. These participants should be followed for safety and at unscheduled visits from week 10 onward (from date of the first infusion) per the SOE, until the second infusion can be rescheduled.

NOTE C: If the second infusion is rescheduled for a later date, then a subsequent protocol visit should be timed in relationship to the second infusion (e.g., week 7 would occur 1 week following the second infusion and so forth).

NOTE D: If the second infusion is delayed, the week 4 visit should be repeated if it has been >4 weeks since collection of the week 4 laboratory evaluations before the date of the rescheduled second infusion. Do not, however, re-draw stored blood for gene expression assays or stored PBMCs for RO studies.

Assessment Prior to Week 6 Cemiplimab/Placebo Administration
Prior to administering the second infusion at week 6 in all dose cohorts, the safety-related items in sections 4.1 and 4.2 should be re-assessed by a site investigator or designee based on the week 4 evaluations (or the visit prior to the week 6 infusion, as appropriate). If the following are not confirmed, then the second infusion should not be given:

- Negative results for TPO antibody, GAD65/GAD antibody, and islet cell antibody.
- Negative or within normal range results for metabolic studies (fasting glucose, AM cortisol, TSH, and free T4).

These must be done at a laboratory that possesses a CLIA certification or equivalent.

Also, if any irAEs were identified following the first infusion or suspected irAEs are under investigation for relatedness, the second infusion must not be given.

NOTE A: If enrollment safety pause criteria are met (see section 10.4.1), participants already enrolled on study should not receive the second infusion pending SMC review, but should be followed for safety per NOTE B above. The study leadership will notify sites if and when a safety pause is needed and will also notify sites when the pause is lifted.

NOTE B: If enrollment is re-opened following SMC review, the above safety labs designated for week 4 should be repeated if collected >4 weeks prior to the rescheduled second infusion.

This information should be captured on the appropriate eCRF.

Telephone Contact
Participants will be contacted by telephone (2 to 3 days post-infusion) to assess for changes in health status and to answer questions about infusion-related signs and/or symptoms. This information should be captured on the appropriate eCRF. See pre-specified telephone script in the A5370 Manual of Procedures (MOPS).

NOTE: If participants prefer not to be contacted by telephone, then they may return to the clinic and the same procedures should be followed as noted above.

6.3.6 Electrocardiogram

ECG will be performed prior to cemiplimab/placebo infusion at pre-entry, per the SOE and should be read per institutional protocol within 72 hours to establish baseline for further evaluation as clinically indicated.

6.3.7 Laboratory Evaluations

At screening, pre-entry, and entry all laboratory values must be recorded on the eCRF. The entry laboratory values must be obtained prior to initiating cemiplimab/placebo infusion.

For post-entry assessments, record on the eCRF all laboratory values for creatinine, AST, ALT, total bilirubin, hemoglobin, white blood cell count, ANC, platelets, absolute lymphocyte count (ALC), TSH, free T4, HgbA1c, fasting blood glucose, cortisol, FSH, free testosterone, anti-TPO antibody, anti-GAD65 antibody, anti-islet cell antibody, and other autoimmune studies (if indicated) regardless of grade; record abnormal laboratory findings as per section 7.2.

At entry and week 6, all lab tests should be drawn pre-infusion unless otherwise specified.

Hematology
Hemoglobin, hematocrit, red blood cells, mean corpuscular volume, white blood cell count (WBC), differential WBC, ANC, platelets, ALC.

Liver Function Tests
Total bilirubin, AST [SGOT], ALT [SGPT], alkaline phosphatase.

NOTE: For participants on ritonavir-boosted atazanavir, direct bilirubin should be measured.

Blood Chemistries
Glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, creatinine, creatinine clearance, blood urea nitrogen (BUN), uric acid, albumin.

NOTE: A program for calculating creatinine clearance by the Cockcroft-Gault method is available on www.frontierscience.org.

Autoimmune Studies
TPO antibody, GAD65 antibody, and islet cell antibody, per the SOE. ANA titer and pattern will only be done at screening.

Potential participants who are found to be ineligible based on positive autoimmune results at screening will be provided with these results and referred for further clinical evaluation as appropriate.

If a participant receives a positive antibody result for any of those listed above at week 4, he/she will not receive a second infusion of cemiplimab/placebo.

Autoantibody test results should be shared with study participants and appropriate clinical follow-up should be arranged, as needed.

Stored Samples for Autoimmune Studies
Serum will be stored for autoimmune studies per the SOE.

Hepatitis Screen
HCV antibody, HCV RNA (if HCV antibody positive), and HBsAg testing per the SOE.

These values should be captured on an eCRF.

TB Screen
Interferon-gamma Release Assay (IGRA) per the SOE.

NOTE A: TB test results do not need to be entered on the eCRF.

NOTE B: Participants with a prior positive TB IGRA or positive PPD and documented evidence of completed prophylaxis treatment may enroll in the study and do not need to undergo IGRA at screening.

FSH
For female participants, FSH should be measured at screening if they are believed to be not of reproductive potential but lack medical record.

NOTE: Female participants who have not had a menses for at least 24 consecutive months and have an FSH greater than 40 international units (IU) documented by medical record or have documentation of a hysterectomy, bilateral oophorectomy and/or bilateral salpingectomy, do not require an FSH at screening.

Free Testosterone
For male participants, free testosterone should be measured per the SOE. Samples should be drawn prior to 12 noon or per local lab requirements.

Urinalysis
A dipstick urinalysis with microscopic examination will be performed per the SOE to assess for nephritis.

Pregnancy Test
For females of reproductive potential or if they are believed to be not of reproductive potential but lack medical record, a serum pregnancy test with a sensitivity of at least 25mIU/mL must be performed at screening. A serum or urine pregnancy test must be completed within 48 hours of entry, and again prior to infusion of cemiplimab/placebo at week 6, and at weeks 12, 24, and 48 or if suspected, at weeks 1, 2, 4, 7, 8, 10, 16, 20, 28, and 36. Record pregnancy and pregnancy outcome per section 8.8.

6.3.8 Metabolic Studies

HgbA1c values should be obtained at screening only.

Fasting glucose and AM cortisol (drawn prior to 10:00 AM) values should be obtained at screening (cortisol only), pre-entry, and weeks 4, 6, 12, 16, 20, 24, 28, 36, and 48.

TSH and Free T4 should be obtained at screening (TSH only) and weeks 4, 6, 12, 16, 20, 24, 28, 36, and 48.

NOTE: Fasting refers to nothing to eat or drink except oral medications and plain water for at least 8 hours. Participants must be fasting for the screening visit. For subsequent visits if participants are in a non-fasting state, the visit should proceed and the fact that the participant is not fasting should be documented.

6.3.9 Adherence Assessment

A standardized assessment to monitor ART adherence will be administered per the SOE and will include assessment for ART interruption of more than 7 consecutive days. An interruption of more than 7 days will be considered treatment discontinuation. For ART discontinuation, see section 6.2.5.

At Entry/Day 0 and week 6, the adherence assessment should be performed prior to infusion.

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

6.3.10 Immunologic Studies

Documentation of the availability of the stored pre-entry plasma specimens for virology assays and stored pre-entry peripheral blood mononuclear cell (PBMC) specimens for CD8+ T-cell assays is required. Sites must receive confirmation from the processing lab via phone, e-mail, or fax, that specimens have been entered into the ACTG's LDMS.

CD4+/CD8+ T cells
Obtain absolute CD4+/CD8+ T cell counts and percentages within 90 days prior to entry from a laboratory that possesses a CLIA certification or equivalent.

For entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

Stored Plasma/PBMC for Immunologic Studies
Cryopreserved PBMC will be stored for HIV-1-specific immune response assays as well as T-cell immune analysis by flow cytometry per the SOE. Specific testing will include the following:

- Determination of HIV-specific T cell responses measured by intracellular cytokine staining (a validated assay) pre- and post-administration of cemiplimab.
- Determination of cytolytic potential of HIV-1-specific CD8+ T cells.
- Poly-functionality of HIV-1-specific CD8+ and CD4+ T cells.
- Activation and cycling of CD4+ and CD8+ T cells.
- The proportion of total and HIV-1-specific CD4+ and CD8+ T cells that express exhaustion markers by multi-parameter flow cytometry. The expression profile on dendritic cells and monocyte-derived macrophages will also be determined.
- Ex vivo proliferation of HIV-specific T cell responses in the presence of anti-PD-1.

NOTE: Stored PBMCs for T Cell Proliferation and Gene Expression Assays, and Stored Plasma/PBMC for Immunology Studies are not necessary for participants who discontinue ART for any reason. After the start of infusion, for participants who do not complete cemiplimab/placebo infusion, the necessity for these studies will be determined on a case-by-case basis in discussion with the core team. The duration of the infusion and the volume of cemiplimab/placebo infused should be recorded (see section 6.3.5 for details of Study Treatment Administration Documentation).

Advanced Flow
Stored PBMCs for advanced flow analysis requires a CD4+/CD8+ T cell ratio and WBC with differential from a sample obtained at the same time.

6.3.11 Virologic Studies

Plasma HIV-1 RNA Assay
Screening HIV-1 RNA must be performed within 90 days prior to study entry using an FDA-approved assay by a laboratory that possesses a CLIA certification or equivalent, and should be performed between 60 and 90 days prior to entry to optimally manage blood volume. Eligibility will be determined based on the screening value.

Entry and post-entry plasma HIV-1 RNA should be performed per the SOE. Samples should be processed and shipped to the designated central ACTG testing laboratory (refer to LPC for shipping information).

All occurrences of confirmed HIV viral loads above 200 copies/mL must be recorded on the eCRF.

Stored Plasma for HIV-1 RNA SCA
Plasma for HIV-1 RNA SCA will be obtained as required per the SOE and stored for batched analyses. The sample at entry for SCA must be collected prior to initiating cemiplimab/placebo infusion.

See the LPC located on the A5370 PSWP, for details on processing plasma samples for SCA.

The baseline SCA value will be the mean of the pre-entry and entry determinations, which must have been obtained at least 7 days apart.

CD4+ T cell-associated HIV-1 RNA
Cell-associated HIV-1 RNA will be measured in total CD4+ T cells isolated from cryopreserved PBMC obtained at pre-entry, prior to cemiplimab/placebo infusion at entry/day 0 and week 6, and thereafter per the SOE.

CD4+ T cell-associated HIV-1 DNA
Total HIV-1 DNA in total CD4+ T cells isolated from cryopreserved PBMC will be measured to normalize cell-associated HIV-1 RNA data, at pre-entry, prior to cemiplimab/placebo infusion at entry/day 0 and week 6, and thereafter per the SOE.

Stored PBMCs for Quantification of Intact Proviral Genomes
PBMCs will be stored for quantification of intact proviral genomes per the SOE. See the LPC for details on processing PBMC samples.

T cell-associated HIV-1 RNA: DNA Ratios
Cell-associated HIV-1 RNA: DNA ratios in total CD4+T cells isolated from cryopreserved PBMC will be calculated from the cell-associated HIV-1 DNA and RNA data described above.

HIV-1 Drug Resistance Genotype
An HIV-1 drug resistance genotype (virus population sequencing) will be performed at local CLIA-certified commercial laboratories in those individuals with confirmed virologic failure.

NOTE: Standard Plasma HIV-1 RNA Assay, CD4+ T cell-associated HIV-1 RNA, and CD4+ T cell-associated HIV-1 DNA are not necessary for participants who discontinue ART for any reason. After the start of infusion, for participants who

do not complete cemiplimab/placebo infusion, the necessity for these studies will be determined on a case-by-case basis in discussion with the core team. The duration of the infusion and the volume of cemiplimab/placebo infused should be recorded.

6.3.12 Pharmacokinetic Studies (refer to section 11.0)

Cemiplimab Serum Concentrations
Blood will be collected for determination of cemiplimab in serum using a validated ligand binding assay. A pre-entry sample will be drawn. At entry/day 0 and week 6, samples are drawn within 15 minutes following infusion (and must be obtained from the contralateral arm), and within 15 minutes prior to the infusion on week 6. At weeks 1, 2, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48, samples can be drawn at any time during the visit. Record the date and actual time of dosing and of sample drawn in the eCRF.

Stored Blood for Gene Expression Assays
Samples will be collected for the gene expression analysis as per the SOE. Samples collected on infusion days (day 0 and week 6), should be collected pre-infusion. All samples that are collected may not be tested. Please refer to the LPC for specimen collection and processing instructions.

RO Studies
Cryopreserved PBMC samples will be used to assay PD-1 RO by cemiplimab by flow cytometry. At pre-entry and within 15 minutes prior to infusion at week 6, samples are drawn. At weeks 1, 2, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48, samples can be drawn at any time during the visit. Record the actual date and time of dosing and of sample drawn in the eCRF.

Stored Plasma for ARV PK Studies
At entry/day 0 (prior to infusion). At weeks 2, 4, 6 (prior to infusion), 8, and 10. Samples obtained on non-infusion days can be drawn during the participant's visit (a specific time of day is not required), documentation of the date and time samples are drawn is required in the eCRF. Documentation of the date and time of the 3 previous doses of all antiretroviral medication(s) are to also be recorded in the eCRF. Samples will undergo testing as indicated if the participant is viremic.

6.3.13 Anti-drug Antibody (ADA) Assessments

Serum samples for the assessment of anti-cemiplimab antibody may be collected at Entry/Day 0 (prior to infusion), weeks 12, 24, 48, and at premature study discontinuation. Additional ADA samples may be collected at or near any suspected immune mediated adverse events of special interest (AESI) in collaboration with the investigator of record and A5370 core team.

On a case-by-case basis, in discussion with the core team, remaining serum from cemiplimab samples may be assessed for ADA, if deemed necessary based on the PK profile seen.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events (AEs)

An 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 AE Collection Requirements for This Protocol

Post-entry, all AEs must be recorded on the eCRFs if any of the following criteria have been met.

- All Grade ≥1 AEs
- All suspected or confirmed irAEs
- All infusion reactions
- All AEs that led to a change in study intervention
- All AEs meeting SAE definition or Expedited Adverse Event (EAE) reporting requirement
- All targeted events listed in section 6.3.4

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 SAEs, irAEs, and AESIs will be recorded in DAERS, regardless of causality.

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 website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Infusion reactions, adrenal insufficiency, and pneumonitis should be graded per the National Cancer Institute's (NCI) Common Terminology Criteria for AEs (CTCAE) guidelines as outlined in section 8.0, and can also be found in the National Cancer Institute's Table for CTCAE, version 5.0, found on the National Cancer Institute Web site:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results 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.

Adverse Events of Special Interest (AESI)
An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

AESIs include all cases of irAEs, felt to be related to study treatment, including:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- All irAEs regardless of grade, including but not limited to: dermatitis, pneumonitis, myocarditis, colitis, adrenal insufficiency/crisis, hypo- or hyperthyroidism, thyroiditis, diabetes, hypophysitis, hepatitis, systemic lupus erythematosus, nephritis, myasthenia gravis, and/or drug-induced liver injury (DILI)

For all AESIs, the core team should be contacted immediately via email at actg.coreA5370@fstrf.org (See section 7.3.2).

NOTE: Participants with an ongoing AESI at week 48, should be followed until the AE has resolved or stabilized in the opinion of the core team (see section 6.2.4).

Infusion Reactions
Infusion reactions are defined as any AE that occurs during the infusion or within 24 hours after the infusion is completed. All infusion reactions must be reported as AEs and graded using the grading scales as instructed in section 8.2.

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

DAERS must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using 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 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: cemiplimab (anti-PD-1 mAb) and placebo for cemiplimab.
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are: All AESIs as noted in section 7.2 felt related to study treatment.

If a particular sign/symptom is not specifically listed in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, refer to the Estimating Severity Grade section for the 'Clinical Adverse Events Not Otherwise Identified in the DAIDS AE Grading Table' grading scale.

NOTE: Possible DILI (or Hy's Law) is defined as any elevated ALT and/or AST of Grade 2 or greater (≥3 x ULN), alkaline phosphatase <2 x ULN, and an increase in bilirubin ≥2 x ULN with no other immediately apparent possible causes of AST or ALT elevation and hyperbilirubinemia (such as concomitant use of atazanavir), including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

AESI: All AESIs, serious and non-serious, must be reported using the same reporting process as for SAE reporting.

Other AEs that must be reported in an expedited manner (i.e., within 3 business days to the sponsor or designee) are as follows.

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 3 business days of identification, any pregnancy occurring in a female or female partner of a male participant, during the study or within 26 weeks of the last dose of study drug.

Any complication of pregnancy affecting a female study participant or female partner of a male study participant, and/or fetus, and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

7.3.3 Grading Severity of Events

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, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The grading system for suspected or confirmed infusion-related reactions, adrenal insufficiency, and pneumonitis is listed in sections 8.2, 8.3.4, and 8.3.5, and can also be found in the National Cancer Institute's Table for CTCAE, version 5.0, found on the National Cancer Institute Web site: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information). See Reference Safety Information table as found in the IB for determination of SUSARs.

7.4 Study Monitoring

The Protocol Core Team will monitor the conduct and safety of the study via regular summaries by cohort pooled over treatment arms of accrual, baseline characteristics, study conduct (including premature study discontinuations and premature study treatment discontinuations), any missed doses of study treatment/placebo, any reported interruptions of ART, HIV-1 RNA levels ≥200 copies/mL (see section 6.2.4/Confirmation of Virologic Failure), data completeness, specimen collection, and AEs. The core protocol team will review the individual participant-level safety data frequently to assess the relation of all reported AEs to study treatment/placebo.

