A Randomized, Double-Blind, Placebo-Controlled Study of a Single Dose of Pembrolizumab in HIV-infected Patients

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine transaminase
AR	Adverse reaction
ART	Antiretroviral therapy
ARV	Antiretroviral drug
AST	Aspartate transaminase
BTRIS	Biomedical Translational Research Information System
cART	Combined antiretroviral therapy
CBC/diff	Complete blood count with differential
CC	Clinical Center
CCMD	Clinical Care Medicine Department
CFR	United States Code of Federal Regulations
CRADA	Cooperative research and development agreement
CRIMSON	Clinical Research Information Management System of the NIAID
CSO	Clinical Safety Office
DAIDS	Division of AIDS
DCR	Division of Clinical Research
DM	Diabetes mellitus
DSMB	Data and safety monitoring board
ECI	Event of clinical interest
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBS	Hepatitis B surface antigen
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HRPP	Human Research Protections Program
HSV	Herpes simplex virus
ICH	International Council on Harmonisation
Ig	Immunoglobulin
IND	Investigational new drug
INR	Immunologic nonresponder
IRB	Institutional review board
IV	Intravenous(ly)
LIR	Laboratory of Immunoregulation
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OCD	Office of the Clinical Director
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
OHSRP	Office of Human Subjects Research Protections

PI	Principal investigator
PML	Progressive multifocal encephalopathy
SAE	Serious adverse event
SAR	Suspected adverse reaction
SERF	Safety expedited report form
SINS	Section of Infections of the Nervous System
SIV	Simian immunodeficiency virus
SRCP	Safety review and communications plan
SUSAR	Serious and unexpected suspected adverse reaction
SVR	Sustained virologic response
T4	Thyroxine
TB	Tuberculosis
Tfh	T follicular helper
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UP	Unanticipated problem
UPnonAE	Unanticipated problem that is not an adverse event
USP	United States Pharmacopeia
VZV	Varicella-zoster virus

Protocol Summary

Short Title:	Pembrolizumab in HIV+ Patients
Clinical Phase:	I
Sample Size:	N = 20
Accrual Ceiling:	N = 60
Study Population:	All participants are ≥ 18 years old, have human immunodeficiency virus (HIV) infection, are currently on a combined antiretroviral therapy (cART) regimen, and are immunologic non-responders (INRs), who have suppressed viremia (viral load < 40 copies/mL for at least 12 months before screening) and have been on a stable cART regimen for at least 4 weeks, but have a CD4+ T-cell count >100 cells/mm^3 and ≤ 350 cells/mm^3.
Accrual Period:	2 years
Study Duration:	Start Date: January 2018 End Date: January 2022 Total length of individual participation: Up to 102 weeks
Study Design:	Randomized, double-blind, placebo-controlled study. Twenty HIV-infected patients with poor immunologic response will be randomized 3:1 to receive a single dose of either pembrolizumab or placebo and be followed for safety for 96 weeks. Blood will be drawn at each visit for research evaluations. Participants will undergo leukapheresis at screening (after confirmation of eligibility), with optional leukapheresis at weeks 3-4 and 12.
Study Agent/ Intervention Description:	Pembrolizumab, 200 mg, or placebo via intravenous (IV) infusion, single dose.
Primary Objective:	To evaluate safety and tolerability of a single dose of pembrolizumab in people with HIV infection and poor immunologic response.

Secondary Objective:	To evaluate the expression of PD-1 on CD4+ and CD8+ T cells following a single dose of pembrolizumab.
Primary Endpoint:	Frequency of either Grade 3 or higher adverse events or Grade 2 or higher autoimmune events requiring corticosteroid therapy that are possibly, probably, or definitely related to pembrolizumab.
Secondary Endpoint:	Magnitude and duration of decreased expression of PD-1 relative to baseline levels on lymphocytes.

Précis

A subset of HIV-infected patients, those with poor immunologic response to combined antiretroviral therapy (CD4+ T-cell count of less than 300-350 cells/mm^3) despite control of viremia, are at increased risk for both HIV-related and non–HIV-related complications compared to immunologic responders. Thus, novel approaches for treating HIV infection are needed to facilitate management of this patient population.

One potential drug target for HIV treatment is the T-cell receptor PD-1. Binding of PD-1 to its ligands, PD-L1 and PD-L2, inhibits proliferation of T cells and production of cytokines. This naturally serves to dampen potentially harmful excessive immune responses. Upregulation of PD-1 and/or its ligands can be observed in tumors and people with chronic viral infection, including HIV. This upregulation can inhibit T-cell immune surveillance, which may result in tumor growth or poor control of infection.

Pembrolizumab is an IgG4 kappa monoclonal antibody that binds to PD-1, thus blocking the receptor from binding with its ligands. In cancer indications, inhibition of PD-1 induces an antitumor immune response, which in turn reduces tumor growth. The Food and Drug Administration has approved pembrolizumab for treatment of unresectable or metastatic melanoma, non–small cell lung cancer, head and neck squamous cell carcinoma, and other cancers. Similarly, in animal models of HIV and in vitro studies, PD-1 blockade was associated with a decrease in viral load and an increase in CD8+ T cells. A clinical trial to examine the effects of PD-1 inhibition by pembrolizumab on HIV infection is thus supported by the data.

The purpose of this study is to evaluate, in a randomized, double-blind, placebo-controlled study, the safety and tolerability of a single dose of pembrolizumab in HIV-infected participants who have controlled viremia with a low T-cell count (> 100 cells/mm^3 and ≤ 350 cells/mm^3). Study participants will be followed for 96 weeks after receiving the study drug and will be assessed for adverse events, CD4+ and CD8+ T-cell counts, PD-1 expression, CD8+ T-cell anti-HIV activity, and viral load. If a single dose of pembrolizumab appears to be safe and tolerable, then larger multi-dose and efficacy studies can be planned.

1 Background Information and Scientific Rationale

1.1 Background Information

Since 1981, an estimated 78 million people worldwide have become infected with human immunodeficiency virus (HIV) and an estimated 35 million people have died from HIV-related causes.[1] Current estimates indicate that there are 37 million people living with HIV worldwide, with approximately 1 million deaths annually. Over the last 2 decades there have been major advances in prevention, diagnosis, and treatment of HIV infection, including the development of well-tolerated antiretroviral drug (ARV) regimens, which have led to major improvements in survival and the quality of life in HIV-infected patients. Despite these advances, it is estimated that in the United States alone, there are approximately 1.2 million people infected with HIV, with approximately 39,000 new infections diagnosed in 2015.[2] Without treatment, the majority of people infected with HIV eventually develop AIDS.