The DAIDS clinical representative will review and assess 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 at least annually by an independent ACTG-appointed SMC. The first review is anticipated to be review of the first cohort, regarding dose escalation to the second cohort. The SMC will review information by cohort on accrual, baseline characteristics, conduct of the study (including premature study discontinuations and premature study treatment discontinuations), AEs by treatment arm (including core protocol team assessment of relationship to study treatment), CD4+ T cell counts, virologic failures, and HIV-1 RNA levels/suppression over time by treatment arm, and completeness of follow-up and sample availability. In particular, irAEs will be monitored.

After the last enrolled participant in each cohort receives study treatment and completes follow-up through the week 12 visit and the blinded data become available for review by the core team, safety data including the core team decision on relation of AEs to study treatment will be reviewed by the SMC, unblinded to treatment arm, to determine whether to dose escalate or modify the study. Complementing the SMC reviews, a designated study chair or co-chair may notify the SMC of Grade 4 AEs or deaths, as wells as notable Grade 3 AEs among the events that the sites email to the core team per section 8.0. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team. See also section 10.4 for statistical considerations related to interim monitoring.

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

8.0 CLINICAL MANAGEMENT ISSUES

The recommendations and toxicity management guidelines within this section should be seen as guidelines, and the treating physician should exercise clinical judgment regarding best clinical management, based on the symptoms and condition of the individual participant.

Criteria for participant management, dose interruption (i.e., withholding doses), and treatment discontinuation will be mandated only for toxicities related to cemiplimab /placebo. Toxicities due to drugs in the antiretroviral regimen should be managed according to standard clinical practice, with the goal of maintaining continuous therapy, if possible. Participants must remain at the clinic for observation for 2 hours following the first infusion of cemiplimab/placebo and 30 minutes following the second infusion (see section 5.1.2 for cemiplimab/placebo administration instructions). All participants who receive at least one infusion, including those participants who have an AE, either related or unrelated, are strongly encouraged to stay on study for the duration of the protocol to collect potential AE data and may continue study procedures unless clinically contraindicated.

The grading system for drug toxicities is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 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.

The grading system for suspected or confirmed infusion-related reactions, adrenal insufficiency, and pneumonitis is listed in sections 8.2, 8.3.4, and 8.3.5, and can also be found in the National Cancer Institute's Table for CTCAE, version 5.0, found on the National Cancer Institute Web site: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

NOTE A: The core A5370 study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org regarding any toxicities considered to be associated with cemiplimab/placebo that result in the discontinuation of the infusion.

NOTE B: The core team must be notified within 48 hours by email at actg.coreA5370@fstrf.org regarding any Grade 3 or 4 adverse reactions that are related to study treatment.

NOTE C: The core team must be notified within 24 hours by email at actg.coreA5370@fstrf.org regarding any suspected or confirmed irAE of any grade that are considered to be related to study treatment. In such cases, cemiplimab/placebo should be withheld.

NOTE D: Should there be any question about whether an AE is considered an irAE, sites should withhold cemiplimab/placebo and immediately contact one of the protocol chairs (see contact information in Protocol Team Roster on page 6).

NOTE E: For toxicities that cause DISCONTINUATION of cemiplimab/placebo, future doses of cemiplimab/placebo should not be given to the participant. Whereas, for toxicities that cause WITHHOLDING of cemiplimab/placebo, there is potential for continued/future doses to be given once the toxicity(ies) in question have been further investigated by site investigator and the study core team.

Guidelines for Management of Adverse Events of Special Interest (AESI)
All participants who receive treatment/placebo on this study should be closely monitored for any symptoms or signs related to irAEs including: gastrointestinal (colitis), endocrinopathies (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes), symptoms or signs suggestive of pneumonitis, myocarditis, hepatitis, uveitis, dermatitis, or other irAEs. Such participants must be carefully followed, and managed at the first onset of these clinical symptoms. Sites should discuss any potential immune-related symptom with the A5370 core study team. For example, a high index of

suspicion for immune-related colitis should be maintained in participants who present with diarrhea or other abdominal symptoms, and a high index of suspicion for immune-related pneumonitis should be maintained in participants who present with respiratory symptoms.

Documentation of the immunopathologic nature of a suspected irAE by biopsy confirmation should be considered if there is no other clear cause, and/or when symptoms are severe or persistent. Discussion with the A5370 core study team prior to biopsy or institution of steroid therapy is strongly recommended if feasible. Prompt initiation of appropriate therapy should be instituted as outlined in the specific toxicity sections of the protocol (sections 8.1-8.6). Additional information is in the IB and a copy of the most current version of the IB should be readily available to study and other medical personnel following study participants.

Infusions of cemiplimab/placebo should be held in any participant who develops a suspected irAE regardless of grade. If the suspected irAE is confirmed as an irAE of any grade OR if the suspected irAE cannot be excluded, infusions should be discontinued. If, however, the AE is attributed to another cause, then infusions can be continued.

Case Definitions for irAEs
Based on the emerging safety profile of cemiplimab and other antibodies targeting the PD-1/PDL1 axis [53, 54] the following working case definitions are provided to help investigators distinguish irAEs from non-immune AEs. These case definitions pertain to the more commonly reported irAEs associated with PD-1 inhibition [53, 54] and is not exhaustive of all possible irAEs. Clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events [55, 56] should be reviewed in participants with concerning presentations.

The case definitions below have not been validated and are intended only as guidance for investigators to help distinguish irAEs from non-immune AEs. Investigators' clinical judgment may include other factors when determining immune-relatedness. The case definitions for irAEs may evolve as clinical experience increases with cemiplimab and other antibodies targeting the PD-1/PD-L1 axis.

a. Immune-related rash: Skin examination demonstrates a rash that is usually maculopapular, but other presentations may occur, including papulopustular, follicular, or urticarial dermatitis. Consider dermatologic consultation and biopsy for atypical presentations. Exclude other cause such as virally-induced rash or contact dermatitis.
b. Immune-related diarrhea/colitis: These events are on a continuum, with diarrhea defined as increased stool frequency, and colitis involving abdominal pain and/or radiologic evidence of colonic inflammation [54]. Onset at 4 to 6 weeks is common [53]. A computed tomography (CT) scan usually demonstrates diffuse colitis [57]. Exclude clostridium difficile or other infectious etiologies and exclude laxative misuse.
c. Immune-related hepatitis: Laboratory findings are notable for elevated ALT and/or AST that is usually asymptomatic. Viral or other drug-induced hepatitis is excluded. Exclude alcohol-related liver toxicity. If clinically appropriate, consider radiologic

imaging to exclude malignant causes.

d. Immune-related hypothyroidism: Laboratory findings are notable for elevated TSH associated with low serum free T4. If elevated TSH is detected, it is recommended that free T4 level also be tested. Elevated TSH with low free T4 establishes the diagnosis of hypothyroidism. Hypothyroidism may be asymptomatic or associated with symptoms such as fatigue, constipation, cold intolerance, dry skin, weight gain, and/or bradycardia.
e. Immune-related hyperthyroidism: Hyperthyroidism should be managed with standard antithyroid pharmacotherapy, and consultation with an endocrinologist is recommended.
f. Immune-related pneumonitis: Pneumonitis, defined as inflammation of the lung parenchyma, may present as shortness of breath, cough, fever, and/or chest pain. Median time from start of anti-PD-1 therapy to onset of pneumonitis is 2.6 months [57], but delayed onset of pneumonitis has been reported. The most common radiologic pattern on chest CT scan has been described as cryptogenic organizing pneumonia, but other radiographic patterns may occur [58]. If performed, biopsy may demonstrate lymphocyte-predominant interstitial pneumonitis with areas of organizing pneumonia [58]. Exclude infectious causes of pneumonitis.

NOTE: For any severe (Grades 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine, mycophenolate mofetil). Referral of the participant to a specialized unit for assessment and treatment should be considered.

8.1 Toxicity

All AESIs must be reported and the study team notified within 24 hours of identification (see sections 7.2, 7.3, and 8.0), and include the following:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- All immune-related, treatment-related toxicities (irAEs) regardless of grade

8.1.1 Grade 1 or 2 Toxicity

Participants who develop a Grade 1 or 2 AE or toxicity that occurs following infusion of cemiplimab/placebo, not specifically discussed below nor a possible irAE, and that is associated with symptoms and thought to be related to cemiplimab/placebo should be discussed with the study team. The site should notify the A5370 core team as soon as possible by email at actg.coreA5370@fstrf.org.

Participants who experience a Grade 1 or 2 AE that is judged not to be related to the study drug by the investigator, may continue study treatment at the discretion of the site investigator.

8.1.2 Grade 3 Toxicity

Participants who develop a Grade 3 AE that occurs following an infusion of cemiplimab/placebo not specifically discussed below nor a possible irAE, and that is thought to be related to cemiplimab/placebo should be discussed with the study team. The A5370 core study team must be notified within 48 hours by email at actg.coreA5370@fstrf.org. The participant should be followed closely and if the AE does not return to Grade ≤2 within 2 weeks, the study team should again be notified within 48 hours by email at actg.coreA5370@fstrf.org.

Participants who experience a Grade 3 AE that is judged not to be related to the study drug by the investigator, may continue study participation at the discretion of the site investigator in consultation with the study team.

8.1.3 Grade 4 Toxicity

Participants who develop a Grade 4 AE that occurs following an infusion of cemiplimab/placebo not specifically discussed below nor a possible irAE, and that is judged by the site investigator to be study drug-related, should be discussed with the study team. The core team must be notified within 48 hours by email at actg.coreA5370@fstrf.org.

All participants experiencing Grade 4 AEs should be followed closely with additional clinical assessments and laboratory testing as clinically indicated in consultation with the study team. If the AE does not return to Grade ≤2 within 2 weeks, the study team should again be notified within 48 hours by email at actg.coreA5370@fstrf.org.

8.2 Infusion-related Toxicities and Management

Infusion reactions should be graded according to the criteria for infusion-related reaction located in the National Cancer Institute's Table for CTCAE, version 5.0, found on the National Cancer Institute Web site:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

These reactions may manifest with signs and symptoms that may include, but are not limited to, fever, chills, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms. Severe infusion (Grade 3 or 4) reactions require the immediate interruption of study drug. The infusion should not be restarted and no further study medication (cemiplimab/placebo) should be given. Appropriate medical therapy including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and supplemental oxygen should be available for use in the treatment of such reactions. Participants should be carefully observed until complete resolution of all signs and symptoms occurs. In each case of an infusion reaction, the site investigator should

institute treatment measures according to the best available medical practice. The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org regarding toxicities associated with cemiplimab/placebo that result in the discontinuation of the infusion.

8.2.1 Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

For participants who develop a Grade 1 AE or toxicity during infusion, it is recommended that the study drug infusion rate be decreased by 50% and the participant should be monitored closely for any worsening of the initial signs of symptoms. If the infusion reaction recurs and/or persists at the decreased rate of infusion, the rate of the infusion may be further reduced. The maximum time of infusion should not exceed 3 hours (180 minutes). If symptoms persist but do not worsen, completion of the cemiplimab/placebo infusion will be at the discretion of the site investigator with careful monitoring.

NOTE: Blood draws for PK analysis should be timed to occur within 15 minutes after the end of the infusion.

If a participant chooses to discontinue a cemiplimab/placebo infusion, the site should notify the A5370 core study team by email at actg.coreA5370@fstrf.org and encourage the participant to complete subsequent study visits until the end of the study. Refer to section 6.2.5 for discontinuation evaluation instructions.

8.2.2 Grade 2: Moderate reaction; infusion interruption indicated but participant responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

For participants who develop a Grade 2 AE or toxicity during a cemiplimab/placebo infusion, the infusion should be stopped and the core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org. Administer epinephrine, corticosteroids, IV antihistamines, bronchodilators, and/or supplemental oxygen as medically indicated. At the discretion of the site investigator, the infusion may be continued at 50% of the previous infusion rate once the adverse reaction has resolved or has decreased to Grade 1 in severity. Participant must be monitored closely for any recurrence or worsening or signs or symptoms. If the infusion reaction recurs at this rate of infusion, the rate may be further reduced, again at the discretion of the site investigator. The maximum time of infusion should not exceed 3 hours (180 minutes).

Participants who develop a Grade 2 AE or toxicity during a cemiplimab/placebo infusion may complete the infusion at the discretion of the site investigator, with careful monitoring. Grade 2 AEs that may be related to cemiplimab/placebo should be handled according to standard clinical practice and documented on the eCRF.

8.2.3 Grade 3: Prolonged reaction (participant not rapidly responsive to symptomatic medication and/or brief interruption of infusion) or recurrence of symptoms following initial improvement or hospitalization indicated for clinical sequelae

DISCONTINUE further doses of cemiplimab/placebo.

Participants who develop a Grade 3 AE or toxicity during a cemiplimab/placebo infusion should have infusion discontinued immediately and be disconnected from the infusion tubing. Administer epinephrine, corticosteroids, IV antihistamines, bronchodilators, and/or supplemental oxygen as medically indicated. No further study drug treatment should be administered. The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org.

8.2.4 Grade 4: Life-threatening consequences; urgent intervention indicated

DISCONTINUE further doses of cemiplimab/placebo.

Participants who develop a Grade 4 AE or toxicity during a cemiplimab/placebo infusion should have infusion discontinued immediately and be disconnected from the infusion tubing. Administer epinephrine, corticosteroids, IV antihistamines, bronchodilators, and/or supplemental oxygen as medically indicated. No further study drug treatment should be administered. The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org.

8.3 Other Potential AEs/Toxicity

8.3.1 Diarrhea or Colitis

Diarrhea, blood, or mucus in stool, and/or abdominal pain
A high index of suspicion for immune-related colitis should be maintained in participants who present with diarrhea or other abdominal symptoms. The core study team must be notified immediately of all suspected cases of immune-related colitis by email at actg.coreA5370@fstrf.org.

For any suspected or defined immune-related colitis diagnosed following cemiplimab/placebo infusion, further doses of the study drug MUST BE WITHHELD until the etiology of the colitis is evaluated and determined.

If there is evidence or history supporting a non-cemiplimab/placebo-related cause, documentation of this evidence and treatment of the non-cemiplimab/placebo-related cause should proceed. Routine, comprehensive medical assessment of diarrheal illness should be considered including stool culture, *C. difficile* testing as well as appropriate testing for ova and parasites, if indicated.

If there is no evidence of a non-cemiplimab-related cause, then manage diarrhea or colitis as per grade of severity (DAIDS, corrected version 2.1) as follows:

8.3.1.1 Grade 1: Transient or intermittent episodes of unformed stools OR increase of ≤three stools over baseline per 24-hour period

Participants who develop Grade 1 diarrhea should be treated symptomatically with medically indicated anti-diarrheal agents but without systemic steroids. Participants will continue study procedures as per protocol. Routine, comprehensive medical assessment of diarrheal illness should be considered including stool culture, *C. difficile* testing as well as appropriate testing for parasitic infestation with ova and parasite (O&P) diagnostic studies, if indicated. If above diagnostic tests are negative and diarrhea persists for 3 days, then obtain flexible sigmoidoscopy and biopsy to evaluate for immune mediated colitis. If there is an alternative diagnosis and/or symptoms resolve and the participant has not been diagnosed with immune-related colitis, then cemiplimab/placebo administration can proceed.

8.3.1.2 Grade 2: Persistent episodes of unformed to watery stools OR increase of four to six stools over baseline per 24-hour period

WITHHOLD further doses of cemiplimab/placebo.

Participants who develop Grade 2 diarrhea should be treated symptomatically with medically indicated anti-diarrheal agents but without systemic steroids and continue study procedures as per protocol. If symptoms worsen or do not improve to Grade ≤1 within 1 week, the following should be completed immediately:

- Stool WBC
- Stool culture
- *Clostridium difficile* toxin
- Stool O&P (if indicated)

The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org.

If stool studies reveal an infectious cause, specific treatment for the infection should be started. If stool studies are negative and/or inconclusive and Grade 2 symptoms persist, obtain endoscopic studies and/or abdominal CT scan. If colitis is observed per any diagnostic modality or clinically suspected, treatment with systemic corticosteroids should be started (recommended: prednisone 60 mg/day orally or methylprednisolone 0.5-1 mg/kg/day IV). Discussion with the A5370 study team prior to performing gastrointestinal biopsy and/or institution of systemic steroid therapy is strongly recommended.

If symptoms do not improve or worsen within 3 days of initiating steroids, obtain appropriate gastrointestinal or immunologic clinical consultation and consider use of high-dose steroids (recommended methylprednisolone 1-2 mg/kg/day IV) and taper over 4-6 weeks. Discussion with the A5370 study team prior to starting higher doses of steroid therapy is strongly recommended. Participants may continue study procedures unless clinically contraindicated.

8.3.1.3 Grade 3: Increase of ≥seven stools per 24-hour period OR IV fluid replacement indicated

WITHHOLD further doses of cemiplimab/placebo.

Participants who develop Grade 3 diarrhea should have the following diagnostic evaluations completed immediately:

- Stool WBC
- Stool culture
- *Clostridium difficile* toxin
- Endoscopy or abdominal CT scan

The core team must be notified within 24 hours by email at: actg.coreA5370@fstrf.org.