A subset of patients with poor immunologic response to cART are known as immunologic non-responders (INRs), who, despite having plasma viral load below detection limits of commercial assays for more than 1 year, nevertheless have a CD4+ T-cell count of less than 300-350 cells/mm^3.[3,4] Such patients are at increased risk for both HIV-related and non-HIV-related complications compared to immunologic responders, though they are at lower risk than patients with uncontrolled viremia.[5-7] Thus, novel approaches for treating HIV infection are needed to facilitate management of this patient population.

Cell-mediated immunity appears critical to controlling HIV infection.[8] Both CD4+ and CD8+ T cells play important roles in controlling infections by many intracellular pathogens, including viruses such as HIV.[9] However, HIV avoids immune regulation by undermining T-cell control through effects on the function of both CD4+ and CD8+ T cells. HIV-specific CD8+ T-cell responses are a component of the immune response to HIV and appear to play an important role in the ability of the immune system to restrict viral replication. This is true even, as suggested by macaque studies, in the setting of effective cART.[10] In most patients, however, the anti-HIV activity of CD8+ T cells is limited, allowing varying degrees of ongoing viral replication that leads to inevitable declines in CD4+ T cells.

One potential contributor to this limited efficacy is the development of anergy, or exhaustion, of HIV-specific CD8+ T cells. This anergy is mediated in part by upregulation of surface-expressed co-inhibitory molecules such as PD-1, a member of the B7-CD28 family of co-signaling molecules. PD-1 can be expressed on CD4+ and CD8+ T cells, natural killer cells, B cells, and monocytes after activation. When PD-1 is

engaged by one of its ligand, PD-L1, in conjunction with T-cell receptor activation, it down-modulates T-cell proliferation and effector functions. During normal activity, this serves to dampen potentially harmful excessive immune responses, including autoimmunity. However, as initially demonstrated in animal models, during chronic viral infection (e.g., lymphocytic choriomeningitis virus), persistently high levels of PD-1 expression are associated with poor control of infection, and blockade of the PD-1/PD-L1 interaction resulted in improved T-cell function and better viral control.[11]

The potential role of PD-1 in HIV infection has been evaluated in vitro and in animal models. In a 2006 study, PD-1 was shown to be upregulated on HIV-specific CD8+ T cells compared to total or cytomegalovirus-specific CD8+ T cells, and expression levels inversely correlated with antigen-specific proliferation.[12] Subsequent studies have confirmed this upregulation.[13-16] In INRs, PD-1 expression has been reported to be increased on CD4+ but not CD8+ T cells.[13,17] PD-1 also is a marker of T follicular helper (Tfh) cells, and Tfh cells appear to be a site of ongoing HIV transcription and a potential reservoir for active virus production in patients with controlled viremia who are on cART.[18]

In simian immunodeficiency virus (SIV)-infected macaques, PD-1 blockade using an anti-PD-1 antibody was associated with an expansion of SIV-specific CD8+ T cells, with improved functionality, decreased viral load, and improved survival.[19] In a BLT humanized mouse model of HIV infection, PD-1 blockade was associated with a decrease in viral load and an increase in the percentage of CD8+ T cells in animals with high, but not low, PD-1 expression.[20] In vitro PD-L1 blockade resulted in an increase of HIV-specific cytokine secretion by CD4+ cells, most prominently in cells from viremic individuals.[21,22] In a small study of SIV-infected macaques who were taking cART, administration of a fully human anti-PD-L1 antibody (n = 3) was associated with a non-significant trend ($p = 0.15$) toward lower viral loads after discontinuation of cART compared to a control group that did not receive the antibody (n = 3).[23] Administration of multiple doses of a primatized anti-PD-1 antibody to SIV-infected macaques during initiation of cART resulted in more rapid viral suppression, and administration while on cART resulted in up to an 80-fold reduction in SIV viral set point compared to pre-cART levels.[24]

A single study has treated HIV-infected patients with an antibody that interferes with PD-1/PD-L1 signaling.[25] In ACTG A5326 (ClinicalTrials.gov identifier NCT02028403), originally designed as a dose-escalation study, patients on cART with CD4+ T-cell count greater than 350 cells/mm^3 and HIV levels below detection limits for at least 2 years received a single dose of BMS 936559 (an anti-PD-L1 monoclonal antibody) or placebo. The study was stopped after the first (lowest dose) of a planned 4 cohorts had enrolled, because of the development of retinal toxicity in a 3-month animal study, although no

similar findings were seen in ACTG A5326. In 2 of 6 BMS 936559 recipients, an increase in gag-specific CD8+ T-cell responses was seen, though there was no significant increase in the 6 patients overall. No significant changes in HIV RNA or DNA levels were seen. The single dose was overall well tolerated; however, one patient developed apparent hypophysitis, manifested as hypoadrenalism and hypogonadism, approximately 9 months after dosing, which was determined to be consistent with an autoimmune event; this resolved 11 months after the initial diagnosis.

1.2 Description of Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (immunoglobulin [Ig] G4 kappa isotype) that binds with high affinity to the T-cell receptor PD-1, thus blocking it from interacting with its ligands, PD-L1 and PD-L2.[26] In cancer indications, inhibition of PD-1 induces an antitumor immune response, which in turn reduces tumor growth.

Pembrolizumab is marketed in the United States as Keytruda™ by Merck & Co, Inc (Kenilworth, NJ). Keytruda was first approved by the Food and Drug Administration (FDA) for treatment of unresectable or metastatic melanoma in 2014.[26] Approval for non–small cell lung cancer in tumors with high PD-L1 expression was granted in 2015, followed by approval in 2016 and 2017 for subsets of patients with head and neck squamous cell carcinoma, urothelial carcinoma, and microsatellite instability-high cancer. Infusions of pembrolizumab are generally well tolerated. However, in cancer patients, pembrolizumab therapy has been associated with the development of immune-related adverse reactions, most commonly pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and thyroid disease (described in greater detail in Section 8.1).

For further background information on pembrolizumab (MK-3475), and approved prescription drug labeling, please refer to the Investigator's Brochure.

1.3 Scientific Rationale

Upregulation of PD-1 is observed in CD4+ and CD8+ T cells in people with chronic viral infections, including HIV infection. This overexpression may contribute to persistent immune dysfunction. Inhibition of the interaction of PD-1 with its ligands, PD-L1 and PD-L2, can therefore potentially impede or reverse this dysfunction. A clinical trial to examine the immunologic and virologic effects of PD-1 inhibition by pembrolizumab is supported by available preclinical data.

There are no published studies evaluating the safety and biologic effects of pembrolizumab in HIV-infected patients. Pembrolizumab is currently being studied in patients with HIV infection in one other clinical study, "Pembrolizumab in Treating

Patients with HIV and Relapsed, Refractory, or Disseminated Malignant Neoplasms" (NIH protocol 16-C-0066, ClinicalTrials.gov identifier NCT02595866), which is being conducted by intramural National Cancer Institute (NCI) investigators as well as other sites. The purpose of this study is to evaluate the safety and tolerability of pembrolizumab in people with both HIV infection (on a stable cART regimen with controlled viremia) and relapsed, refractory, or disseminated cancer. To date they have treated 17 patients with approximately 100 doses of pembrolizumab. Two patients developed hypothyroidism that was detected on routine screening. In addition, 2 patients developed hepatotoxicity and 2 developed pneumonitis that were possibly immune-related toxicities and were treated with corticosteroids, though tumor burdens at the site of toxicity complicated this assessment.

Intramural investigators at NINDS have also administered pembrolizumab to 2 patients with HIV-associated progressive multifocal leukoencephalopathy. In both patients, the infusions were well tolerated. One patient experienced a mild transient increase in subjective progressive multifocal encephalopathy (PML) symptoms that were associated with magnetic resonance imaging changes suggesting increased immune response in the areas of the PML lesions; symptoms resolved after approximately 1 week.

Given the demonstrated, presumably immune-based clinical activity of pembrolizumab seen in cancer patients, and the potential role of PD-1 in impairing control of HIV infection, a clinical trial of pembrolizumab in HIV-infected patients who do not have cancer is warranted. The current study will focus on the safety of a single dose of pembrolizumab and will enroll patients who have controlled viremia but poor immunologic response (CD4+ T cells > 100 cells/mm^3 ≤ 350 cells/mm^3), since they are at greater risk for HIV-related disease progression than well-controlled patients with greater numbers of CD4+ T cells. If a single dose of pembrolizumab appears to be safe and tolerable for this population, then larger multi-dose and efficacy studies can be undertaken either as an amendment to the current protocol or as new protocols. We will also examine the duration of downregulation of PD-1 expression on CD4+ and CD8+ T cells, to explore if dosing less frequently than every 3 weeks (which is currently utilized in cancer studies) may be sufficient to maintain downregulation of PD-1 on these cells.

2 Study Objectives

2.1 Primary Objective

To evaluate safety and tolerability of a single dose of pembrolizumab in people with HIV infection and poor immunologic response.

2.2 Secondary Objective

To evaluate the expression of PD-1 on CD4+ and CD8+ T cells following a single dose of pembrolizumab.

2.3 Exploratory Objective

To evaluate changes in T lymphocyte subsets, HIV plasma viral load, cell-associated HIV RNA and DNA levels, plasma cytokine, chemokine, and other biomarker levels, and CD8 anti-HIV activity following a single dose of pembrolizumab.

3 Study Design

3.1 Description of the Study Design

Twenty adults (≥ 18 years) with HIV infection will be enrolled. Eligible participants will be INRs, with a recent CD4+ T-cell count >100 cells/mm^3 and ≤ 350 cells/mm^3, who have been on a cART regimen for at least 12 months and on a stable regimen for at least 4 weeks and have evidence of viral suppression.

Participants will be randomized 3:1 to receive either a single 200-mg dose of pembrolizumab or placebo via IV infusion at baseline. The dosage is based on the recommendation of Merck investigators and is the dose currently recommended on their product label. Inclusion of a placebo group will allow a blinded assessment of adverse events (AEs) and provide a control group with which to compare PD-1 expression levels over time. Participants will return for follow-up visits at weeks 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, and 48, and will have phone calls with the study team at weeks 60, 72, 84, and 96. Blood will be collected at every visit for clinical and research evaluations. Participants will undergo leukapheresis at screening (after confirmation of eligibility) with optional leukapheresis at week 3 or 4 and week 12.

Five participants will be enrolled initially and followed for 90 days for safety outcomes. No additional participants will be enrolled until the DSMB has reviewed the 90-day safety data and recommended that the protocol can resume enrollment.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Frequency of either Grade 3 or higher AEs or Grade 2 or higher autoimmune events requiring corticosteroid therapy that are possibly, probably, or definitely related to pembrolizumab.

3.2.2 Secondary Endpoint

Magnitude and duration of decreased expression of PD-1 relative to baseline levels on lymphocytes.

4 Study Population

4.1 Recruitment Plan

Participants will be recruited from existing NIH protocols/cohorts, e.g., protocols 09-I-0013 “Biomarkers of Inflammation, Coagulation, and Endothelial Function in HIV-infected Adults “and 09-I-0030 “Clinical and Immunologic Monitoring of Patients with Known or Suspected HIV Infection,” as well as locally and nationally from HIV care providers and clinics. We will use the OP8 Clinic recruitment strategies that are in place and include a full-time patient recruiter and community-based outreach within local area clinics specializing in HIV. Additional recruitment may be done using IRB-approved internet ad campaigns, social media outlets, print ads, and direct mailings to infectious disease physicians and HIV clinics.

Recruitment of NIH employees: NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the “NIH Information Sheet on Employee Research Participation.”

For NIH employees:

- NIH staff may be a vulnerable class of participants.
- Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant’s employment or work situation.
- The NIH information sheet regarding NIH employee research participation will be distributed to all potential participants who are NIH employees.
- The employee participant’s privacy and confidentiality will be preserved in accordance with NIH CC and NIAID policies, which define the scope and limitations of the protections.
- For NIH employee participants, consent will be obtained by an individual independent of the employee’s team. Those in a supervisory position to any employee and co-workers of the employee will not obtain consent.
- The importance of maintaining confidentiality when obtaining potentially sensitive and private information from co-workers or subordinates will be reviewed with the study staff at least annually and more often if warranted.

4.2 Participant Inclusion Criteria

Individuals must meet all of the following criteria to be eligible for study participation:

1. ≥ 18 years of age.
2. Documented HIV-1 infection (e.g., positive standard enzyme-linked immunosorbent assay or rapid HIV-1/HIV-2 antibody test with a confirmatory test such as western blot, or documentation of repeated HIV RNA of > 1000 copies/mL). Outside documentation will be acceptable.
3. Absolute neutrophil count > 1000/μL.
4. Platelet count > 125,000/μL.
5. Hemoglobin > 10 g/dL.
6. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.1 times the upper limit of normal (ULN). Total bilirubin < 1.1 x ULN (unless participant is taking atazanavir or has Gilbert syndrome).
7. Calculated creatinine clearance (estimated glomerular filtration rate) ≥ 60 mL/min/1.73 m^2.
8. Thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) within normal limits. If TSH is not within normal limits, then the participant may be eligible if thyroxine (T4) is within normal limits. Participants will not be excluded if they are on a stable dose of replacement thyroid medication; dose may be adjusted as needed.
9. No significant underlying pulmonary, cardiac, renal, or hepatic disease, as defined by a need for drug treatment or ongoing physician care.
10. Under the care of a primary care physician.
11. Willing to comply with study requirements and procedures including storage of biological specimens for future use in medical research.
12. Willing to allow genetic testing.
13. Able to provide informed consent.
14. Participants of reproductive potential must agree to not become pregnant or to impregnate a partner beginning 30 days before the dose of pembrolizumab through 120 days postdose. Non-reproductive potential is defined as azoospermia, postmenopausal, surgical sterilization at least 6 weeks before screening, or a congenital or acquired condition that definitively prevents conception. Further, postmenopausal is defined as at least 12 consecutive months with no menses at age 50 or older, and also a high follicle-stimulating hormone level in postmenopausal range at ages 45-50 years, for participants not using hormonal contraception or hormone replacement therapy.