If stool studies reveal an infectious cause, treatment for the specific infection should be started. If colitis is observed per endoscopy or abdominal CT scan or highly clinically suspected and infectious disease work-up is negative, appropriate subspecialty clinical consultation should be obtained. Discussion with the A5370 study team prior to biopsy or institution of systemic steroid therapy is strongly recommended. Consider systemic corticosteroids (recommend: methylprednisolone 1-2 mg/kg/day IV for 3 days then reduced to 1 mg/kg/day and taper over at least 1 month [59]). Participants may continue study procedures unless clinically contraindicated.

8.3.1.4 Grade 4: Life-threatening consequences (e.g., hypotensive shock)

DISCONTINUE further doses of cemiplimab/placebo.

Participants who develop Grade 4 diarrhea should have the following diagnostic studies completed immediately:

- Stool WBC
- Stool culture
- Clostridium difficile toxin
- Endoscopy or abdominal CT scan

The core study team must be notified within 24 hours by email at: actg.coreA5370@fstrf.org.

- If stool studies reveal an infectious cause, treatment for specific infection should be started. If colitis is observed per endoscopy or abdominal CT scan or highly clinically suspected and infectious disease work-up is negative, appropriate subspecialty clinical consultation should be obtained. Consider systemic corticosteroids (recommend: methylprednisolone 1-2 mg/kg/day IV for 3 days, then reduced to 1 mg/kg/day and tapered over at least 1 month. Discussion with the A5370 study team prior to biopsy or institution of systemic steroid therapy is strongly recommended. Participants may continue study procedures unless clinically contraindicated.

8.3.2 Suspected Hepatotoxicity

Abnormal AST, ALT, or total bilirubin (if total bilirubin is elevated, direct and indirect bilirubin should be obtained).

NOTE: Regarding reporting of suspected hepatotoxicity, the following combination of hepatic laboratory results raise significant concern for potentially severe DILI and should prompt expedited reporting: an elevated AST and/or ALT of Grade 2 (2.5 to <5.0 x ULN) or greater, alkaline phosphatase <2 x ULN and bilirubin ≥2 x ULN with no other immediately apparent possible causes of AST or ALT elevation and hyperbilirubinemia (such as concomitant use of atazanavir), including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic (Hy's law, see Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation Https://www.fda.gov/downloads/Drugs/.../guidances/UCM174090.pdf).

Management of suspected hepatotoxicity should be addressed as outlined below.

8.3.2.1 Grade 1: AST or ALT (1.25 to <2.5 x ULN); total bilirubin (1.1 to <1.6 x ULN)

Participants who develop Grade 1 elevation in ALT, AST, or total bilirubin should have routine monitoring of ALT, AST, and total bilirubin, per protocol. If associated symptoms are present, additional work-up may be indicated to rule out other etiologies for hepatitis.

8.3.2.2 Grade 2: AST or ALT (2.5 to <5.0 x ULN); total bilirubin (1.6 to <2.6 x ULN)

WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined.

Participants who develop Grade 2 elevation in ALT, AST or total bilirubin should have additional labs to rule out non-cemiplimab/placebo-related causes of hepatitis.

NOTE: For participants with a Grade 1 elevation in total bilirubin at baseline due to atazanavir, additional labs and imaging may not be indicated for an isolated Grade 2 total bilirubin elevation in the absence of symptoms or ≥two-fold increase in total bilirubin from baseline.

If a non-cemiplimab/placebo-related cause is found, it is important to document the supporting scientific evidence for this cause and treat the underlying etiology per standard clinical practice.

- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Radiographic imaging should be considered to rule out biliary obstruction.
- Repeat AST, ALT, total bilirubin, and alkaline phosphatase within 48 hours (via non-scheduled visit if necessary)
- Follow AST/ALT/total bilirubin/direct bilirubin/albumin/International normalized ratio (INR) at least every 3 days until stable or resolving, then weekly thereafter until AST and ALT decline to Grade <2, then monitor per protocol.
- If any or all AST, ALT, total bilirubin or alkaline phosphatase values continue to increase, obtain immediate appropriate subspecialty clinical consultation and consider liver biopsy.
- Consider use of corticosteroids (recommended: prednisone 60 mg/day orally or methylprednisolone 1 mg/kg/day IV). If corticosteroids are begun, complete a taper over at least 1 month.
- Discussion with the core study team prior to biopsy or institution of corticosteroid therapy is strongly recommended.

8.3.2.3 Grade 3: AST or ALT (5.0 to <10.0 x ULN); total bilirubin (2.6 to <5.0 x ULN) with other signs and symptoms of hepatotoxicity

WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined.

Participants who develop Grade 3 elevations in ALT, AST, or total bilirubin should have the following diagnostic evaluations completed as soon as possible and within 48 hours after receiving the abnormal results:

- Repeat ALT, AST, and total bilirubin
- Additional labs to rule out non-cemiplimab-related causes of hepatitis including testing for acute hepatitis A, B, and C, as appropriate

- Repeat ALT/AST/total bilirubin/direct bilirubin/albumin/INR at least every 3 days until stable or resolving, then weekly thereafter until ALT and AST decline to Grade <2, then monitor per SOE.
- Imaging to rule out biliary obstruction
- Appropriate subspecialty clinical consultation (hepatologist, immunologist)
- Consider liver biopsy in consultation with a hepatologist
- Treat with high-dose IV corticosteroids for 24-48 hours
- If transaminase levels do not decrease 48 hours after initiation of systemic corticosteroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- When AST/ALT improve to Grade 1 or less, begin a corticosteroid taper with prednisone 1-2 mg/kg/day orally or methylprednisolone 1 mg/kg/day (IV) over no less than 4 weeks.

The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org.

If a non-cemiplimab/placebo-related cause is found, it is important to document the scientific evidence for this conclusion and treat the underlying etiology per standard clinical practice.

Discussion with the A5370 study team prior to biopsy or institution of corticosteroid therapy is strongly recommended. If corticosteroids are begun, complete a taper over at least 1 month.

8.3.2.4 Grade 4: AST or ALT (≥10.0 x ULN); total bilirubin (≥5.0 x ULN) with life-threatening consequences (e.g., signs and symptoms of liver failure)

DISCONTINUE further doses of cemiplimab/placebo.

Participants who develop Grade 4 elevations in ALT, AST, or total bilirubin should have the following diagnostic evaluations completed as soon as possible and within 48 hours after receiving the abnormal results:

- Repeat AST, ALT, total bilirubin, and alkaline phosphatase
- Appropriate subspecialty clinical consultation (hepatologist, immunologist)
- Consider liver biopsy in consultation with a hepatologist
- Additional labs to rule out non-cemiplimab-related causes of hepatitis including testing for acute hepatitis A, B and C, as appropriate
- Imaging to rule out biliary obstruction
- Consider hospitalization

- Treat with high-dose IV corticosteroids for 24-48 hours (recommended: prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV).
- If transaminase levels do not decrease 48 hours after initiation of systemic corticosteroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- When AST/ALT improve to Grade 1 or less, begin a corticosteroid taper with prednisone 1-2 mg/kg/day orally or methylprednisolone 1 mg/kg/day (IV) over no less than 4 weeks.
- After 48 hours, repeat ALT/AST/total bilirubin/direct bilirubin/albumin/INR every 2 to 3 days until AST/ALT decreases to ≤10x ULN and/or total bilirubin decreases to ≤5x ULN, then repeat at least weekly until decline to Grade <2, then resume routine monitoring per protocol.

Participants may continue study procedures unless clinically contraindicated.

The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org. Discussion with the team prior to biopsy or institution of steroid therapy is strongly recommended.

8.3.3 Suspected Hyperthyroidism or Hypothyroidism

Suspected hyperthyroidism or hypothyroidism are most commonly based on clinical symptoms and/or laboratory abnormalities

NOTE: Cases of thyroid dysfunction have typically been identified through routine monitoring of laboratories or as part of a work-up for symptoms such as fatigue.

As Grade 1 hypothyroidism and hyperthyroidism are defined per the DAIDS AE grading table as asymptomatic, the protocol includes repeat testing for TSH and free T4 to allow detection of asymptomatic abnormalities and allow prompt detection and management. Criteria for Grade 1 hypothyroidism and hyperthyroidism based on laboratory results are as follows:

Grade 1 hypothyroidism is defined as a TSH >4.0 mIU/L (the upper limit of normal) in conjunction with a free T4 below the lower limit of normal range of the laboratory where testing is performed and are confirmed on a subsequent visit.

Grade 1 hyperthyroidism is defined as a TSH <0.5 mIU/L (lower limit of normal) in conjunction with a free T4 result that is above the upper limit of normal of the laboratory where testing is performed and are confirmed on a subsequent visit.

The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org.

8.3.3.1 For suspected hypothyroidism or hyperthyroidism proceed with the following:

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Prompt consultation with endocrinology immediately
- If based on asymptomatic TSH or free T4 levels, repeat the TSH and free T4 assays, and obtain thyroglobulin and TPO antibodies and thyroid stimulating immunoglobulin
- If the participant has symptoms consistent with hypo- or hyperthyroidism, obtain TSH and free T4 assays, and obtain thyroglobulin and TPO antibodies and thyroid stimulating immunoglobulin
- Obtain serum cortisol and/or adrenocorticotropic hormone (ACTH) stimulation test if adrenal insufficiency suspected

NOTE: If TSH, free T4 and thyroglobulin and TPO antibodies and thyroid stimulating immunoglobulin labs are normal, consider other etiologies for the participant's symptoms.

If any of the above endocrine labs are abnormal, proceed with the following:

- Consult endocrinology immediately
- Initiate appropriate hormone replacement to manage endocrinopathy in consultation with endocrinologist
- Consider corticosteroids in consultation with endocrinology for Grade ≥3 hyperthyroidism
- If evidence of non-cemiplimab/placebo-related cause, it is important to document the scientific evidence for and treat the underlying cause identified for the symptoms or laboratory abnormalities.
- Continue hormone replacement as needed
- Monitor TSH and free T4 as appropriate, at least every 2 weeks
- Participants may continue study procedures unless clinically contraindicated.

8.3.4 Suspected Adrenal Insufficiency/Adrenal Crisis

Suspected adrenal insufficiency or adrenal crisis is most commonly based on clinical symptoms and/or laboratory abnormalities

NOTE: Cases have typically been identified through routine monitoring of laboratories or as part of a work-up for symptoms such as fatigue, hypotension, and shock.

Adrenal insufficiency should be graded per the National Cancer Institute's CTCAE guidelines as outlined below and available at the NCI Web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

NOTE A: It is important to draw labs outlined below at appropriate times; for example, serum cortisol and ACTH should be obtained at 8:00 AM if feasible and will not delay work-up.

NOTE B: If endocrine labs are normal, consider other etiologies of symptoms. If adrenal insufficiency is suspected, WITHHOLD further doses of cemiplimab/placebo and proceed with management per Grade of severity (see sections 8.3.4.1 to 8.3.4.4).

The core study team must be notified within 24 hours by email at actg.coreA5370@fstrf.org.

8.3.4.1 Grade 1: Asymptomatic (clinical or diagnostic observations only; intervention not indicated)

- Obtain cortisol level, renin, plasma ACTH, ACTH stimulation test, and chemistries
- Obtain TSH and free T4 if fatigue is present or thyroid disorder suspected
- If evidence of non-cemiplimab-related cause, treat underlying cause and document evidence of non-cemiplimab/placebo-related cause
- If labs are abnormal, consider consulting an endocrinologist

8.3.4.2 Grade 2: Moderate symptoms (medical intervention indicated)

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Obtain serum cortisol level, renin, plasma ACTH, ACTH stimulation test, and chemistries
- Obtain TSH, free T4, thyroglobulin, TPO antibodies, and thyroid stimulating immunoglobulin if fatigue is present or thyroid disorder suspected
- Consult endocrinology immediately
- If any of above labs are abnormal, consider short course of high-dose steroids (recommend methylprednisolone 1 g/day IV) in consultation with an endocrinologist

8.3.4.3 Grade 3: Severe symptoms (hospitalization indicated)

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Obtain stat labs including serum cortisol, plasma ACTH, ACTH stimulation test, TSH, free T4, and if abnormal obtain thyroglobulin TPO antibodies, thyroid stimulating immunoglobulin, and chemistries
- Consult endocrinology immediately
- Consider hospitalization
- Initiate high dose steroids (recommend methylprednisolone 1 g/day IV) in consultation with an endocrinologist
- Rule out sepsis
- If evidence of non-cemiplimab-related cause, treat underlying cause and document evidence of non-cemiplimab-related cause
- High dose steroids should be tapered, if used, in consultation with an endocrinologist
- Monitor endocrine labs as appropriate

8.3.4.4 Grade 4: Life-threatening consequences (urgent intervention indicated)

- DISCONTINUE cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Obtain stat labs including serum cortisol, plasma ACTH, ACTH stimulation test, TSH, free T4, thyroglobulin, TPO antibodies, thyroid stimulating immunoglobulin, and chemistries
- Immediately hospitalize participant
- Consult endocrinology immediately
- Initiate high dose steroids (recommend methylprednisolone 1 g/day IV) in consultation with an endocrinologist
- Rule out sepsis
- If evidence of non-cemiplimab/placebo-related cause, treat underlying cause and document evidence of non-cemiplimab-related cause
- High dose steroids should be tapered, if used, in consultation with an endocrinologist
- Monitor endocrine labs as appropriate

8.3.5 Suspected Pulmonary Toxicity

New or worsening pulmonary symptoms

A high index of suspicion for pulmonary toxicity or immune-related pneumonitis should be maintained in participants who present with respiratory symptoms.

Signs and symptoms include dyspnea, cough, hypoxia, and other respiratory complaints. The core study team must be notified immediately of all suspected cases by email at actg.coreA5370@fstrf.org. For participants who have new or worsening pulmonary-related signs or symptoms or radiographic changes, radiographic imaging should be obtained/repeated immediately (chest X-ray, chest CT, chest CT with pulmonary embolism protocol) if not yet obtained.

For any suspected immune-related pneumonitis, WITHOLD further doses of cemiplimab/placebo until diagnostic evaluation has been completed and etiology of the signs and symptoms has been determined.

If grading criteria for a particular pulmonary diagnosis or sign/symptom is not specifically listed in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, refer to the Estimating Severity Grade section for the "Clinical Adverse Events Not Otherwise Identified in the DAIDS AE Grading Table" grading scale.

Of note, pneumonitis should be graded per the National Cancer Institute's CTCAE guidelines as outlined below and available at the NCI Web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

The categories listed below are for management of suspected cemiplimab/placebo related pulmonary toxicity.

If evaluation provides evidence for a non-cemiplimab/placebo-related cause, it is important to document the scientific evidence for and treat per standard clinical practice. Participants may continue study procedures unless clinically contraindicated.

If there is no evidence of a non-cemiplimab/placebo-related cause, then manage respiratory symptoms per category below which best describes changes:

8.3.5.1 Grade 1: Asymptomatic; (clinical or diagnostic observations only; intervention not indicated). (Examples: asymptomatic findings on physical exam or abnormality on chest X-ray obtained outside of the study)

The following steps should be taken:

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Monitor symptoms every 2-3 days

- Pulmonary and ID consultation as clinically indicated
- Consider steroids (recommend: prednisone 60 mg/day orally or methylprednisolone 1 mg/kg/day IV)
- Consider empiric antibiotics (if concurrent infection suspected)
- Repeat radiologic assessment within 3 weeks

Re-assess management at least every 3 weeks until resolution, clinical stabilization or documented as non-cemiplimab-related cause.

8.3.5.2 Grade 2: Symptomatic; medical intervention indicated; limiting instrumental Activities of Daily Living (ADLs)

The following steps should be taken:

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Pulmonary and ID consultation as clinically indicated
- Consider diagnostic BAL or VATS as indicated
- Monitor symptoms daily
- Consider hospitalization
- Treat with moderate-dose steroids (recommend: prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV)
- Consider empiric antibiotics (if concurrent infection suspected)
- Repeat radiologic assessment

Re-assess management every 1-3 days. If participant stabilizes, continue daily monitoring and consideration of other medical management as above. If participant improves, begin steroid taper to be completed over several weeks.

8.3.5.3 Grade 3: Severe symptoms; limiting self-care; oxygen indicated

The following steps should be taken:

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Hospitalization
- Pulmonary and ID consultation
- Treat with high-dose steroids (recommended methylprednisolone 1 g/day IV)
- Consider empiric broad spectrum antibiotics (if concurrent infection suspected)

- Consider bronchoscopy if clinically feasible
- Consider lung biopsy (via VATS, open-lung, or bronchoscopic procedures)

Re-assess management at least daily. If participant is improving, initiate steroid taper to be completed over several weeks. If participant is not improving after 48 hours or worsening, consider the following:

- Additional immunosuppressive medication (e.g., infliximab, mycophenolate mofetil, cyclophosphamide, IVIG) in consultation with the core team.
- Additional antibiotics.
- When improving, slow taper of immunosuppression in consultation with pulmonologist and core team.

8.3.5.4 Grade 4: Life-threatening respiratory compromise (urgent intervention indicated (e.g., tracheotomy or intubation)

The following steps should be taken:

- DISCONTINUE cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Hospitalization
- Pulmonary and ID consultation
- Treat with high-dose steroids (recommend methylprednisolone 1 g/day IV)
- Consider empiric broad spectrum antibiotics (if concurrent infection suspected)
- Consider bronchoscopy if clinically feasible
- Consider lung biopsy (via VATS, open-lung, or bronchoscopic procedures)

Re-assess management at least daily. If participant is improving, initiate steroid taper to be completed over several weeks. If participant is not improving after 48 hours or worsening, consider the following:

- Additional immunosuppressive medication (e.g., infliximab, mycophenolate mofetil, cyclophosphamide, IVIG) in consultation with the core team.
- Additional antibiotics.
- When improving, slow taper of immunosuppression in consultation with pulmonologist and core team.

8.3.6 Suspected Myocarditis

For participants who have new or worsening signs or symptoms of myocarditis (see below), an ECG should be obtained immediately. Signs and symptoms of myocarditis include chest pain, rapid or abnormal heart rhythms, shortness of breath, and lower extremity edema. For any suspected immune-related cardiac toxicity, WITHHOLD further doses of cemiplimab/placebo until diagnostic evaluation has been completed and etiology of the signs and symptoms has been determined.

Signs and symptoms related to the cardiovascular system other than myocarditis (as diagnosed by a cardiologist) should be managed in accordance with standard clinical care in conjunction with a cardiologist.

If grading criteria for a particular cardiovascular diagnosis or sign/symptom is not specifically listed in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, refer to the Estimating Severity Grade section for the Clinical Adverse Events Not Otherwise Identified in the DAIDS AE Grading Table grading scale.

Management of potentially associated ECG abnormalities:

8.3.6.1 Grade 1 Arrhythmia: No symptoms AND no intervention indicated

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Repeat ECG within 24 hours of notification
- Consult cardiologist
- Consider systemic corticosteroids (starting with 1 mg/kg prednisone orally or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days; when symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist)

8.3.6.2 Grade 2 Arrhythmia: No symptoms AND non-urgent intervention indicated

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org

- Consult cardiologist immediately
- Consider systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days; when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist)

8.3.6.3 Grade 3 Arrhythmia: Non-life-threatening symptoms AND non-urgent intervention indicated
WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined

- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult cardiologist immediately
- Treat with moderate-dose steroids (recommend prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist
- If no significant response to initial corticosteroid treatment, consider high-dose corticosteroids (recommended methylprednisolone 1 g/day IV); if high-dose corticosteroids used, they should be tapered in consultation with a cardiologist

8.3.6.4 Grade 4 Arrhythmia: Life-threatening arrhythmia OR Urgent intervention indicated

- WITHHOLD further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Immediate hospitalization
- Consult cardiologist immediately
- Treat with high-dose steroids (recommended methylprednisolone 1 g/day IV) in consultation with a cardiologist
- High-dose corticosteroids should be tapered in consultation with a cardiologist

8.3.6.5 Grade 1 Heart Failure: No symptoms AND laboratory or cardiac imaging abnormalities

- Consult cardiologist immediately
- Repeat ECG within 24 hours of notification
- Obtain echocardiogram

- Consider systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days); when symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist.
- Proceed with standard of care diagnostics and management for new onset heart failure

8.3.6.6 Grade 2 Heart Failure: Symptoms with mild to moderate activity or exertion

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult cardiologist immediately
- Initiate systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days); when symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist.
- If no response to initial corticosteroids, consider moderate dose steroids (recommend: prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist.
- Repeat ECG within 24 hours notification
- Obtain echocardiogram
- Proceed with standard of care diagnostics and management for new onset heart failure

8.3.6.7 Grade 3 Heart Failure: Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR intervention indicated (e.g., oxygen)

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult cardiologist immediately
- Initiate moderate dose steroids (recommend prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a cardiologist.

- If no response to initial corticosteroids, consider high-dose steroids (recommended methylprednisolone 1 g/day IV) in consultation with a cardiologist
- Repeat ECG within 24 hours notification
- Obtain echocardiogram
- Proceed with standard of care diagnostics and management for new onset heart failure

8.3.6.8 Grade 4 Heart Failure: Life-threatening consequences OR urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

- DISCONTINUE further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult cardiologist immediately
- Initiate high-dose steroids (recommended methylprednisolone 1 g/day IV) in consultation with a cardiologist
- Repeat ECG within 24 hours notification
- Obtain echocardiogram
- Proceed with standard of care diagnostics and management for new onset heart failure

8.3.7 Suspected Immune-related Renal Dysfunction

For participants with worsening renal function, the following should be obtained: repeat BUN, serum creatinine, and serum electrolytes within 48 hours of the first abnormal value. For any suspected immune-related renal toxicity, WITHHOLD further doses of cemiplimab/placebo until diagnostic evaluation has been completed and etiology of the signs and symptoms has been determined.

NOTE: The DAIDS AE Grading Table, corrected Version 2.1, July 2017, for grading creatinine should be used, and can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

8.3.7.1 Grade 1 Creatinine Abnormality: Serum creatinine of 1.1 to 1.3 x ULN

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Ensure participant is well-hydrated and repeat serum creatinine
- Obtain urinalysis, erythrocyte sedimentation rate (ESR), complement levels (C3, C4, CH50), anti-DNA levels, and antineutrophil cytoplasmic antibody (ANCA)
- Monitor serum creatinine weekly until it returns to <1.1 x ULN

8.3.7.2 Grade 2 Creatinine Abnormality: Serum creatinine of >1.3 to 1.8 x ULN OR increase to 1.3 to <1.5 x participant's baseline

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Ensure participant is well-hydrated and repeat serum creatinine
- Obtain urinalysis, erythrocyte sedimentation rate (ESR), complement levels (C3, C4, CH50), anti-DNA levels, and antineutrophil cytoplasmic antibody (ANCA)
- Monitor serum creatinine every 72 hours
- Consider renal ultrasound and 24 hour urine studies
- Consider consulting nephrologist
- Consider systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for four days); when creatinine improves to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a nephrologist.

8.3.7.3 Grade 3 Creatinine Abnormality: >1.8 to <3.5 x ULN OR increase to 1.5 to <2.0 x participant's baseline

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Consult nephrologist immediately
- Obtain urinalysis, erythrocyte sedimentation rate (ESR), complement levels (C3, C4, CH50), anti-DNA levels, and antineutrophil cytoplasmic antibody (ANCA)
- Monitor creatinine every 72 hours
- Obtain renal ultrasound and 24 hour urine studies
- Initiate moderate-dose steroids (recommend prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV); when creatinine improves to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a nephrologist.
- If no response to initial corticosteroids, consider high-dose steroids (recommended methylprednisolone 1 g/day IV) in consultation with a nephrologist; high-dose corticosteroids should be tapered, if used, in consultation with a nephrologist.

8.3.7.4 Grade 4 Creatinine Abnormality: ≥3.5 x ULN OR increase of ≥2.0 x participant's baseline

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined

- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult nephrologist immediately
- Obtain urinalysis, erythrocyte sedimentation rate (ESR), complement levels (C3, C4, CH50), anti-DNA levels, and antineutrophil cytoplasmic antibody (ANCA)
- Monitor creatinine every 72 hours
- Obtain renal ultrasound and 24 hour urine studies
- Initiate high-dose steroids (recommended methylprednisolone 1 g/day IV) in consultation with a nephrologist; high-dose corticosteroids should be tapered, if used, in consultation with a nephrologist.

8.3.8 Suspected Immune-related Neurologic Dysfunction

8.3.8.1 Grades 1-4 Altered mental status, neuromuscular weakness, or seizures

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Perform appropriate diagnostics which may include but are not limited to imaging with MRI with contrast of affected region and CSF sampling
- Hospitalization as per standard of care
- Consult neurologist immediately
- Initiate systemic corticosteroids in consultation with a neurologist
- High-dose corticosteroids should be tapered, if used, in consultation with a neurologist.

8.3.8.2 Grades 1 and 2 Headache or Neurosensory Alteration

(See DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 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).

- Monitor participant as outpatient daily for 72 hours for worsening or improvement of headache or neurosensory alteration.
- Consider consultation with a neurologist

8.3.8.3 Grades 3 and 4 Headache or Neurosensory Alteration

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org

- Perform appropriate diagnostics which may include but are not limited to imaging with MRI with contrast of affected region and CSF sampling
- Hospitalization as per standard of care
- Consult neurologist immediately
- Initiate systemic corticosteroids (e.g., hydrocortisone) in consultation with a neurologist
- High dose corticosteroids should be tapered, if used, in consultation with a neurologist.

8.3.9 Suspected Development of Diabetes

8.3.9.1 Development of hyperglycemia meeting the diagnosis of diabetes (see below) of any grade is considered an immune mediated adverse event and results in the discontinuation of any further infusions.

(See DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 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)

The diagnosis of diabetes for this study is made on the basis of one of the following criteria:

1. HgbA1c ≥6.5%. This lab is drawn at screening only. The test should be performed using CLIA-certified laboratory standard methods.*

OR

2. Fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) measured from any fasting lab draw during screening or post-screening. Fasting is defined as no caloric intake for at least 8 hours.*

OR

3. Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a participant with classic symptoms of hyperglycemia or hyperglycemic crisis (polyuria, polydipsia, blurred vision, confusion, nausea/vomiting, disesthesias), or in labs drawn in a non-fasting participant for other study reasons, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

8.3.9.2 Grades 1-4 Diabetes

- DISCONTINUE further doses of cemiplimab/placebo
- *In the absence of unequivocal hyperglycemia, criteria 1-3 (above) should be confirmed by repeat testing with preference given to a repeat fasting blood glucose level
- Immediately contact the core team via email at actg.coreA5370@fstrf.org when a diagnosis of diabetes is suspected or confirmed
- New onset diabetes of any grade should be managed with the assistance of an endocrinologist who may order additional, confirmatory testing (i.e., oral glucose tolerance testing).

8.4 Suspected Ocular Toxicity

New or worsening eye symptoms
A high index of suspicion for ocular toxicity or immune-related uveitis should be maintained in participants who present with eye or visual symptoms. The core team must be notified immediately of all suspected cases of uveitis by e-mail at actg.coreA5370@fstrf.org.

For participants who have new or worsening ocular signs or symptoms, ophthalmologic evaluation should be obtained immediately. Signs and symptoms include eye pain, redness, irritation, swelling of the eye and conjunctiva, and changes in vision.

All grades, signs and symptoms related to the eye other than uveitis (as diagnosed by an ophthalmologist) should be managed in accordance with standard clinical care in conjunction with an ophthalmologist.

If grading criteria for a particular ocular diagnosis or sign/symptom is not specifically listed in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, refer to the Estimating Severity Grade section for the “Clinical Adverse Events Not Otherwise Identified in the DAIDS AE Grading Table” grading scale.

8.4.1 Grade 1 Uveitis: Asymptomatic but detectable on exam.

- DISCONTINUE further doses of cemiplimab/placebo if uveitis confirmed by ophthalmologist
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult ophthalmologist for examination of the conjunctiva, anterior and posterior chambers, and retina
- Consider topical steroids such as 1% prednisolone acetate suspension and iridocyclitics in consultation with an ophthalmologist

8.4.2 Grade 2 Uveitis: Symptomatic anterior uveitis or medical intervention indicated.

- DISCONTINUE further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org

- Consult ophthalmologist immediately
- Treat with topical corticosteroids such as 1% prednisolone acetate suspension and iridocyclitics in consultation with an ophthalmologist
- Consider systemic corticosteroids if symptoms do not improve within 3-5 days in consultation with an ophthalmologist, (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days)

8.4.3 Grade 3 Uveitis: Posterior or pan-uveitis OR operative intervention indicated.

- DISCONTINUE further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult ophthalmologist immediately
- Consider systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days); when symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with an ophthalmologist.
- If no response to initial systemic corticosteroids, consider moderate-dose steroids (recommend prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with an ophthalmologist.
- If evidence of non-cemiplimab/placebo-related cause, treat underlying cause and document evidence of non-cemiplimab/placebo-related cause

8.4.4 Grade 4 Uveitis: Disabling visual loss in affected eye(s).

- DISCONTINUE cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult ophthalmologist immediately
- Initiate high-dose corticosteroids (recommended methylprednisolone 1 g/day IV) in consultation with an ophthalmologist; high-dose corticosteroids should be tapered, if used, in consultation with an ophthalmologist
- If evidence of non-cemiplimab/placebo-related cause, treat underlying cause and document evidence of non-cemiplimab/placebo-related cause

8.5 Suspected Dermatologic Toxicity

New or worsening dermatologic signs or symptoms
A high index of suspicion for dermatologic toxicity or immune-related dermatitis should be maintained in participants who present with skin-related signs and/or symptoms. The core team must be notified immediately of all suspected cases of suspected immune-related dermatitis by e-mail at actg.coreA5370@fstrf.org.

Dermatologic toxicity is the most common irAE associated with checkpoint inhibitors. Approximately 50% of patients treated with ipilimumab experience rash and/or pruritus, and approximately 30% to 40% of those treated with nivolumab or pembrolizumab will have dermatologic complications [28]. For most patients, dermatologic toxicity is the earliest irAE experienced, with onset an average of 3.6 weeks after treatment initiation

[59]. Typical physical examination findings consist of a reticular, maculopapular, faintly erythematous rash on the trunk or extremities. Vitiligo is also seen commonly [60]. Oral mucositis and/or complaints of dry mouth appear to be more frequent with PD-1 receptor checkpoint inhibitors than with CTLA-4 blockade. In the phase I study of nivolumab; this was observed in 6.5% of patients, including one case with Grade 3 toxicity [61].

The types of suspected skin-related AEs include but are not limited to the following: exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and TEN.

For participants who have new or worsening dermatologic signs or symptoms, prompt dermatologic consultation should be obtained immediately [62, 63].

8.5.1 Grade 1 Dermatitis: Macules/papules covering <10% body surface area (BSA) with or without symptoms (e.g., pruritus, burning, tightness)
- Consult dermatologist for examination of the affected skin
- Symptomatic treatment should be given in consultation with the dermatologist such as topical corticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).

8.5.2 Grade 2 Dermatitis: Macules/papules covering 10%-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs
- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult dermatologist immediately
- Symptomatic treatment should be given such as topical corticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl)
- Consider systemic corticosteroids if symptoms do not improve within 3-5 days (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days). When symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with a dermatologist

8.5.3 Grade 3 Dermatitis: Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs
- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult dermatologist immediately and biopsy skin lesions for confirmation of diagnosis.
- Treatment with moderate-dose oral corticosteroids is recommended

(prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a dermatologist.
- If evidence of non-cemiplimab/placebo-related cause, treat underlying cause and document evidence of non-cemiplimab/placebo-related cause

8.5.4 Grade 4 Dermatitis: Stevens-Johnson Syndrome, TEN defined as skin sloughing covering with associated signs (e.g., erythema, purpura epidermal detachment, and/or mucous membrane detachment)
- DISCONTINUE further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult dermatologist immediately and biopsy skin lesions for confirmation of diagnosis
- Initiate high-dose corticosteroids (recommend methylprednisolone 1 g/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a dermatologist
- If evidence of non-cemiplimab/placebo-related cause, treat underlying cause and document evidence of non-cemiplimab-related cause

8.6 Suspected Hematologic Toxicity

8.6.1 Thrombocytopenia

8.6.1.1 Grade 1 Platelet Count: 100,000 to <125,000/mm^3
- No change in cemiplimab/placebo dose

8.6.1.2 Grade 2 Platelet Count: 50,000 to <100,000/mm^3
- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consider systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days); when symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with a hematologist

8.6.1.3 Grade 3 Platelet Count: 25,000 to <50,000/mm^3
- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult a hematologist

- Treatment with moderate-dose oral corticosteroids is recommended (prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a hematologist

8.6.1.4 Grade 4 Platelet Count: <25,000/mm^3

- DISCONTINUE cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult a hematologist
- Initiate high-dose corticosteroids (recommend methylprednisolone 1 g/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a hematologist

8.6.2 Neutropenia

8.6.2.1 Grade 1 Absolute Neutrophil Count (ANC): 800 to 1000/mm^3

- No change in cemiplimab/placebo dose

8.6.2.2 Grade 2 ANC of 600 to 799/mm^3

- WITHHOLD further doses of cemiplimab/placebo until clinical and laboratory evaluation are completed and diagnosis and etiology of the symptoms or laboratory abnormalities are defined
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consider systemic corticosteroids (starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg orally once daily for 4 days); when symptoms improve, steroid taper should be started and continued over no less than 4 weeks in consultation with a hematologist
- Participants may continue study procedures and cemiplimab/placebo unless clinically contraindicated

8.6.2.3 Grade 3 ANC of 400 to 599/mm^3

- DISCONTINUE further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult a hematologist
- Treatment with moderate-dose oral corticosteroids is recommended (prednisone 240 mg/day orally or methylprednisolone 4 mg/kg/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with a hematologist.

8.6.2.4 Grade 4 ANC of <400 cells/mm^3

- DISCONTINUE further doses of cemiplimab/placebo
- Immediately contact the core team via email at actg.coreA5370@fstrf.org
- Consult a hematologist
- Initiate high-dose corticosteroids (recommend methylprednisolone 1 g/day IV); when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks in consultation with hematologist

8.7 Virologic Failure

If two consecutive plasma HIV-1 RNA ≥200 copies/mL are resulted at any time on study, the participant will be considered to have virologic failure. Adherence to antiretroviral therapy should be carefully assessed.

If the participant discontinues ART before the first infusion, the first infusion should not be given and the participant can end the study prematurely.