    Participants of reproductive potential must either practice complete and uninterrupted abstinence from heterosexual activity or use two of the following

methods of contraception with their partners. The 2 methods must include one from each group, both of which must be consistently use:

Barrier methods:

a. Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide).
b. Cervical cap with spermicide (only for nulliparous partners).
c. Contraceptive sponge (only for nulliparous partners).
d. Male or female condom (cannot be used together).

Non-barrier methods:

a. Intrauterine device.
b. Hormonal contraception: pill (estrogen/progestin or progestin-only), skin patch, vaginal ring, rod implanted in the skin, or subcutaneous injection.

15. Participants must meet criteria for INR, defined as follows:
    a. Has been on a cART regimen for at least 12 months and on a stable regimen for at least 4 weeks.
    b. Has evidence of viral suppression, defined as viral load < 40 copies/mL, and documented suppression for at least 12 months prior to screening. A viral load of < 500 copies/mL once in the year preceding screening will be allowed if there is documentation of a viral load < 40 copies/mL on subsequent testing and at screening.
    c. CD4+ T-cell count > 100 cells/mm^3 and ≤ 350 cells/mm^3.

4.3 Participant Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from study participation:

1. Has used an investigational drug agent or investigational device within 12 weeks of baseline. However, ARVs obtained through expanded access programs are permitted.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
3. Known allergy to any component of the pembrolizumab formulation.
4. Systemic steroid therapy or other immunosuppressive therapy in the 3 months prior to enrollment. (Inhaled or topical corticosteroids are permitted.)
5. Has used an immunotherapeutic agent (e.g., cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, sirolimus, therapies targeting tumor necrosis factor-α) within 6 months of baseline.
6. Has received any vaccine, live or inactivated, within 30 days of baseline, or plans to receive any vaccine within 16 weeks of receiving pembrolizumab.
7. Has active autoimmune disease or a history of autoimmune disease that has required systemic treatment (e.g., with use of disease-modifying agents,

corticosteroids, or immunosuppressive drugs). Such autoimmune diseases include for example psoriasis, systemic lupus erythematosus, autoimmune uveitis, autoimmune hepatitis, inflammatory colitis, rheumatoid arthritis, Guillain-Barré syndrome, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Replacement therapy (e.g., T4) is not considered a form of systemic treatment.

8. Has known history of, or any evidence of active, non-infectious pneumonitis.
9. Malignancy requiring systemic therapy, or a history of malignancy that required systemic therapy within the past 5 years. However, cutaneous basal cell carcinoma or cutaneous Kaposi sarcoma not requiring systemic therapy will not be exclusionary.
10. Has known active hepatitis B (HBV) or potential for HBV reactivation (e.g., hepatitis B surface antigen [HBS] reactive, HBV DNA positive, or isolated anti-core antibody positive; individuals who are anti-HBS antibody positive with or without anti-core Ab are eligible).
11. Has known active hepatitis C (HCV; e.g., HCV RNA [qualitative] is detected). Patients who have sustained virologic response (SVR) to anti-HCV treatment are eligible if at least 24 weeks have passed since achieving SVR.
12. Females who are pregnant, planning to become pregnant, or are breastfeeding.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
14. History or other clinical evidence of:
    a. Significant or unstable cardiac disease (e.g., angina, congestive heart failure, myocardial infarction).
    b. Significant pulmonary disease (e.g., chronic obstructive pulmonary disease, asthma requiring systemic therapy).
    c. Severe illness, chronic liver disease, malignancy, immunodeficiency other than HIV, active systemic infection (other than HIV) requiring therapy.
15. Opportunistic infection requiring maintenance therapy, including toxoplasmosis, fungal infections other than candida (e.g., cryptococcosis, histoplasmosis, coccidioidomycosis), atypical mycobacterial infection. Secondary *Pneumocystis*, candida, varicella-zoster virus (VZV), and herpes simplex virus (HSV) prophylaxis will be permitted.
16. Active or history of tuberculosis (TB), or positive TB QuantiFERON Gold test.
17. Known osteoporosis or diabetes mellitus.
18. Hemoglobin A1c > 6%.
19. Fasting triglyceride > 300 mg/dL.
20. Any condition that, in the opinion of the investigator, would make the participant unsuitable for the study.

Co-enrollment guidelines: Co-enrollment in other trials is restricted, other than enrollment on observational studies or expanded access studies for antiretroviral agents, during the first 48 weeks of the study. If NIH blood volume limits are exceeded due to the requirements of the combined studies, then co-enrollment will not be permitted.

4.4 Justification for Exclusion of Special Populations

Females who are pregnant or of reproductive potential: Dedicated developmental and fetal toxicity studies of pembrolizumab have not been conducted in humans or animals. However, animal models of the PD-1/PD-L1 pathway suggest that perturbations may affect the maternal immune response to fetal tissue. Human IgG4 antibodies (the IgG subtype of pembrolizumab) are also known to cross the placental barrier and be transmitted from mother to fetus. Additionally, pregnancy may affect the participant's immune response. Therefore, pregnant participants are excluded from this study. Per recommendations in the pembrolizumab package insert, contraception (for this study, two forms, one of which must be a barrier-based method, see Section 4.2) will be required from 30 days prior through 120 days after the pembrolizumab dose.

Breastfeeding: It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions (ARs) in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

Exclusion of children: Because there are insufficient data regarding dosing or AEs available in adults to judge the potential risk in children, and because this is the first safety study in HIV-infected patients without cancer, children are excluded from this study.

5 Study Agent/Interventions

5.1 Disposition, Dispensation, and Accountability

Study agent or placebo will be distributed and accounted for by the NIH pharmacy according to standard pharmacy procedures.

5.2 Formulation, Packaging, and Labeling

Each pembrolizumab ready-for-injection vial will be further diluted according to the manufacturer's label instructions and administered as an IV infusion to the study subject. Each IV infusion bag for both study agent and placebo will be individually labeled with the subject ID number, administration instructions, and the Investigational

Use Statement (“Caution: New Drug-Limited by Federal [USA] Law to Investigational Use’).