If the participant discontinues ART after the first infusion but before the second infusion, the second infusion should not be given but the participant should continue on study for safety follow-up, assessment of PK and RO as noted in the SOE. Stored plasma/PBMC for immunologic studies, stored plasma for SCA and samples for CD4+ T cell-associated HIV-1 RNA, DNA, and 2-LTR do not need to be obtained.

If the participant is adherent to ART, then ART should be managed by the site investigator and primary care provider in discussion with the A5370 core team (actg.coreA5370@fstrf.org), and all study evaluations should proceed as scheduled.

8.8 Pregnancy

If pregnancy is suspected in a woman on study after receiving cemiplimab/placebo, then a pregnancy test should be obtained. Confirmed pregnancy will result in immediate discontinuation of the study medication and initiation of counseling regarding the lack of information on safety of cemiplimab in pregnancy. Participants who become pregnant while on study should contact the site to schedule an unplanned study visit and will be followed on study/off-treatment until study completion. Male participants whose partners become pregnant will continue treatment as outlined in the SOE.

Pregnant women should be encouraged to continue on study (off study medication) for safety follow-up, and assessment of PK and RO as noted in the SOE. Stored plasma/PBMC for immunologic studies, stored plasma for SCA and samples for CD4+ T cell-associated HIV-1 RNA, DNA, and 2-LTR should not be obtained to minimize blood volume.

Pregnancy Outcomes and Reporting
Pregnancy outcomes will be submitted on an outcome eCRF at the end of the pregnancy and again at 6 months following the end of pregnancy.

If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Sites must collect and record information on pregnancy complications and outcome for all pregnancies that occur during study follow-up.

Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 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.)

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

Study treatment is two single infusions of cemiplimab (anti-PD-1 antibody) or placebo. Study treatment should be discontinued for:

- Drug-related toxicity (see section 8.1)
- A Grade 3 or 4 infusion reaction occurs (see section 8.2)
- Discontinuation of ART
- Requirement for prohibited concomitant medications (see section 5.4)
- Pregnancy or breastfeeding
- Request by participant to terminate treatment
- Clinical reasons believed life-threatening by the physician, even if not addressed in section 8.1 of the protocol
- Positive results for antibodies to TPO, GAD65/GAD or islet cell antigen
- An irAE of any grade occurs
- Prolonged need (>7 days) for systemic steroids

NOTE A: Participants who receive one infusion but for whom treatment was discontinued prematurely will be followed on study off treatment per the schedule of events.

NOTE B: If the study participant experiences an irAE after the first infusion of cemiplimab/placebo at entry, study treatment should be discontinued (i.e., the participant would not receive the second infusion).

9.2 Premature Study Discontinuation

A primary goal of this study is to assess the safety of two single infusions of cemiplimab/placebo. Therefore, every effort should be made to retain participants on study to assess safety outcomes. Participants should discontinue study if:

- Request by the participant to withdraw
- At the discretion of the IRB/EC, 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

A5370 is a phase I/II, double-blinded (within each cohort), dose-escalating, placebo-controlled study of the safety and immunotherapeutic activity of two infusions of anti-PD-1 (cemiplimab) in HIV-1-infected participants on cART who have HIV-1 RNA below the limit of quantification and CD4+ T-cell counts ≥350/mm^3. Each participant will be followed for 48 weeks, with frequent visits in the first 12 weeks. The decision to enroll into each successively higher dose cohort will be based on review of the safety data seen in participants who received cemiplimab or placebo doses in the previous dose cohorts (see sections 7.4 and 10.4.1). Accrual for each dose cohort is anticipated to take 3-4 months. Taking into account the time needed for data review regarding dose escalation between each cohort (data entry, core team review, SMC report generation, and SMC review) and assuming that all three cohorts complete enrollment, the total time to complete accrual is expected to be about 20 months. This may take longer if participant replacements are needed. Laboratory assays and study analyses may commence, and findings reported, after each cohort has completed accrual and follow-up through the week 12 visit.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov. Outcomes of interest for exploratory objectives or for secondary objectives intended for subsequent publications are listed under Exploratory Outcome Measures.

10.2.1 Primary Outcome Measures

10.2.1.1 Safety

Occurrence of a Grade ≥3 AE, or Grade ≥1 irAE (such as, but not limited to, pneumonitis, colitis, adrenal insufficiency, or hypothyroidism), that is related to study treatment (as judged by the

core team, blinded to treatment arm) any time from study treatment administration through the week 48 visit.

10.2.2 Secondary Outcome Measures

10.2.2.1 Frequency of HIV-1 gag-specific CD8+ T cells by intracellular staining for CD107a and IFN-γ at baseline and through week 12

10.2.2.2 Frequency of HIV-1 gag-specific CD8+ T cells by intracellular staining for CD107a and IFN-γ at baseline, after the first dose (average of weeks 2-6) and after the second dose (average of weeks 8-12)

10.2.2.3 Frequency of HIV-1 gag-specific CD8+ T cells by intracellular staining for IFN-γ or CD107a alone at baseline and through week 12

10.2.2.4 Polyfunctional response of HIV-1 gag-specific CD8+ T cells by intracellular staining for IFN-γ, CD107a, IL-2, and TNFα at baseline and through week 12

10.2.3 Exploratory Outcome Measures

10.2.3.1 Total HIV-1 DNA, cell-associated HIV-1 RNA and RNA/DNA ratios in CD4+ T cells, and plasma HIV RNA by SCA at baseline, prior to the second infusion at week 6, and also at week 12

10.2.3.2 Gene array analysis

10.2.3.3 Intact proviral HIV-1 genomes at baseline and following treatment

10.2.3.4 Ex vivo HIV-specific T cell responses following cemiplimab exposure

10.2.3.5 Expression of PD-1, PD-L1 and other exhaustion markers on CD4+ and CD8+ T cells and expression of PD-L2 on dendritic and monocyte-derived macrophages, at baseline and following treatment

10.2.3.6 Polyfunctional response of HIV-1-specific CD4+ T cells by intracellular staining at baseline and through week 12

10.2.3.7 Immune activation and cell cycling (expression of CD38/HLA-DR and Ki67 on CD4+ and CD8+ T cells) at baseline and following treatment

10.2.3.8 Levels of immunologic and virologic measures through week 48

10.2.3.9 Pharmacokinetic parameters (including C_{max}, $t_{1/2}$) and RO of anti-PD-1 antibody following treatment

10.3 Randomization and Stratification

The three dose cohorts will enroll sequentially. Within each cohort, 15 eligible participants will be randomized 4:1 to receive cemiplimab (n=12) or placebo (n=3). Randomization will use the permuted block method without institutional balancing or stratification. After enrollment of each dose cohort is complete, study enrollment will be suspended until a decision is made on opening the next (higher dose) cohort to enrollment, based on the dose escalation criterion and SMC review.

10.4 Sample Size and Accrual

The total sample size of this study is 45 evaluable participants. Within each dose cohort, there will be 12 active-treated participants and 3 placebo participants. Ultimately, there will be a total of nine placebo recipients for comparison of immunologic and virologic outcomes. Participants who do not receive study treatment will be replaced. In addition, any participant who does not receive ≥90% of both study treatment infusions, or discontinues the study prior to week 12 without having met the primary safety endpoint (section 10.2.1.1), will be replaced.

10.4.1 Safety

The criteria to be used to guide the SMC when determining dose resumption or dose escalation for each cohort are defined as not having observed:

A. Three or more active-treated participants have experienced a Grade ≥3 AE that is related to study treatment (as judged by the core team, blinded to treatment arm and by the SMC who will receive unblinded data);
B. Two or more active-treated participants have experienced an irAE (not including an infusion reaction AE) that is related to study treatment (as judged by the core team, blinded to treatment arm, and by the SMC who will receive unblinded data) as defined by:
   i Grade ≥1 pneumonitis, adrenal insufficiency, myocarditis, diabetes, or uveitis;
   ii Grade ≥2 colitis, myositis, rash, hyperthyroidism or hypothyroidism, or elevated AST or ALT.
C. One or more active-treated participants have experienced a Grade ≥4 clinical AE (excluding asymptomatic laboratory abnormalities) that is related to study treatment (as judged by the core team, blinded to treatment and by the SMC who will receive unblinded data).

NOTE A: Asymptomatic Grade 4 laboratory abnormalities are addressed within A.

NOTE B: The following probability calculations assume a deterministic dose-escalation rule and do not reflect the essential element of SMC review and clinical consideration by the SMC of the data presented with respect to dose-escalation decisions.

Table 10.4.1-1 below shows the probabilities of dose escalation under various assumed true rates for the three types of AEs as described above, considering 12 participants receiving active treatment. In the table, the column “True participant-specific probability of AE event type A” is the probability of a Grade ≥3 AE conditional on not having an event of type C (Grade 4 or higher clinical AE). Similarly, the column “True participant-specific probability of AE event type B” is the probability of observing an irAE conditional on not having an event of type C. To calculate these probabilities of dose escalation, event types A and B were subdivided into three mutually exclusive groups: X=Grade ≤2 events in B, Y=Grade ≥3 events in B, and Z=Grade ≥3 events in A not part of B. Participant-specific probabilities of X, Y, and Z were assumed (conditional on not having an event of type C) and the events X, Y, and Z were assumed independent (conditional on not having an event of type C). Probabilities of A and B (conditional on not having an event of type C) as displayed in the table were each then calculated (i.e., Pr(A|C=0) = Pr(Y|C=0) + Pr(Z|C=0) - Pr(Y|C=0)*Pr(Z|C=0)). The probability of dose escalation was computed by numerical simulation with 100,000 replicates based on Pr(C), Pr(X|C=0), Pr(Y|C=0), and Pr(Z|C=0) for each listed scenario in the table.

The proposed sample size provides a reasonably high probability of dose escalation when the true event rates are, in fact, acceptable. For example, if the probability of a participant in the active treatment arm of a given dose cohort experiencing an AE of type A as described above is 0.03 (3%), the probability of experiencing an AE listed in B above is 0.02 (2%) and the corresponding probability of experiencing a Grade 4 or higher AE as described in C above is 0.01 (1%), then the probability that the study will dose escalate to the next higher dose is 0.86 (86%). Given that this is an acceptable safety profile, this means that the probability of incorrectly concluding the current dose is unsafe is 0.14 (14%). On the other hand, the proposed sample size provides a low probability of dose escalation when the true event rates are unacceptable. For example, if the probability of a participant in the active treatment arm of a given dose cohort experiencing an AE of type A as described above is 0.2 (20%), the probability of experiencing an AE listed in B above is 0.2 (20%) and the corresponding probability of experiencing a Grade 4 or higher AE as described in C above is 0.1 (10%), then the probability that the study will dose escalate to the next higher dose is 0.06 (6%); the corresponding probability of not dose escalating and correctly concluding the dose unsafe is 0.94 (1-0.06).

Table 10.4.1-1: Probabilities of Meeting the Dose Escalation Criterion under Various Assumed True Rates

True Participant-specific Probability of AE Type A (Grade ≥3 AE related to study drug)	True Participant-specific Probability of AE Type B (irAE related to study drug)	True Participant-specific Probability of AE Type C (Grade 4 or higher clinical AE related to study drug)	Probability of Dose Escalation Criterion
0.008	0.009	0.005	0.94
0.03	0.02	0.01	0.86
0.03	0.02	0.02	0.76
0.04	0.04	0.03	0.64
0.06	0.06	0.05	0.44
0.14	0.10	0.07	0.22
0.18	0.18	0.08	0.11
0.20	0.20	0.10	0.06
0.25	0.25	0.15	0.015

Considering 12 treated participants in a cohort, Table 10.4.1-2 displays the probability of observing at least one participant with an event, and the probability of observing at least two participants with an event, for various underlying event probabilities. For example, consider an irAE as the event. Then 12 treated participants provides >70% likelihood of observing such an event if the participant-specific probability is at least 0.10 (10%).

Table 10.4.1-2: Probability of Observing at Least One Participant with an Event, and the Probability of Observing at Least Two Participants with an Event, for Various Underlying Event Probabilities

Participant-specific Probability of Event	Probability of Observing ≥1 Participant with Event, N=12 Treated	Probability of Observing ≥2 Participants with an Event, N=12 Treated
.1	0.72	0.34
.2	0.93	0.73
.3	0.99	0.91

10.4.2 Efficacy

For the secondary outcome measure of efficacy, statistical power is described for the paired t-test which will be used (two-sided, alpha=0.05), testing that CD8+ T cell responses (10.2.2.1) increase pre- to post-treatment among the active-treated study participants. The key assumption is that CD8+ T cell responses would be stable (mean change of zero) without intervention (i.e., with continued cART). Because estimates of the anticipated standard deviation (SD) of the change are not available, power is described in terms of SD units. With 11 evaluable treated participants in a dose group (allowing for one unevaluable, e.g., due to issues with the sample or assay), power is >80% to detect a treatment effect in a dose group if the mean change is at least 0.94 SD units; this

corresponds under assumed normality to a probability of 0.83 or larger that a participant would have an observed increase in CD8+ T cell responses after treatment (the null hypothesis is that the probability is 0.5, corresponding to zero mean change). Combining the three dose groups (n=33), power is >80% to detect a treatment effect of 0.504 SD units, corresponding to a probability of 0.69 or larger that a participant would have an observed increase in CD8+ T cell responses after treatment.

Adjustments for separate statistical testing in each of the dose cohorts have not been incorporated into power calculations for this study.

10.5 Data and Safety Monitoring

If at any time within a given dose cohort:

a) Three or more participants experience a Grade ≥3 AE related to study treatment (section 10.2.1.1) (as judged by the core team, blinded to treatment arm); or
b) Two or more participants experienced an irAE (not including an infusion reaction AE) (see section 10.4.1B) that is related to study treatment (as judged by the core team, blinded to treatment arm); or
c) One or more participants experience a Grade 4 clinical AE or death and related to study treatment (as judged by the core team, blinded to treatment arm);

then enrollment into the study and treatment infusions will be temporarily suspended and the SMC, unblinded to treatment assignment, will be asked to review all safety data; review the relation to study treatment of the event(s) thought by the blinded core team to be a primary safety outcome; and recommend how the study should proceed with respect to resuming enrollment, continuing study treatment and dose escalation.

10.6 Analyses

10.6.1 Primary Analyses

For the primary safety analysis, AEs attributed to study treatment (see section 10.2.1.1) will be described separately for the treatment arm of each dose cohort, and for the combined placebo arms. All participants who have been exposed to the study treatment/placebo will be included in this analysis. As supplemental/secondary analyses, all other reported AEs will be summarized for the treatment arm of each dose cohort, and combined placebo arm.

10.6.2 Secondary Analyses

For the HIV-1-specific CD8+ T cell efficacy outcome (section 10.2.2.1), post-treatment changes will be evaluated, comparing measurements at baseline (averaging the pre-treatment measures) to an average of post-treatment measurements through week 12, jointly analyzing the actively treated participants from all dose cohorts using the paired t-test. As supplemental analyses, the

same methods will separately analyze each dose cohort. The rationale to average over multiple post-treatment timepoints is that the timing and dynamics of treatment-induced immunologic (or virologic) effects is not known; the average of multiple time points aims to capture both early effects that may wane (for example, as seen in one of the immunologic responders to a single-dose of the anti-PD-L1 antibody [26]; or, for example, a response that only appears following the second infusion). Graphical approaches will display the means at each visit and mean changes from baseline to each follow-up visit (and separately to the average of weeks 2-6 and to weeks 8-12), by dose cohort and separately for the placebo participants. Longitudinal participant-specific plots will also be presented for each treatment dose and for the placebo participants.

Because the aim of this phase I/II study is to investigate the biologic effects of the treatment (anti-PD-1 antibody cemiplimab), efficacy analyses will be "as-treated" and also, to maximize the ability to identify treatment effects, efficacy analyses will be based only on participants who completed ≥90% of both study treatment infusions. In addition, if any participant interrupts cART for more than 7 consecutive days during the study, only measurements prior to cART interruption will be used in efficacy analyses.

Analyses of other immunologic and virologic measures will parallel the efficacy analyses as outlined above. For example, cell-associated HIV-1 RNA levels will be compared pre-treatment to post-treatment using paired t-tests separately by dose group (and for the combined treated participants) and for the placebo participants. Virologic measures such as cell-associated HIV-1 RNA will be log-transformed prior to analyses. Because low-level viremia as measured by SCA is anticipated to be below assay limit in a substantial fraction (~50%) of participants, binary (GEE) or censored-data [64] longitudinal analysis approaches are planned to assess treatment effects on SCA.

Descriptive summaries, by dose group, will be presented for the estimated PK parameters (see section 11.0). Graphical approaches will display concentration curves over time, as well as RO over time.

Designated staff at identified laboratories may be unblinded prior to database lock to facilitate bioanalytical analyses of pharmacokinetic samples and ex vivo immunogenicity studies.

The timing of treatment effects on immunologic and virologic outcome measures will be investigated by identifying, for each measure, the post-treatment timepoint with the greatest magnitude change from baseline. It is also of interest to evaluate whether there is evidence that the second dose of treatment further "boosts" responses following the first dose. For this reason, samples are collected at a comparable schedule following the first and second doses.

The associations between ex vivo HIV-specific T-cell responses following cemiplimab exposure (based on pre-treatment samples) and in vivo HIV-specific immune responses to treatment will be evaluated using Spearman correlations. Bioinformatics approaches will be used to evaluate changes in gene expression profiles before versus after treatment.

Regression models, graphical displays and correlation analyses will investigate dose-response relationships with respect to immunologic and virologic changes after treatment across the dose groups, and in relation to PK parameters estimated as outlined in section 11.0.

10.7 Unblinding

For unblinding requests, including emergency unblinding, refer to ACTG Standard Operating Procedure (SOP)-123, Unblinding Participants, (https://member.actgnetwork.org/cms/folder/6184).

In the event that emergency disclosure of treatment assignment is thought to be required, the site investigator must follow ACTG SOP- 123, Unblinding Participants.

(1) Sudden (or unplanned) unblinding of one or more arms due to interim analysis results or results of another trial: 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 DSMB or an SMC or the results of another trial (also see the DAIDS SOP “Termination of a Trial or a Single Treatment Arm”).

(2) Participant contact: 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.

(3) Implications of unblinding on study data: 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.

Unblinding will not occur to allow replacement of participants (see section 6.2.5). Premature treatment discontinuation, other than for a treatment-related AE, would result in an increase in the applicable limit for enrollment into the active or placebo arm (as appropriate) for the designated cohort by the ACTG randomization department.

All site e-mails to the team should be carefully worded to prevent unblinding the team, if possible.
Unblinding of all study participants will take place after the last participant has completed the study, all data have been entered into the database and cleaned for primary and secondary endpoints.

11.0 PHARMACOLOGY PLAN

A5370 will examine the safety, PK, and immune responses in HIV-1 infected participants on suppressive cART receiving cemiplimab. The pharmacology plan will be integrated into the overall protocol objectives and provide valuable information that will guide subsequent studies of cemiplimab in HIV-1-infected individuals on suppressive cART. Animal and human studies of the clinical pharmacology of cemiplimab indicate bi-exponential decline following an IV dose. The systemic CL of mAbs is primarily though intracellular catabolism and therefore direct interaction with antiretrovirals is likely to be minimal. However, the pharmacodynamics (PD) response to cemiplimab binding to the PD-1 receptor results in enhanced immune function mediated by T cell activation with subsequent cytokine production. This increase in cytokines may alter certain antiretroviral PK, therefore stored antiretroviral plasma samples will be collected within the pharmacology plan.

Noteworthy pharmacologic characteristics of cemiplimab include nM activity with regard to PD-1 receptor competitive binding. Peak and trough serum cemiplimab concentrations achieved in cancer studies using every-2-weeks IV dosing are in the mcg/ml range following doses of 1-3 mg/kg. The serum elimination half-life is prolonged (~19 days), with an estimate of ~80% PD-1 RO expected for the current dosage regimens proposed in this protocol, based on data from a currently approved PD-1 receptor blocker, nivolumab [28, 34].

A population PK model for cemiplimab was built using data from 505 patients, combining rich data from Study 1423 in patients with solid tumors (26 patients with CSCC), together with data from 114 patients with advanced CSCC from study 1540 (IB, Edition 6). The majority of patients in the population PK model received cemiplimab at the 3 mg/kg dose twice a week. A two-compartment model with zero-order IV infusion and first-order elimination was selected as a structural model. Inclusion of a function describing a time-varying change in CL significantly improved the model fit. In the overall oncology patient population after repeated dosing, the total CL of cemiplimab appears to decrease over time by about 34.6% over the first 2 months of treatment, i.e., from a baseline value of 0.325 L/day down to 0.211 L/day. However, this decrease in CL was not considered clinically relevant. Based on the population PK analysis, the total volume of distribution at steady-state was 5.20 L. Following a single dose of cemiplimab, mean exposure

generally increased in a dose proportional manner over the dose range of cemiplimab studied (1 mg/kg to 10 mg/kg once every two weeks). These observations were consistent with the results in the base model development, in which a linear-elimination model was considered to adequately describe the PK of cemiplimab. Systemic accumulation was evident based on an accumulation index of approximately 2.0-fold in $AUC_{6wk,ss}$. The following intrinsic factors were found to have no clinically important effect on the exposure of cemiplimab: age (27-96 years), sex, body weight (31-156 kg), race (white, black, Asian, and other), cancer type, tumor burden, albumin level (22-48 g/L), renal function (creatinine clearance 25-420 mL/min), and hepatic function (total bilirubin 0.35-45 µmol/L). To be noted, cemiplimab has not been studied in patients with moderate or severe hepatic impairment.

The incidence of treatment-emergent ADA in all patients with solid tumors and in the subset of patients who received cemiplimab 3 mg/kg once every two weeks was 1.26% (5/398) and 1.17% (4/341), respectively. Antibody titers were considered low to moderate (titer levels: low [<1,000], moderate [≥1000 to ≤10,000] and high [>10,000]). Of the patients who developed treatment-emergent antibodies to cemiplimab, none developed neutralizing antibodies. The incidence of persistent ADA was low (0.251%) in all patients receiving cemiplimab. There was no evidence of altered PK profile in the small number of patients with treatment emergent ADA responses. The presence of ADA was not associated with AEs or irAE.

Pharmacokinetic sampling of cemiplimab reported in the IB, Edition 6, for participants with advanced solid tumors provided a more intensive sampling strategy for obtainment of data to understand the pharmacokinetic properties of this drug in humans. Target mediated drug disposition (non-linear PK) likely occurs at lower concentrations, i.e., at lower doses and/or at later time points than those observed in the FIH studies. To date, there is no available data on RO with cemiplimab. For our design, a strategy will be implemented that aims to capture cemiplimab maximum concentration and terminal elimination phase, possibly including the target-mediated component of elimination with corresponding peripheral RO at similar time points. The later time points planned in the current pharmacology section include the duration of evaluation since this is the first clinical trial of cemiplimab in a population of HIV- infected participants. Based on the possibility of prolonged RO with this drug, the data provided from later sampling time points can provide valuable information in the event of prolonged responses or delayed AEs.

11.1 Pharmacology Objectives

11.1.1 To characterize the systemic exposure of cemiplimab and determine PK parameters.

11.1.2 To investigate the relationship of cemiplimab exposure and PD-1 peripheral RO with baseline participant-specific factors and investigate the relationship to PD responses in HIV-infected individuals on suppressive cART.

11.1.3 To collect and store antiretroviral plasma concentrations before and after

administration of cemiplimab, to be assayed for pharmacokinetic analysis based on determination by core team of participant response.

11.2 Pharmacology Study Design

11.2.1 Pharmacokinetics

Sampling will be obtained:

For cemiplimab
- Pre-entry sample
- Entry/day 0: Within 15 minutes following the end of infusion.
- Week 6 (within 15 minutes prior to infusion and within 15 minutes following the end of infusion); any time during the visit at weeks 1, 2, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48.
- Samples obtained on non-infusion days can be drawn during the participant's visit (a specific time of day is not required), documentation of the date and time of dosing, and of all PK samples drawn is required in the eCRF.

For Stored Antiretroviral Sampling
- Entry/day 0: Prior to infusion.
- Weeks 2, 4, 6 (prior to infusion), 8, and 10.
- Samples obtained on non-infusion days can be drawn during the participant's visit (a specific time of day is not required), documentation of the date and time the sample is drawn is required in the eCRF. Documentation of the date and time of the 3 previous doses of each antiretroviral medication are to be recorded in the eCRF prior to each sample taken.

Peripheral RO
- Pre-entry sample
- Week 6 (within 15 minutes prior to infusion); any time during the visit at weeks 1, 2, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48.
- Determination of the need to assay certain/all samples will be based on the serum cemiplimab concentration seen. Samples obtained on non-infusion days can be drawn during the participant's visit (a specific time of day is not required); documentation of the date and time of dosing and of all RO samples drawn is required in the eCRF.

See section 6.0 for details of sample collection.

11.2.2 Pharmacodynamics

To characterize the relationship of cemiplimab serum concentration and peripheral PD-1 RO with biomarker changes for example, HIV-1 RNA by SCA, total HIV-1 DNA, intact proviral HIV-1 genomes, cell-associated HIV-1 RNA, HIV-1 RNA/DNA ratios in total CD4+ T cells, and markers of immune response. Relationships will be evaluated through PK/PD modeling. These PK/PD analyses will include exposure-response analyses for safety and efficacy endpoints as appropriate.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

11.3.1 Serum cemiplimab concentrations will be assayed at Regeneron Pharmaceuticals, Inc., using a validated ligand-binding assay.

11.3.1.1 The cemiplimab assay validation report will be provided to the ACTG Clinical Pharmacology Quality Assurance Program for peer review prior to analysis of protocol samples.

11.3.2 Plasma antiretroviral samples will be assayed at the University at Buffalo Pharmacology Specialty Laboratory by a DAIDS Clinical Pharmacology Quality Assurance Program validated assay.

11.3.3 Cryopreserved PBMCs will be used to assay PD-1 RO by cemiplimab by flow cytometry.

11.3.4 Pharmacokinetic analysis will include cemiplimab serum concentration data, and evaluate the influence of PD-1 receptor binding on cemiplimab PK. The formation of ADA will be evaluated and may be incorporated into the model building process as a covariate, if appropriate. Population and individual cemiplimab PK parameters, including C_{max}, AUC, half-life, and C_{min}, will be determined using population PK approaches. The population PK model will provide an assessment of the influence of specific covariates on the disposition and variability in exposure of cemiplimab in HIV-infected adults on suppressive antiretroviral therapy.

In addition, cemiplimab serum concentration data will be related to peripheral RO data in a PK/PD analysis.

11.4 Anticipated Outcomes

We anticipate that participants receiving cemiplimab will have similar disposition to previous studies by Regeneron in participants with malignancies. This will be evaluated by comparing the C_{max}, T_{max}, AUC, and dose-normalized exposure values in this study to those reported in the IB, Edition 6, for participants with malignancies. In addition, we anticipate that exposure to cemiplimab and blocking of the PD-1 receptor will enhance HIV-1-specific immune responses that promote the CL of HIV-1-expressing cells. The clinical pharmacology objectives will provide an important evaluation of cemiplimab serum concentrations, the impact of participant-specific characteristics, RO, the relationship between cemiplimab serum concentrations and peripheral RO, and their relationship with safety, virologic, and immunologic responses.

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 assure 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

12.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

12.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporter(s), other local, US, and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) 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. Study physician investigators will directly participate in the informed consent process. 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, 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 entities as part of their duties, or the industry supporter(s).

13.3 Study Discontinuation

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

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(s) 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 CDC 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.

16.0 REFERENCES

1. Archin NM, Liberty AL, Kashuba AD, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature 2012;487:482-5.
2. Rasmussen TA, Tolstrup M, Brinkmann CR, et al. Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. Lancet HIV 2014;1:e13-21.
3. Sogaard OS, Graversen ME, Leth S, et al. The depsipeptide romidepsin reverses HIV-1 latency in vivo. PLoS Pathog 2015;11:e1005142.
4. Shan L, Deng K, Shroff NS, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity 2012;36:491-501.
5. Maldarelli F, Palmer S, King MS, et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathog 2007;3:e46.
6. Palmer S, Maldarelli F, Wiegand A, et al. Low-level viremia persists for at least 7 years in patients on suppressive antiretroviral therapy. Proc Natl Acad Sci U S A 2008;105:3879-84.
7. Zajac AJ, Blattman JN, Murali-Krishna K, et al. Viral immune evasion due to persistence of activated T cells without effector function. J Exp Med 1998;188:2205-13.
8. Wherry EJ. T cell exhaustion. Nat Immunol 2011;12:492-9.
9. Pauken KE, Sammons MA, Odorizzi PM, et al. Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. Science 2016;354:1160-5.
10. Khoury G, Fromentin R, Solomon A, et al. Human immunodeficiency virus persistence and T-cell activation in blood, rectal, and lymph node tissue in human immunodeficiency virus-infected individuals receiving suppressive ART. J Infect Dis 2017;215:911-19.
11. Fromentin R, Bakeman W, Lawani MB, et al. CD4+ T cells expressing PD-1, TIGIT and LAG-3 contribute to HIV persistence during ART. PLoS Pathog 2016;12:e1005761.
12. Mueller SN, Ahmed R. High antigen levels are the cause of T cell exhaustion during chronic viral infection. Proc Natl Acad Sci U S A 2009;106:8623-8.
13. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 2015;15:486-99.
14. Wherry EJ, Blattman JN, Murali-Krishna K, van der Most R, Ahmed R. Viral persistence alters CD8 T-cell immunodominance and tissue distribution and results in distinct stages of functional impairment. J Virol 2003;77:4911-27.
15. Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature 2006;443:350-4.
16. Kaufmann DE, Kavanagh DG, Pereyra F, et al. Upregulation of CTLA-4 by HIV-specific CD4+ T cells correlates with disease progression and defines a reversible immune dysfunction. Nat Immunol 2007;8:1246-54.

17. Meier A, Bagchi A, Sidhu HK, et al. Upregulation of PD-L1 on monocytes and dendritic cells by HIV-1 derived TLR ligands. AIDS 2008;22:655-8.

18. Boasso A, Hardy AW, Landay AL, et al. PDL-1 upregulation on monocytes and T cells by HIV via type I interferon: restricted expression of type I interferon receptor by CCR5-expressing leukocytes. Clin Immunol 2008;129:132-44.

19. D'Souza M, Fontenot AP, Mack DG, et al. Programmed death 1 expression on HIV-specific CD4+ T cells is driven by viral replication and associated with T cell dysfunction. J Immunol 2007;179:1979-87.

20. Sachdeva M, Fischl MA, Pahwa R, Sachdeva N, Pahwa S. Immune exhaustion occurs concomitantly with immune activation and decrease in regulatory T cells in viremic chronically HIV-1-infected patients. J Acquir Immune Defic Syndr 2010;54:447-54.

21. Nakanjako D, Ssewanyana I, Mayanja-Kizza H, et al. High T-cell immune activation and immune exhaustion among individuals with suboptimal CD4 recovery after 4 years of antiretroviral therapy in an African cohort. BMC Infect Dis 2011;11:43.

22. Cockerham LR, Jain, V, Sinclair E et al. Programmed death-1 expression on CD4+ and CD8+ T cells in treated and untreated HIV disease. AIDS 2014;28:1749-58.

23. Trabattoni D, Saresella M, Biasin M, et al. B7-H1 is up-regulated in HIV infection and is a novel surrogate marker of disease progression. Blood 2003;101:2514-20.

24. Rosignoli G, Cranage A, Burton C, et al. Expression of PD-L1, a marker of disease status, is not reduced by HAART in aviraemic patients. AIDS 2007;21:1379-81.

25. Gay CL, Bosch RJ, Ritz J, et al.; AIDS Clinical Trials 5326 Study Team. Clinical trial of the anti-PD-L1 antibody BMS-936559 in HIV-1 infected participants on suppressive antiretroviral therapy. J Infect Dis 2017;215:1725-33. epub 18 April 2017.

26. Shan L, Deng K, Shroff NS, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity 2012;36:491-501.

27. Fuller MJ, Callendret B, Zhu B, et al. Immunotherapy of chronic hepatitis C virus infection with antibodies against programmed cell death-1 (PD-1). Proc Natl Acad Sci U S A 2013;110:15001-6.

28. Velu V, Titanji K, Zhu B, et al. Enhancing SIV-specific immunity in vivo by PD-1 blockade. Nature 2009;458:206-10.

29. Dyavar Shetty R, Velu V, Titanji K, et al. PD-1 blockade during chronic SIV infection reduces hyperimmune activation and microbial translocation in rhesus macaques. J Clin Invest 2012;122:1712-16.

30. Ha SJ, Mueller SN, Wherry EJ, et al. Enhancing therapeutic vaccination by blocking PD-1-mediated inhibitory signals during chronic infection. J Exp Med 2008;205:543-55.

31. Dai B, Xiao L, Bryson PD, Fang J, Wang P. PD-1/PD-L1 blockade can enhance HIV-1 Gag-specific T cell immunity elicited by dendritic cell-directed lentiviral vaccines. Mol Ther 2012;20:1800-9.

32. Couzin-Franzel J. Breakthrough of the year 2013. Cancer immunotherapy. Science 2013;342:1432-33.

33. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.

34. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

35. Gardiner D, Lalezari J, Lawitz E, et al. A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. PLoS One 2013;8:e63818.

36. Bengsch B, Martin B, Thimme R. Restoration of HBV-specific CD8+ T cell function by PD-1 blockade in inactive carrier patients I linked to T cell differentiation. J Hepatology 2014:61:1212-19.

37. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.

38. Gane EJ, Gaggar A, Nguyen AH, et al. A Phase 1 Study Evaluating Anti-PD-1 Treatment With or Without GS-4774 in HBeAg Negative Chronic Hepatitis B Patients. European Association for the Study of the Liver. April 19-23, 2017. Amsterdam, The Netherlands. Reported by NATAP http://www.natap.org/2017/EASL/EASL_55.htm.

39. Wightman F, Solomon A, Kumar SS, et al. Effect of ipilimumab on the HIV reservoir in an HIV-infected individual with metastatic melanoma. AIDS 2015;29:504-6.

40. Colston E, Grasela D, Gardiner D, et al. An open-label, multiple ascending dose study of the anti-CTLA-4 antibody ipilimumab in viremic HIV patients. PLoS One 2018;13:e0198158.

41. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139-48. Epub 2016 Jan 5. doi: 10.1016/j.ejca.2015.11.016.

42. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res 2015;4:560-75. doi: 10.3978/j.issn.2218-6751.2015.06.06.

43. De Velasco G, Je Y, Bosse D, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 Inhibitors in cancer patients. Cancer Immunol Res 2017;5:312-18. epub 2017 Feb 28. doi: 10.1158/2326-6066.CIR-16-0237.

44. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415-26.

45. Samri A, Lavole A, Even S, et al. PD-1 blockade in 12 HIV-infected patients with lung cancer. IAS 2017, Paris France.

46. Petroff MG, Chen L, Phillips TA, et al. B7 family molecules are favorably positioned at the human maternal-fetal interface. Biol Reprod 2003;68:1496-504.

47. Wafula PO, Teles A, Schumacher A, et al. PD-1 but not CTLA-4 blockage abrogates the protective effect of regulatory T cells in a pregnancy murine model. Am J Reprod Immunol 2009;62:283-92.

48. Guleria I, Khosroshahi A, Ansari MJ, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. J Exp Med 2005;202:231-7.

49. Habicht A, Dada S, Jurewicz M, et al. A link between PDL1 and T regulatory cells in fetomaternal tolerance. J Immunol 2007;179:5211-19.

50. Taglauer ES, Yankee TM, Petroff MG. Maternal PD-1 regulates accumulation of fetal antigen-specific CD8+ T cells in pregnancy. J Reprod Immunol 2009;80:12-21.

51. D'Addio F, Riella LV, Mfarrel BG, et al. The link between the PDL1 costimulatory pathway and Th17 in fetomaternal tolerance. J Immunol 2011;187:4530-41.

52. Brahmer JR, Drake CG, Powderly JD, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75.

53. Weber JS, Yang JC, Atkins MB, et al. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol. 2015; 33:2092-2099.

54. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015;26:2375-91.

55. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60: 210-25.

56. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:190-209.

57. Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic profiling of immune-related adverse events in advanced melanoma patients treated with ipilimumab. Cancer Immunol Res 2015;3:1185-92.

58. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. Clin Cancer Res 2016;22:6051-60.

59. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691-7.

60. Lacouture ME, Wolchok JD,Yosipovitch G, Kähler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol 2014;71:161-9.

61. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014;32:1020-30.

62. Michot JM, Mazeron R, Dercle L, et al. Abscopal effect in a Hodgkin lymphoma patient treated by an anti-programmed death 1 antibody. Eur J Cancer 2016;66:91-4.

63. Patel AB, Pacha O. Skin reactions to immune checkpoint inhibitors. Adv Exp Med Biol 2017;995:175-84. doi: 10.1007/978-3-319-53156-4_9.

64. Riddler SA, Aga E, Bosch RJ, et al. Continued slow decay of the residual plasma viremia level in HIV-1-infected adults receiving long-term antiretroviral therapy. J Infect Dis 2016;213:556-60.

APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For Protocol: A5370

FINAL VERSION 1.0, 11/16/18: Safety and Immunotherapeutic Activity of an Anti-PD-1 Antibody (Cemiplimab) in HIV-1-infected Participants on Suppressive cART: A Phase I/II, Double-blind, Placebo-controlled, Ascending Multiple Dose Study

SHORT TITLE FOR THE STUDY: Anti-PD-1 Antibody Cemiplimab in HIV-1-Infected Participants on Suppressive cART

INTRODUCTION

You are being asked to take part in this research study because you are living with human immunodeficiency virus (HIV-1) and:

1. You have been taking the same combination of antiretroviral drugs (cART) for at least the past 3 months.
2. Your HIV-1 RNA level (viral load, the amount of HIV in your blood) has been below the limit of detection for the past 18 months.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). 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 this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

HIV medications can reduce HIV virus to very low levels in the blood and partially repair the immune system (the way your body responds to diseases). However, these medications do not cure (remove) the HIV and a small amount of the virus continues to live in the body even when the viral load (amount of HIV virus in your body) is very low. In most participants taking HIV medications, very sensitive tests can find small amounts of HIV virus in the blood even when regular viral load test results do not find HIV. This helps explain why the HIV virus levels come back when these medications are stopped. The reason why HIV can still be found in the body is likely because there are cells that live for a long time after becoming infected with HIV. These cells are thought to carry the HIV virus in a latent or hidden form (“non-active state”). As long as the virus exists in this latent, non-active state, persons living with HIV cannot be cured. HIV virus may come from these non-active cells that may at times produce low levels of HIV, or it may come from other cells in the body. The immune system does not seem to be able to get rid of these cells that produce virus. HIV medications are only able to block multiplying (active virus) cells.

Cemiplimab (LIBTAYO) is a drug approved by the Food and Drug Administration (FDA) to treat advanced cutaneous squamous cell carcinoma. It has been tested to treat other types of cancer. It has been tested to treat various types of cancer. Cemiplimab is an antibody (a protein in the body that finds infection) that has been created to help wake up cells in the immune system that do not function well. These cells are called exhausted (tired) T cells. One reason that the immune system does not clear the cells that produce low levels of HIV is that the cells that fight HIV are exhausted and do not work well. If these cells are able to wake up, it is possible that they can function better and help clear the cells infected with HIV. This study is being done to see if cemiplimab is safe in persons living with HIV and whether it can improve the HIV-specific immune response. The overall goals of this study are:

- To see if two doses of cemiplimab will be safe in persons living with HIV on treatment,
- To see whether there is improvement in the body's immune response to HIV,
- To see whether cemiplimab can lower the amount of HIV that is present in the blood and reduce the amount of latent HIV.

In this study, you will receive two infusions of either the active form of cemiplimab or placebo (a salt solution with no medication). You have four out of five chances to receive the active medication and one out of five chances to receive placebo. Cemiplimab and placebo will be provided to you at no cost.

There are 3 doses levels (amount of medication with each infusion) being used in this study to test safety and to look at whether the higher doses are better at improving the immune response to HIV. The doses for this study were chosen based on studies that were done in people with cancer who did not have HIV. The most important goal of this study is to test if cemiplimab is safe. The smallest and first dose of 0.3 mg/kg is much lower than the doses used in studies against cancer. The doses of 1 mg/kg and 3 mg/kg were chosen given their effectiveness in treating cancer in some cancer patients. In prior studies with cemiplimab, participants receiving the higher doses did not have more side effects than with lower doses.

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

Screening

If you would like to be in this study, after you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. You will need to fast before this visit (fasting means that you have had nothing to eat or drink except plain water and required prescription medications for at least 8 hours before this visit). If you are not able to fast before this visit, you will be asked to reschedule your visit. This visit will take about 1-2 hours. At this visit:

- Whether you are living with HIV will be confirmed. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.
- You will be asked questions about your medical history and any medications you are taking or have taken in the past.
- You will have a complete physical exam, including vital signs (temperature, pulse, respiration rate [the number of breaths you take in a minute], and blood pressure), an eye exam, and height and weight.

- You will have about 3.7 tablespoons (56 mL) of blood drawn to see if you have tuberculosis in your body; for metabolic tests (to test how your body uses the food that you eat); autoimmune (studies to see if your immune system is attacking healthy cells in your body); studies for routine lab tests for safety; for virologic studies (to help study the virus); to measure the amount of HIV in your blood; and to measure your CD4+ and CD8+ cell counts (cells that help fight infection).
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy.
- If you are a woman, follicle stimulating hormone-release factor (FSH) will be measured if you are not able to get pregnant and you do not have a medical record that says this.
- You will agree to continue taking combination antiretroviral drugs as prescribed throughout the entire study.

<u>If You Do Not Enroll into the Study</u>
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (age, gender, race), clinical (disease condition, diagnosis), and laboratory (CD4 cell count, viral load) information is being collected from you so that the AIDS Clinical Trials Group (ACTG) researchers may help determine whether there are patterns or common reasons why people do not join a study.

<u>Pre-Entry</u>
- If you are eligible for the study, you will come in for a pre-entry visit. This visit will take about 1 hour. You will need to fast before this visit (fasting means that you have had nothing to eat or drink except plain water and required prescription medications for at least 8 hours before this visit). At this visit:
- Your height may be recorded.
- You will have about 7.2 tablespoons (108 mL) of blood drawn for routine lab tests for safety; to see if you are living with the hepatitis B virus and/or you have been diagnosed with the hepatitis C virus (an infection of the liver); for metabolic tests (to test how your body uses the food that you eat); for virologic studies (to measure the amount of HIV in your blood); for immunologic studies (to test how your body fights infection); pharmacokinetic (PK) studies (to test how the study drug works in your body) studies; and for immunogenicity studies (to test your body's immune response). You will be told the results of these tests when they become available. Some of the blood you provide will be stored for future protocol-required testing.
- You will have an electrocardiogram (ECG). An ECG is a test that checks for problems with the electrical activity of your heart.
- If you are a man, some of your blood will be tested to look at the amount of testosterone in your blood before receiving study treatment.

Entry

After your pre-entry visit, you will come in for an entry visit. This visit will take about 4 hours. At this visit:

- You will be asked questions about your medical history.
- You will be asked about your health and any changes in your medicines since your last visit.
- You will have a brief physical exam including vital signs and weight.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy.
- You will provide a urine sample for a urinalysis to see if you have nephritis (inflammation of the kidneys).
- You will have about 7.1 tablespoons (106.5 mL) of blood drawn for routine lab tests for safety; virologic, immunologic, PK, and autoimmune (studies to see if your immune system is attacking the healthy cells in your body) studies; to measure the amount of HIV in your blood; and to measure your CD4+ and CD8+ cell counts. Some of the blood you provide will be stored for future protocol-required testing, including gene expression assays. Most of our cells have exactly the same genetic information (blueprint) but some of the information is turned off and some is turned on depending on the type of cell. This study will test gene expression (which genes are "on" and which genes are "off") in lymphocytes (immune cells) before and after receiving the study medication.
- You will receive cemiplimab or placebo once during this visit through a small plastic flexible tube placed into a vein in your arm (intravenous [IV] infusion). This IV infusion will take about 30 minutes or in some cases the IV infusion may be slowed to help stop any side effects that you may have. At the entry visit, blood will be drawn to determine cemiplimab amounts in your body. This blood draw will happen right after the infusion.
- You will be asked questions about how well you take your HIV medications.
- You will be contacted by telephone 2 to 3 days after this visit in which you have received the study drug or placebo. Someone from the site will call you to see how you are doing and to ask you about any signs and/or symptoms you may have.

Study Medication

Depending on when you enter this study, you will be assigned to one of the three groups. In each group: 12 participants will receive cemiplimab and 3 participants will receive placebo salt diluent/solution that does not contain cemiplimab. You cannot choose whether you receive cemiplimab or placebo because you will be randomly assigned (like flipping a coin), and neither you nor the study staff will know whether you will receive cemiplimab or the placebo.

- Group 1 will enroll first to receive cemiplimab 0.3 mg/kg or placebo. If this dose is found to be safe, then
- Group 2 will enroll to receive cemiplimab 1 mg/kg or placebo. If this dose is found to be safe, then
- Group 3 will enroll to receive cemiplimab 3 mg/kg or placebo. All participants will receive one dose of cemiplimab/placebo at entry and one dose of cemiplimab/placebo at week 6. However, the second dose at week 6 may not be given to you if any concerning side effects have occurred in you or in other participants enrolled in the study (see section "Risks of Cemiplimab" below). If this occurs, the study monitoring committee (SMC) will review this side effect and decide if it is safe for participants to continue with a second dose of cemiplimab/placebo.

If the second dose is delayed for any reason, you will still come in for your week 6 visit and all week 6 evaluations will be done, except you will not receive the second dose of cemiplimab/placebo. If the SMC decides it is safe for participants to receive a second dose, then another visit will be scheduled for you to receive this second dose. In this case, you may need to have your week 4 evaluations done again before scheduling your second dose.

You will not know whether you received cemiplimab or placebo until all participants have completed the study, unless this information is important to your care in an emergency.

Study Visits
After your entry visit, you will come to the clinic at weeks 1, 2, 4, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48. Most study visits will last about 1 hour with the exception of your week 6 visit, which will last about 2 hours.

During Most Study Visits
- You will be asked about your health and any changes in your medicines since your last visit.
- You will have a brief physical exam including vital signs and weight (only done weeks 6, 12, and 48).
- You will have about 5.3 tablespoons (up to 78.5 mL) of blood drawn to measure the amount of HIV in your blood, for future protocol-required testing, routine lab safety tests, and for immunologic and virologic studies. Some of this blood will be stored for future gene expression assays.
- You will have about 1.0 tablespoon (15 mL) of blood drawn for metabolic studies on weeks 4, 6, 12, 16, 20, 24, 28, 36, and 48. You will need to fast before these study visits (fasting means that you have had nothing to eat or drink except plain water and required prescription medications for at least 8 hours before these visits).
- You will have a little more than 0.5 tablespoon (7 mL) of blood drawn for autoimmune studies on weeks 4, 12, and 48.
- You will have a little more than 0.5 tablespoon (7 mL) of blood drawn and stored for autoimmune studies on weeks 6, 16, 20, 24, 28, and 36.
- You will have about 1 teaspoon (4 mL) of blood drawn to measure your CD4+ and CD8+ T cell counts on weeks 6, 12, 24, and 48.
- You will have about 1.2 tablespoon (up to 18 mL) of blood drawn for PK studies on weeks 1, 2, 4, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48.
- During your week 6 study visit, some of your labs drawn at your week 4 visit will be checked to see whether it is ok for you to receive the second dose of study drug at week 6.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy at week 6 before you receive the second dose of study drug.
- At the week 6 visit, you will receive cemiplimab or placebo once through a small plastic flexible tube placed into a vein in your arm (intravenous [IV] infusion). This IV infusion will take about 30 minutes; in some cases, the IV infusion may be slowed to help stop any side effects that you may have. Blood will be drawn to determine cemiplimab amounts in your body. These blood draws will happen right before and after the infusion.
- On weeks 1, 6, 7, 12, 16, 20, 24, 28, 36, and 48, you will be asked questions about how well you take your HIV medications.
- You will provide a urine sample for a urinalysis on weeks 6, 12, 24, and 48.

- You will be given the results of some of the study tests as soon as they are available, including all standard viral loads, CD4+ counts, and safety blood tests.
- If you are a man, you will have about 0.3 tablespoon (5 mL) of blood drawn to look at the amount of testosterone in your blood on weeks 4, 12, and 48.
- If it has been decided that you will not receive the second dose at week 6, you will still have all week 6 evaluations done. See information above under "Study Medication."
- After you receive the second dose of cemiplimab or placebo at week 6, you will be contacted by telephone 2 to 3 days. Someone from the site will call you to see how you are doing and to ask you about any signs and/or symptoms you may have.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy at weeks 12, 24, and 48 (in addition to week 6), or at weeks 1, 2, 4, 7, 8, 10, 16, 20, 28, or 36 if you might be pregnant.

Confirmation of Virologic Failure

If at any time during the study the result of your viral load test shows measurable virus above the limit of detection of the test, you will be asked to return to the clinic. At this visit:

- You will have about 1.2 tablespoon (18 mL) of blood drawn to measure the amount of HIV in your blood, for an HIV resistance test (resistance means that the drugs are not likely to fight the HIV in your body), and PK studies (to look at the amount of study drug in your body).
- If you are a woman and you think you might be pregnant, some of your blood or urine will be tested for pregnancy.
- You will be asked questions about how well you take your HIV medications.
- You will be asked to stay on the study and complete all of the study visits.

If You Stop Taking Your HIV Drugs during the Study

If you stop taking your HIV drugs during the study:

- You will be asked to stay on the study and complete the study visits so that you can be monitored for safety. You will have all of the regularly scheduled evaluations listed above, except blood for some of the immunologic and virologic studies will not need to be taken.
- If HIV drugs are stopped for more than 7 days before the first infusion of cemiplimab or placebo, the infusion will not be administered.
- If HIV drugs are stopped after the first infusion for more than 7 days, but before the second infusion, the second infusion will not be administered.
- You will be given the results of some of the study tests as soon as they are available, including all standard viral loads, CD4+ counts, and safety blood tests.

If You Have to Stop the Infusion of Cemiplimab Early

If the infusion of cemiplimab or placebo is stopped early for any reason and cannot be completed:

- You will be asked to stay on the study and complete the study visits so that you can be monitored for safety. You will have all of the regularly scheduled evaluations listed above, except you may not have the blood draws to determine the levels of cemiplimab in your body.
- If you are unable to complete the first infusion, the second infusion will not be administered.

- The study team will decide whether blood for the immunologic and virologic studies will need to be taken.

If You Have to Stop the Study Early
If you have to stop the study early, you will be asked to come to the clinic for an additional study visit. At this visit:

- You will have a brief exam physical including vital signs.
- You will have about 7.0 tablespoons (103.5 mL) of blood drawn for routine lab tests for safety; for virologic, immunologic, metabolic, PK, and autoimmune studies; to measure the amount of HIV in your blood; and to measure your CD4+ and CD8+ cell counts. Some of the blood you provide will be stored for future protocol-required testing, including gene expression assays.
- You will provide a urine sample for a urinalysis.
- If you are a man, some of your blood will be tested to look at the amount of testosterone in your blood.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy.

Other
Some of your blood samples will be stored (with usual protectors of identity) and used for testing that is required for this study. Usual protectors of identity are defined as: All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by coded number 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 your written permission, except as necessary for monitoring by the ACTG, Institutional Review Board (IRB), FDA, National Institute of Allergy and Infectious Diseases (NIAID), Office for Human Research Protections (OHRP), other government agencies as part of their duties, or the industry supporter or designee.

While you are in this research study, there will be some remaining blood following the completion of required testing. Researchers will use these unused samples along with your associated health information for future research. This information includes your medical condition(s). It may also include personal facts about you, such as your race, ethnicity, gender identity, and sex at birth. You are free to ask questions at any time. You may discuss it with others.