5.3 Study Agent Storage and Stability

Vials of pembrolizumab injection solution should be stored at 2°C-8°C and should not be shaken or frozen. Vials should be kept in their cartons and protected from light. Diluted study drug may be stored at 2°C-8°C for up to 24 hours, or room temperature (approximately 22°C) for up to 6 hours.

5.4 Preparation, Administration, and Dosage of Study Agents

Pembrolizumab is provided as a ready-for-injection solution at 100 mg/4 mL and should be further diluted for administration.

Participants will receive a single 200-mg dose of pembrolizumab in 5% dextrose or placebo (matching diluent). To maintain the double-blind, pembrolizumab and placebo infusions should be prepared in matching diluent solutions and administered in the same manner (please see administration instructions below).

Preparation: When preparing pembrolizumab, allow the required number of vials to equilibrate to room temperature. For IV infusion, the study drug should be diluted to a final concentration between 1 and 10 mg/mL in 5% dextrose solution for injection, USP. The placebo will be an equivalent volume of 5% dextrose solution for injection, USP.

In the event of a diluent shortage, 0.9% sodium chloride solution may be used in place of 5% dextrose to prepare pembrolizumab and placebo infusions.

Administration: Pembrolizumab and placebo infusion should be administered over 30 minutes through an IV line containing a sterile, non-pyrogenic, low-protein-binding 0.2-5–µm in-line or add-on filter. Pembrolizumab should not be co-administered with other drugs in the same infusion line.

5.5 Randomization and Blinding

Eligible participants will be allocated 3:1 to study agent or placebo. A randomization scheme will be generated by the study statistician who will provide a randomized list of arm assignments to the NIH CC Pharmacy. Block randomization will be designed to ensure that some participants among the first 5 enrolled will receive pembrolizumab.

Study participants and the study team will be blinded through week 16 of the last participant treated.

5.5.1 Emergency Unblinding

If a participant experiences an AE whose management (e.g., diagnostic procedures, treatment) in the opinion of the principal investigator (PI) or designee would differ depending on the study arm, or in the case of pregnancy of a participant's partner, then the PI or designee will contact the NIH CC Pharmacy for release of the randomization code. The sponsor and data and safety monitoring board (DSMB) executive secretary will be informed within 1 business day of any request for unblinding. The participant will remain enrolled in the study and the data will be used for analysis.

5.6 Concomitant Medications and Procedures

All concomitant medications, including those received within 28 days before the administration of pembrolizumab, will be recorded in the Clinical Research Information Management System of the NIAID (CRIMSON), including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. If changes occur during the study period, then documentation of drug dosage, frequency, route, and date may also be included in CRIMSON.

5.7 Prohibited Medications and Procedures

Treatment with systemic corticosteroids, other immunomodulatory drugs, or other drugs targeting PD-1, PD-L1, or PD-L2 will not be permitted during the first 48 weeks of the study except as summarized below, unless discussed with and approved by the PI or designee.

Participants are prohibited from receiving the following therapies during the first 48 weeks of the study:

- Immunotherapy not specified in this protocol (e.g., cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, sirolimus, therapies targeting tumor necrosis factor-α).
- Investigational agents other than pembrolizumab or expanded access ARVs.
- Any vaccine within 30 days pre-dose and through week 16, and live vaccines through week 48 in this study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid.
  Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed after week 16; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic corticosteroids for any purpose other than to modulate symptoms from an event of clinical interest (ECI) of suspected immunologic etiology.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management after receiving the single dose of pembrolizumab will continue to be followed in the study. Participants may receive other medications that the investigator deems to be medically necessary.

5.8 Management of Study Drug-related AEs

In the event of AEs related to the study drug, participants will receive appropriate supportive care measures as deemed necessary by the treating investigator. Given that management may depend on knowledge of the underlying treatment arm, as noted above, the PI or designee may unblind (see emergency procedure for unblinding) to ensure that the diagnostic evaluations and therapeutic interventions are directed appropriately. Suggested supportive care measures for the management of pembrolizumab-related AEs with potential immunologic etiology are outlined in Appendix A. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation, the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined in Appendix A).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of standard clinical evaluation of the event.

6 Study Schedule

NOTE: **Five participants will be enrolled initially and followed for 90 days for safety outcomes. No additional participants will be enrolled until the DSMB has reviewed the 90-day safety data and recommended that the protocol can resume enrollment.**

All study visits will be done at the NIH CC. A table of the study schedule is presented in Appendix B.

6.1 Screening (week −6 to 0)

The participant will sign the informed consent form for this study before undergoing any procedure or evaluation. Screening procedures/evaluations to determine eligibility for this study are listed below. These procedures may occur over more than 1 visit.

- Physical exam with vital signs.
- Review medical and medication history, including past and current ART regimens.
- For participants of reproductive potential, counseling concerning the importance of consistently using two forms of effective birth control in light of the potential risk of pembrolizumab to a developing fetus.
- Blood draw for clinical lab evaluations: complete blood count with differential (CBC/diff), prothrombin/partial thromboplastin time, chemistry panels (acute, hepatic, and mineral), lipid panel, TSH and T4, ACTH, cortisol, hemoglobin A1c, TB QuantiFERON Gold, HIV serology (if not previously documented at NIH), plasma HIV viral load, immune profile including CD4 count, HBV testing (DNA, surface antigen, and antibody), and HCV testing (RNA and antibody).
- Urinalysis.
- Pregnancy test (serum or urine, for participants of childbearing potential only).
- Electrocardiogram.
- HLA typing (unless previously performed at NIH).
- Collection of cells/serum/plasma for research and stored samples.
- Leukapheresis to store cells for research studies, after eligibility is confirmed. If leukapheresis cannot be performed for technical or other reasons (e.g., poor venous access or other contraindication to the procedure), then an additional 80 mL of blood will be drawn.

6.2 Baseline (day 0)

- At baseline, blood for baseline safety and research labs will be drawn. For participants of childbearing potential only, pregnancy test (serum or urine) will be obtained,
- For participants of reproductive potential, counseling concerning the importance of consistently using two forms of effective birth control in light of the potential risk of pembrolizumab to a developing fetus.

Participants will be randomized and will receive either a single 200-mg dose of pembrolizumab or placebo via IV infusion. The infusion will be administered over at least 30 minutes, and the participant will be monitored throughout and for 2 hours after for any signs of infusion or allergic reactions. Infusion-related reactions will be managed

as summarized in Appendix A. If the infusion is discontinued due to an infusion-related reaction, it will not be resumed.