What samples will researchers collect and store?
Researchers will not collect any extra samples for future research. They will only use already collected unused samples.

Where will researchers store my information and samples?
Researchers will store your information electronically in computer databases. This information will include your associated health information and any new information learned from research done with your samples. Researchers will store your samples at the clinical research sites. To maximize research opportunities, researchers may store your samples in other storage facilities or “bio-banks.” There is a possibility that researchers may send your samples to other

researchers in your country or outside of your country. *(For Local Investigators and CRS personnel. Make sure that the shipment of samples outside the country complies with country and local regulations or policies.)*

How will researchers use my information and samples?
Researchers may use your information and samples in different types of future research to fight HIV and other related diseases. Some of these research studies may include genetic testing.

What other research could researchers do with my information?
Researchers may produce a lot of new information or "data" through the research done with your samples. This new information may be placed in large databases for other researchers to use. These databases may be only for genetic information, while others may store non-genetic information or both. All these databases store the information electronically without your personal identifiers, such as your name. No one will know just from looking at the information in any of these databases that the information belongs to you.

How long will researchers store my samples for future research?
Researchers will store your samples indefinitely. However, you can change your mind and withdraw your permission at any time. *(For Local Investigators and CRS personnel, make sure the length of time does not contradict country and local regulations or policies.)*

What are the risks of storing my samples and information for future research?
There is a small risk that someone may use your stored samples or information incorrectly. For example, someone could find out which test results are yours and use this information against you. This incorrect use of information may cause discrimination, distress or other problems to you. For this incorrect use to happen, the person would have to get into a database that links results with your name. To reduce this risk, researchers have security measures in place such as limiting access to databases, not linking names to results, and not placing results in medical records. *(For Local Investigators and CRS personnel. Make sure to consider and insert here any known risks to participants agreeing to have samples stored for future research, e.g., being denied life/disability/long-term care insurance for involvement in HIV research or genetic research.)*

What are the benefits of storing my samples and information for future research?
There will be no direct benefit to you from future research using your stored samples and information. However, the information learned may help others. It may take the researchers many years to have any results. In most cases, you will not receive future research results from the researchers.

What other choices do I have?
It is your choice whether or not to give permission for the storage and use of unused samples, as described in this document. If you choose not to give permission, researchers will not store any of your unused samples.

Can I change my mind about the storage and use of my samples and information?
Yes, you can decide to withdraw your permission for the storage and use of your samples and information for future research, whenever you want. If you decide to withdraw your permission,

contact the research staff. There are two ways to withdraw your permission. You could allow researchers to remove all your personal identifiers from your samples, so that they are not linked to you anymore. These samples will then become anonymous. You could also ask researchers to destroy your samples, so that they cannot be used for future research. Researchers will make reasonable efforts to obtain and destroy information and/or samples if consent is withdrawn. However, in either case, researchers will not be able to destroy samples or information from research that is already underway. If you withdraw your permission, there will be no negative consequences for you. *(For Local Investigators and CRS personnel, insert here local guidelines pertaining to disposal of samples, e.g., need for written request.)*

Your signature below confirms your voluntary decision to give permission for the collection, storage, and use of your blood samples and information in future research.

You do not have to give permission for storage of these samples. This will not affect your participation in the study and you may withdraw your permission at any time.

_____ YES _____ NO

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 45 men and women 18 years of age to 64 years of age will take part in this study. Women who are capable of having a baby are eligible for this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 48 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- The study is stopped or cancelled.
- The IRB, FDA, NIAID, OHRP, or another government agency with the duty to ensure that research participants are protected, or the industry supporters, recommends that the study be stopped early. An SMC is an outside group of experts who monitor the study. An IRB is a committee that watches over the safety and rights of research participants.

The study doctor may also need to take you off the study drug without your permission if:
- Continuing the study drug infusion may be harmful to you.
- You are pregnant or breastfeeding.
- You stop taking your HIV medications.
- You need a treatment that you may not take while on the study.
- You are not able to receive the study drug infusion as required by the study.

- You have positive results for antibodies to TPO, GAD65/GAD, or islet cell antigen (from testing done at week 4 prior to week 6 infusion).

If you must stop participating in this study before completing the study drug infusion or after receiving the study drug before the study is over, the study doctor may ask you to return for one or more study visits.

WHAT ARE THE RISKS OF THE STUDY?

We will now be talking about the known risks of the study medication, some of which are listed below. Before we go through the lists, we want to make you aware that there are serious risks associated with this medication. The study team has tried to minimize the risks to you as much as possible. However, there are still life-altering or life-threatening risks that are possible. The study team will carefully monitor you and act quickly to avoid more danger to you if these risks occur. However, some of these serious risks may not be reversed.

The lists below include only the more serious or common side effects with a known or possible relationship to the study drug. There is minimal data on adverse events and the relationship to specific dose levels. If you have questions concerning additional study drug side effects please ask the medical staff at your site. Safety data from each lower dose level will be carefully reviewed before higher doses are administered.

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

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study as a participant could become known to others if it is not already and that social harms may result (because you could become labeled as living with HIV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Risks of Cemiplimab
As of March 2018, 757 patients with cancer have received at least one dose of cemiplimab (1 mg/kg, 3 mg/kg, 10 mg/kg, or a 200 mg or 350 mg flat dose) alone or in combination with other treatment regimens in cemiplimab studies. Based on experience, the most common side effects related to cemiplimab treatment are as follows:

Very common side effects (>10% or more of patients): fatigue (tiredness), nausea, diarrhea, constipation, and decreased appetite.

Common (1 to ≤10% of cancer patients):
- vomiting
- dizziness

- weakness
- underactive or overactive thyroid gland
- increased blood test of liver function
- increased blood test of renal function
- anemia
- dry mouth
- flu-like illness
- swelling or pain of an arm or leg
- trouble sleeping
- shortness of breath
- itching
- cough
- joint pain
- muscle pain
- fever
- headache
- pneumonia (infection in the lungs)
- pneumonitis (inflammation of the lung)
- pulmonary embolism (blood clot in the lungs)
- abdominal pain
- low white blood counts
- chills
- rash
- dry skin
- stomatitis (inflammation of mouth and lips)
- decreased weight, dehydration
- infusion reactions
- muscle spasms
- back pain
- low phosphate, potassium, or calcium in the blood
- urinary tract infection
- sepsis (infection in your bloodstream)
- blurry vision

Uncommon (≤1% of patients) but serious:

- Encephalomyelitis (inflammation of the brain) which may result in severe memory loss and occasionally death
- Myasthenia gravis, a disease that causes muscle weakness
- Colitis, inflammation of the colon
- Bronchospasm, a narrowing of air passages in the lungs causing shortness of breath
- Diabetes and diabetic ketoacidosis, a severe complication of diabetes (high blood sugar) where the body makes too much acid in the blood
- Myocarditis, inflammation of the heart wall

Because cemiplimab may stimulate the immune system, side effects can include symptoms of increased immune response (autoimmune reactions) targeting specific organs. The symptoms of these immune responses may include:

- Inflammation of the intestines (colitis) which usually includes diarrhea
- Skin rashes or hives
- Low or high thyroid levels (hypothyroidism or hyperthyroidism) which may cause fatigue, feeling hot or cold, or decreased or increase energy and may require treatment
- Low output from the adrenal gland which can cause low blood pressure or dizziness and required treatment
- Inflammation of the liver (hepatitis)
- Diabetes (elevated blood glucose levels), which may cause nausea, abdominal pain and require insulin treatment
- Low levels of white blood cells, red blood cells (anemia), or platelets
- Neuropathy (tingling or numbness in the feet or hands)
- Severe pneumonitis (inflammation of the lungs), which may cause cough and shortness of breath
- Myocarditis (inflammation of the heart wall)
- Myasthenia gravis (muscle weakness and fatigue)
- Uveitis (inflammation of the eye), which can cause eye pain, redness, irritation, and changes in vision
- Encephalitis (inflammation in the brain), causing headache and confusion

In cancer patients, most of these symptoms and syndromes related to immune responses have been reversible, but may require treatment with steroids to suppress the immune system for several weeks. It is important that these syndromes are managed early to avoid severe symptoms which can be life-threatening.

Some of the immune responses (how your body responds to something by making hormones [chemical messengers in your body]) seen in cancer patients may be irreversible (permanent), and require ongoing and possibly lifelong treatment. The different parts of the body that could be involved are the thyroid (makes hormones that are in charge of digestion), adrenal glands (makes many different hormones in your body), and the pituitary (controls the release of all hormones in your body). The risk for irreversible conditions which would require daily, lifelong treatment appears to be highest for hypothyroidism (your thyroid is not as active as it should be; seen in 5-9% of cancer patients, hyperthyroidism (your thyroid is too active; 1-5% patients), and diabetes (<1% patients). It is important that you understand this is a potential risk in being a participant in this study. In a study of a similar anti-PD-L1 antibody given to participants with HIV, there was one potential treatment-related toxicity of inflammation of the pituitary gland following one dose that could have been related to study treatment.

To minimize the possibility of these side effects, participants with diabetes, thyroid problems, abnormal cortisol levels (a hormone released in response to stress), or other known problems with their immune system other than HIV or abnormal results on screening for these disorders are excluded from participating in this study. During this study, you will undergo repeated testing for thyroid problems, diabetes, cortisol levels, and liver problems to detect them early if they occur and allow early treatment. Early treatment for these conditions has been shown to be

important in decreasing the severity of symptoms. As such, you should let the study team know if you develop any symptoms while on study, so we can determine if they are possibly related to the study treatment.

Risks of Drawing Blood or IV Placement
Having blood drawn may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases fainting or infection. Placement of an IV catheter can cause bleeding, swelling, or bruising where the needle enters the body.

Unknown Risks
Other side effects that are not known at this time could happen during the study. There is a risk that waking up immune cells may cause immune problems (your immune cells may cause problems with the normal function of your body). We will monitor you carefully for this. All drugs have a possible risk of an allergic reaction, which if not treated right away, could become life-threatening. There is the potential for a life-threatening risk including death due to an autoimmune or infusion reaction as described above, or an unknown side effect. 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 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?

Treatment in animals with drugs similar to cemiplimab has shown an increased frequency of miscarriage. Given this potential risk to unborn babies, all volunteers participating in sexual acts that could lead to pregnancy for themselves or their partners must agree to use two effective forms of birth control for the duration of the study.

You should not participate in this study if you plan to become pregnant or cannot commit to consistent use of effective birth control for the duration of the study. It is not known if the drug in this study will harm unborn babies. Tests in pregnant animals do show risk and harm to unborn babies. In addition, potential symptoms related to immune responses discussed above could be harmful to unborn babies. The risks to unborn babies is listed in the section called "What Are the Risks of the Study?" If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant.

Because of the risk involved, you and your partner must use two methods of effective birth control that you discuss with the study staff. You must continue to use both methods for the duration of the study. You may choose two of the birth control methods listed below:

- Consistent use of birth control drugs that prevent pregnancy given by pills, shots, or placed under the skin.
- Consistent use of male or female condoms with or without a cream or gel that kills sperm.
- Consistent use of diaphragm or cervical cap with a cream or gel that kills sperm.
- Intrauterine device (IUD).
- Tubal ligation.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away and you will be given a pregnancy test, as needed. If you are pregnant while in the study, you may choose to stay on the study but you will not receive study drug. Blood tests will be limited to safety blood tests and blood tests that measure the levels of cemiplimab/placebo in your body. You will be asked to have an extra visit 6 months after the end of your pregnancy in order for the research team to get information on 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 women 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?

This is the first use of cemiplimab in participants living with HIV. This is mainly a safety study. There is no expected direct benefit to your participating in this study. Information learned from this study may help others who have HIV.

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 experimental drugs, if you qualify
- No treatment

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

WHAT ABOUT CONFIDENTIALITY?

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. Further, the Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects individuals from genetic discrimination in health insurance and employment. Genetic discrimination is the misuse of genetic information.

People who may review your records include the ACTG, OHRP, or other local, US, and international regulatory agencies as part of their duties, FDA, (insert name of site), IRB (a committee that protects the rights and safety of participants in research), NIH, study staff, study monitors, drug companies supporting this study, and their designees. If you are a woman and you become pregnant while on this study, your pregnancy will be reported to the Antiretroviral

Pregnancy Registry. 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 http://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 drug, cemiplimab, or placebo, study-related visits, physical examinations, required laboratory tests, or other procedures. This study will not provide you with antiretroviral drugs. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study. In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants.]

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 will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing 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.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- [Name of the investigator or other study staff]
- [Telephone number of above]

For questions about your rights as a research participant, contact:

- [Name or title of person on the IRB or other organization appropriate for the site]
- [Telephone number of above]

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
_____ Participant's Legal Guardian (print) (As appropriate)	_____ Legal Guardian's Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff's Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date
_____ Study Physician Investigator Conducting Consent Discussion (print)	_____ Study Physician Investigator's Signature and Date

APPENDIX II: PARTICIPANT ASSESSMENT OF UNDERSTANDING

Note for Sites: The below participant assessment of understanding should be administered after the participant has read the consent form. If the participant does not answer all questions correctly, the physician should help the participant to understand the incorrect questions. If after this has occurred, at the judgment of physician, the participant still does not understand the study, the participant should not enroll. Answer key found after assessment. See A5370 MOPS for additional information.

		True	False
1.	Participation in the study will last for about 48 weeks.	☐	☐
2.	You may leave the study at any time, if you choose to do so, without penalties.	☐	☐
3.	You will receive study-related medication during a 30-minute intravenous (IV, directly into your vein in your arm) infusion.	☐	☐
4.	There is no expected direct benefit as a result of your participation in the study.	☐	☐
5.	Some participants in this study will receive a placebo (saline with no study drug) instead of the study drug (cemiplimab - an anti-PD-1 antibody).	☐	☐
6.	One of the purposes of this study is to see if the study drug is safe in your body.	☐	☐
7.	One of the purposes of this study is to see whether the study drug can lower the amount of HIV that is present in the blood and reduce the amount of HIV that may be hiding in the cells (latent reservoir).	☐	☐
8.	You may experience serious immune-related side effects such as: skin rash, diarrhea/colitis (colon inflammation), hepatitis (liver inflammation), or pneumonitis (lung inflammation) as a result of your study participation.	☐	☐
9.	You may experience immune-related side effects such as hypo-/hyperthyroidism (increased/decreased thyroid hormone) or diabetes that could require you to take life-long medications.	☐	☐
10.	You will receive two infusions of placebo or study medication during this study.	☐	☐
11.	The purpose of this study is to find a cure for HIV.	☐	☐
12.	There may be side effects of the study medication that we do not know about yet.	☐	☐
13.	After joining the study, you will <u>not</u> need to practice safer sex by using at least 2 forms of birth control.	☐	☐
14.	Male participants whose female partners become pregnant while on study will continue treatment.	☐	☐
15.	For female participants who are able to become pregnant, after you join the study, it does not matter if you become pregnant.	☐	☐
16.	There is potential for serious side effects/conditions from the infusion of study drug that cannot be reversed (fixed).	☐	☐
17.	Serious and irreversible side effects/conditions THAT MAY BE PERMANENT CAN RESULT from the infusion of study drug AND may require treatment.	☐	☐
18.	Participating in this study may not have a direct health benefit for me, but will help investigators trying to answer a very important scientific question.	☐	☐

ANSWER KEY- *Remove from assessment prior to giving to participant.*		True	False
1.	Participation in the study will last for about 48 weeks.	☒	
2.	You may leave the study at any time, if you choose to do so, without penalties.	☒	
3.	You will receive study-related medication during a 30-minute intravenous (IV, directly into your vein in your arm) infusion.	☒	
4.	You will most likely receive no direct benefit as a result of your participation in the study.	☒	
5.	Some participants in this study will receive a placebo (saline with no study drug) instead of the study drug (cemiplimab - an anti-PD-1 antibody).	☒	
6.	One of the purposes of this study is to see if the study drug is safe in your body.	☒	
7.	One of the purposes of this study is to see whether the study drug can lower the amount of HIV that is present in the blood and reduce the amount of HIV that may be hiding in the cells (latent reservoir).	☒	
8.	You may experience immune-related side effects such as: skin rash, diarrhea/colitis (colon inflammation), hepatitis (liver inflammation), or pneumonitis (lung inflammation) as a result of your study participation.	☒	
9.	You may experience immune-related side effects such as hypo-/hyperthyroidism (increased/decreased thyroid hormone) or diabetes that could require you to take life-long medications.	☒	
10.	You will receive two infusions of placebo or study medication during this study.	☒	
11.	The purpose of this study is to find a cure for HIV.		☒
12.	There may be side effects of the study medication that we do not know about yet.	☒	
13.	After joining the study, you will <u>not</u> need to practice safer sex by using at least 2 forms of birth control.		☒
14.	Male participants whose female partners become pregnant while on study will continue treatment.	☒	
15.	For female participants who are able to become pregnant, after you join the study, it does not matter if you become pregnant.		☒
16.	There is potential for serious side effects/conditions from the infusion of study drug that cannot be reversed (fixed).	☒	
17.	Serious and irreversible side effects/conditions THAT MAY BE PERMANENT CAN RESULT from the infusion of study drug AND may require treatment.	☒	
18.	Participating in this study may not have a direct health benefit for me, but will help investigators trying to answer a very important scientific question.	☒	