6.3 Follow-up (weeks 1-96)

Participants will return for follow-up visits at weeks 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, and 48. All visits through week 6 will have a window of ± 4 days; visits from week 9 onward will have a window of ± 7 days. At all visits, participants will have the following:

- Review of medical and medication history.
- Targeted physical exam, including weight, vital signs, and a symptom-directed evaluation.
- Assessment of AEs.
- For participants of reproductive potential, counseling concerning the importance of consistently using two forms of effective birth control in light of the potential risk of pembrolizumab to a developing fetus.
- Blood draw for clinical and research evaluations (see Section 7).
- Pregnancy test (serum or urine, for participants of childbearing potential only).
- Optional follow-up leukapheresis at weeks 3 or 4 and 12. Refusal to undergo leukapheresis will not otherwise affect participation in the study.

Follow-up telephone calls at weeks 60, 72, 84, and 96 (± 2 weeks) will be conducted to see if any AEs potentially related to pembrolizumab occurred during the prior 12 weeks. Participation in this study will end after the week 96 call.

6.4 Early Termination Visit

Participants who leave the study before week 48 (the final scheduled visit to the NIH), voluntarily or otherwise, will be urged to return to the NIH CC for an early termination visit. As with the follow-up visits, participants will have a physical exam, have their medical and medication history reviewed, be assessed for AEs, and have blood drawn for clinical and research evaluations. If a participant decides to leave the study between weeks 48 and 96, then the telephone call follow-up will be conducted at that time, with the participant's agreement.

7 Research Procedures/Evaluations

Medical history and physical exam.

Blood draw: The amount of blood drawn for research purposes will be within the limits allowed for adult research participants by the NIH CC (Medical Administrative Policy

95-9, Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

Safety labs at each visit will include CBC/diff, chemistry panels (acute, hepatic, and mineral), lipid panel, TSH and T4, ACTH, cortisol, plasma HIV viral load, and immune profile including CD4 count.

Research evaluations on blood and/or leukapheresis will include the following:

- Fluorescence-activated cell sorting analysis, including CD4+ and CD8+ populations and subsets, and PD-1 expression on CD4+ and CD8+ T cells.
- Assays to measure CD8+ T-cell anti-HIV activity.

Other research evaluations may include but are not limited to the following:

- Frequency of $CD4^+$ T cells carrying HIV pro-viral DNA and cell-associated HIV RNA.
- Frequency of HIV-specific CD4+ and CD8+ T cells.
- T-cell activation and soluble markers of inflammation.
- Gene expression profiling of T cells.
- Antibodies to HIV-specific and other proteins using the luciferase immunoprecipitation system assay.
- Cell-associated p24 antigen levels (to be performed at Merck).
- Plasma levels of pembrolizumab (to be performed at Merck).

Leukapheresis: Leukapheresis will be performed by trained members of the Apheresis Unit under supervision of the medical staff of the Department of Transfusion Medicine at the NIH CC according to CC standard operating procedures. If leukapheresis cannot be performed for technical reasons (eg, poor venous access) or due to scheduling or logistical issues, then 80 mL of blood will be drawn instead. Samples collected from this procedure will be used for assays to measure CD8+ T-cell anti-HIV activity and may be utilized for research evaluations as summarized above.

8 Potential Risks and Benefits

8.1 Potential Risks

Pembrolizumab [26]**:** The clinical safety profile of pembrolizumab is based on studies conducted exclusively in patients with a variety of cancers, the majority with melanoma and non–small cell lung cancer; many of these patients had received prior chemotherapy as well as other immunomodulatory drugs, and most patients received multiple doses of pembrolizumab, with dosing every 2 to 3 weeks. Thus, it is currently

unknown if, and with what frequency, the AEs seen in these patient populations will occur in HIV-infected patients.

The most commonly reported AEs of pembrolizumab (> 5% of patients) are fatigue, fever, pruritus, diarrhea, nausea, vomiting, decreased appetite, rash, dyspnea, constipation, asthenia, arthralgia, back pain, cough, headache, peripheral edema, anemia, myalgias, and vitiligo. Other AEs include chills, constipation, abdominal pain, dizziness, insomnia, upper respiratory tract infection, and laboratory abnormalities including increased ALT and AST, hyperglycemia, hyponatremia, hypoalbuminemia, and hypertriglyceridemia.

Pembrolizumab inhibits an immune checkpoint, and thus there is the potential for development of immune-related complications. Treatment-emergent immune-mediated diseases have been observed in cancer trials, and include pneumonitis, colitis, hepatitis, hypophysitis, thyroid disorders (hyper- and hypothyroidism, and thyroiditis), type 1 diabetes mellitus (DM), and nephritis and renal dysfunction (Table 1).[27] Rare potentially immune-mediated diseases include uveitis (0.5%) and other ocular disorders, myositis (0.5%), pancreatitis (0.3%), arthritis (1.5%), and Guillain-Barre syndrome (0.1%). There have been rare reports of primary adrenal insufficiency, hypoparathyroidism, myasthenia gravis, vasculitis, hemolytic anemia, autoimmune thrombocytopenia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis, sarcoidosis, gastritis, duodenitis, polymyalgia rheumatica, meningitis, myelitis, encephalitis and other neurologic disorders, pericarditis, myocarditis, some of which have been fatal, as well as severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid. Onset of immune-mediated complications typically occurred between 1 and 5 months, though onset has been reported as early as 1 day and as late as 21 months after initiation of pembrolizumab, and can occur after discontinuation of the drug.[27] Management (Appendix A) includes treating with corticosteroids (e.g., prednisone, 1-2 mg/kg/day followed by a taper); hypothyroidism may be treated with levothyroxine. Very rarely, immune-mediated pneumonitis has been fatal.

Of the 2799 patients treated with pembrolizumab in the Merck Reference Safety Dataset, there were 10 deaths attributed to the drug: respiratory failure (n = 1), cardio-respiratory arrest (n = 1), interstitial lung disease (n = 1), general physical health deterioration (n = 1), myocardial infarction (n = 1), pneumonia (n = 2), and pneumonitis (n = 3).[27]

Table 1. Immune-mediated Adverse Reactions

Adverse Reaction	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Hypothyroidism	8.5	6.2	0.1	0	0
Hyperthyroidism	3.4	0.8	0.1	0	0
Pneumonitis	3.4	1.3	0.9	0.3	0.1
Colitis	1.7	0.4	1.1	< 0.1	0
Hepatitis	0.7	0.1	0.4	< 0.1	0
Hypophysitis	0.6	0.2	0.3	< 0.1	0
Nephritis	0.3	0.1	0.1	< 0.1	0
Type 1 diabetes mellitus	0.2	< 0.1	0.1	0.1	0

Pembrolizumab dose = 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks.
n = 2799.

Anti-pembrolizumab antibodies can potentially develop with treatment since pembrolizumab is a monoclonal antibody. In clinical studies, the incidence of development of anti-pembrolizumab antibodies was 2% of 1289 evaluable patients.[27] The clinical significance of these antibodies is uncertain. There is also the risk of allergic or anaphylactic reactions. Infusion-related reactions reported in other clinical trials include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, with an overall incidence of 2.5%.[27] In this study, all participants will be monitored during and for 2 hours after infusion so these potential reactions can be immediately cared for.

There may be other risks of pembrolizumab that are currently unknown.

Leukapheresis: The potential risks associated with leukapheresis include lightheadedness, dizziness, possible fainting, tingling around the mouth and in the fingers and toes, nausea, chills, vomiting, mild muscle cramps, loss of less than 1 pint of blood, or pain, bruising, or discomfort at the needle insertion sites. Most procedures are performed without an incident. Blood components removed during leukapheresis are generally replaced by the body within a few hours or a few days. No infections

associated with this procedure have been reported in thousands of cases performed over the last 10 years at the NIH.

Temporary or permanent nerve damage may also occur at the needle placement sites. This is very rare. There have been no cases of permanent nerve damage with apheresis reported at the NIH.

Blood draw and IV catheter: The risks of drawing blood or inserting an IV catheter for study drug/placebo infusion include pain, bruising, bleeding, and, rarely, fainting or infection.

HLA typing: HLA typing will be performed on samples collected from all enrolled participants, unless previously performed at NIH. Results from the HLA typing will become part of each participant's medical record at the NIH. Medical records containing this information are maintained in a secure place. Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic disorders, or a faster progression to AIDS. Therefore, results of genetic testing may have psychological implications for participants. Genetic counseling and advice is available from the NIH to help participants with the implications of findings, where appropriate.

8.2 Potential Benefits

Participants will likely not receive direct benefit in this study. It is possible that pembrolizumab may result in temporary improvement in anti-HIV host immunity. The information collected in this study may enhance the investigators' understanding of the use of pembrolizumab as an immunomodulatory drug for treating HIV infection.

9 Research Use of Stored Human Samples, Specimens, or Data

Intended Use: Samples, specimens, and data collected under this protocol will be used to study the potential role of pembrolizumab for treatment of HIV infection and may be used to study immune function and immune mechanisms, HIV infection and its complications, and HIV immunopathogenesis.

Storage: All of the stored study research samples are labeled by a code that only the investigators can link to the participant. Samples are stored at the NCI at Frederick Central Repository, which is a secure facility with limited access. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data.

Tracking: Samples will be tracked using the NCI at Frederick Central Repository. Data will be stored and maintained in the CRIMSON database.

Disposition at the Completion of the Protocol:

- In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. Before any sharing of samples, data, or clinical information, either IRB approval must be obtained or the NIH Office of Human Subjects Research Protections (OHSRP) must determine that the research is exempt from IRB oversight. OHSRP can make this determination for some research where the samples or data have no personal identifying information about the study participant and the researcher is not able to ascertain it.
- At the time of protocol termination, samples will either be destroyed, or after IRB approval, transferred to another existing protocol. Data will be archived by the study team in compliance with requirements for retention of research records; alternatively, after IRB and study sponsor approval, the data may be either destroyed or transferred to another repository.

Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:

- Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of protocol deviation, unanticipated problem (UP), and/or compromises the scientific integrity of the data collected for the study will be reported to the NIAID IRB.
- Additionally, participants may decide at any point not to have their samples stored. In this case, the PI will destroy all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual's participation in this protocol or any other protocols at NIH.

10 Data Sharing Plan

Human data generated in this study will be shared for future research as follows:

- Identified data in the Biomedical Translational Research Information System (BTRIS; automatic for activities in the CC).
- De-identified or identified data with approved outside collaborators under appropriate agreements.
- Through publication and/or public presentations.
- Data sharing may be complicated or limited in certain cases by contractual obligations or agreements with outside collaborators, such as a cooperative

research and development agreements, clinical trial agreements, other restraints, etc.

Data will be shared at the time of publication.

11 Remuneration Plan for Participants

Eligible participants will be compensated for travel according to the NIAID/NIH travel policy. Participants will receive financial compensation for time and inconvenience according to the NIH CC volunteer guidelines: screening ($50), 2-pass leukapheresis ($200 for a procedure; $50 for unsuccessful apheresis attempts), research blood draw and clinic visits ($75), pembrolizumab/placebo infusion ($150). If a participant does not qualify or declines leukapheresis, then an additional 80 mL of research blood will be drawn, and the participant may be compensated an additional $25 for inconvenience. If a participant completes all visits in the follow up phase of the study, there is a $200 completion bonus. Actual compensation is based on the number and type of study visits participants complete. Therefore, the maximum remuneration for a participant is $1900.

12 Assessment of Safety

AEs and other reportable events are defined in Policy 801: Reporting Research Events

Adverse Reaction: An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An AE for which there is a reasonable possibility that the investigational agent caused the AE. “Reasonable possibility” means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which implies a high degree of certainty.

12.1 Documenting, Recording, and Reporting Adverse Events

All AEs occurring from the time of the initial leukapheresis through week 48 will be documented, recorded, and reported. If no leukapheresis is performed, then all AEs occurring from the time of pembrolizumab administration through week 48 will be documented, recorded, and reported. Between weeks 48 and 96, reporting will be limited to only those SAEs and autoimmune events that are possibly, probably, or definitely related to pembrolizumab.

At each contact with the participant, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- documented in the participant's medical record/source document,
- recorded in CRIMSON, and
- reported as outlined below (e.g., IND sponsor and FDA).

If a diagnosis is clinically evident (or subsequently determined), then the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

All abnormal laboratory findings will be reviewed on a routine basis by the PI to identify potential safety signals. An abnormal lab not included on the toxicity table should be assessed in a similar fashion to the criteria above.

12.2 Investigator Assessment of Adverse Events

The investigator will assess all AEs with respect to severity (intensity or grade), and causality (relationship to study agent and relationship to research) according to the following guidelines.

12.2.1 Severity

The Investigator will grade the severity of each AE according to the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events" most recent Version 2.1, July 2017, which can be found at: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf

Because the DAIDS toxicity table does not have specific criteria for infusion-related reactions, we will use the following criteria, based on the Common Terminology Criteria for Adverse Events Version 4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). This is very similar to the grading criteria for "Cytokine release syndrome" that is part of the DAIDS table.

Table 2. CTCAE Infusion Reaction Severity Grading Criteria

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction.	Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Life-threatening consequences; urgent intervention indicated.	Death.

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

Some Grade 1 lab parameters on the DAIDS Toxicity Table fall within the NIH lab reference range for normal values. These normal values will not be reported as Grade 1 AEs.

12.2.2 Causality

Causality (likelihood that the event is caused by the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship
  OR
- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship
  OR
- definitely due to an alternative etiology

Note: Other factors should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

12.3 Investigator Reporting Responsibilities to the Sponsor

12.3.1 Adverse Events

AE data will be submitted to the IND sponsor when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

12.3.2 Reporting to the Sponsor's Safety Office

12.3.2.1 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the safety expedited report form (SERF) and sent to the Clinical Safety Office (CSO) by fax or email attachment. Deaths and immediately life-threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

CSO CONTACT INFORMATION:

Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
E-mail: rchspsafety@mail.nih.gov

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g., the participant is lost to follow-up), then the reason a final outcome could not be obtained will be recorded by the investigator in CRIMSON and the SERF.

SAEs that occur after week 96 that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

12.3.2.2 Unanticipated Problems

UPs that are also AEs must be reported to the CSO by fax or e-mail attachment using the NIH Problem Report Form no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the CSO.

12.3.2.3 Events of Clinical Interest

The following ECIs must be reported to the CSO on a SERF within 3 business days of site awareness:

- Immune-mediated AEs other than hypothyroidism (Section 8.1).
- Opportunistic infections.
- An elevated AST or ALT lab value that is greater than or equal to 3 x ULN and an elevated total bilirubin lab value that is greater than or equal to 2 x ULN (excluding patients with Gilbert syndrome or those receiving atazanavir) and, at the same time, an alkaline phosphatase lab value that is less than 2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. (These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.)
- Development of a new cancer.
- AEs that occur in reasonable temporal association with an overdose of pembrolizumab. (Overdose, in and of itself, without an associated AE, is reportable in an expedited fashion to the sponsor and IRB as a UP but is not considered an SAE. An overdose is defined as any dose greater than the protocol-defined dose of 200 mg.)

12.3.2.4 Pregnancy

Participants who inadvertently impregnate a partner after receiving study agent will be instructed to immediately inform the investigator. All pregnancies occurring within 120 days of pembrolizumab administration will be reported on the Pregnancy Notification/Outcome Form to the CSO within 1 business day from site awareness.

The investigator will make every effort to obtain pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy). SAEs and the outcome of the pregnancy will be reported to the CSO within 3 business days of the site's awareness.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (eg, miscarriage, congenital anomaly/birth defect) are reportable on the SERF.

In the event of pregnancy, the following steps will be taken:

- Report to the CSO, IRB, and DSMB.
- Unblind participant.
- If participant received pembrolizumab, advise research participant that his partner should notify her obstetrician of study participation and study agent exposure.
- Maintain regular (e.g., monthly) contact with the participant to track the progress and outcome of the pregnancy, including any untoward events, AEs, and SAEs.

12.3.3 Investigator Reporting Responsibilities to the NIAID IRB

Unanticipated problems, non-compliance, and other resportable events will be reported to the NIH IRB as per Policy 801.

12.4 Sponsor's Reporting Responsibilities

SUSARs, as defined in Title 21 of the United States Code of Federal Regulations (CFR) Part 312.32 and determined by the IND sponsor, will be reported to FDA and all participating investigators as IND Safety Reports.

The IND sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

12.5 Halting Rules for the Protocol

Halting the study requires immediate discontinuation of study agent administered for all participants and suspension of enrollment until a decision is made whether or not to continue enrollment and study agent administration.

The halting rules are:

- Any SAE that is unexpected and possibly, probably, or definitely related to the study agent;

OR

- 2 or more of the same or similar AEs in different participants that are Grade 3 or above (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, or chills, or elevated total bilirubin in patients with Gilbert syndrome or those receiving atazanavir) and are possibly, probably, or definitely related to the study agent;

OR

- 2 or more Grade 2 or higher autoimmune events requiring corticosteroid therapy that are possibly, probably, or definitely related to the study agent;

OR

- Any safety issue that the PI and/or the CSO determines should halt the study.

The PI and/or CSO will determine if the study should be halted. In addition, the FDA may halt the study at any time following review of any safety concerns.

12.5.1 Reporting a Study Halt

If a halting rule is met, then a description of the AE(s) or safety issue must be reported by the PI within 1 business day to the CSO, the IRB, and the DSMB by fax or email. The FDA will also be notified when a study is halted.

12.5.2 Resumption of a Halted Study

The IND sponsor, in collaboration with the PI and the DSMB, will determine if it is safe to resume the study. The PI will notify the IRB of the decision on resumption of the study; the FDA will also be notified of this decision.

12.6 Withdrawal Criteria for an Individual Participant

An individual participant will be withdrawn for any of the following:

- An individual participant’s decision. (The investigator should attempt to determine the reason for the participant’s decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the participant or to the integrity of the study data.
- Co-enrollment in a study with an investigational research agent other than expanded access antiretroviral medications.

- The investigator determines that continued participation in the study would not be in the best interest of the participant.

Prior to withdrawal, participants will be offered the opportunity to continue in the study for safety follow-up only, unless in the opinion of the investigator such follow-up would be potentially harmful to the participant.

Only participants who receive pembrolizumab or placebo will be included in the safety assessment. Once a participant has received the pembrolizumab or placebo infusion they will be included in the safety assessment regardless of early withdrawal. Participants who withdraw prior to receiving the infusion of pembrolizumab or placebo, or who receive the infusion but withdraw prior to week 6 for reasons unrelated to safety (eg, personal decision) may be replaced with a participant who is assigned to the same study arm.

12.7 Safety Oversight

12.7.1 Safety Review and Communications Plan

A safety review and communications plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

12.7.2 Sponsor Medical Monitor

A medical monitor, representing the IND sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The sponsor medical monitor will be responsible for performing safety assessments as outlined in the SRCP.

12.7.3 Data and Safety Monitoring Board

The NIAID intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The DSMB will review the study prior to initiation and twice a year thereafter and may convene additional reviews as necessary.

The DSMB will also review the safety data after 5 participants have been enrolled and followed for 90 days (this review may be one of the twice-yearly reviews); no additional participants will be enrolled until the DSMB recommends that study enrollment can be resumed.

The board will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All SAEs, all UPs, and all IND Safety Reports will be reported by the PI to the DSMB at the same time they are submitted to the IRB or IND sponsor. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI will notify the board at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB.

13 Site Monitoring Plan

According to the International Council on Harmonization (ICH) E6(R2) Good Clinical Practice (GCP) guidelines, section 5.18, and 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the “NIAID Intramural Clinical Monitoring Guidelines.” Monitors under contract to the NIAID/OCRPRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the consent process for each monitored participant; 2) to verify the prompt and accurate recording of all monitored data points in CRIMSON and prompt reporting of all SAEs; 3) to compare abstracted information entered into CRIMSON with individual participants’ records and source documents (participants’ charts, laboratory analyses and test results, physicians’ progress notes, nurses’ notes, and any other relevant original participant information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP]), FDA, and applicable guidelines (ICH GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (eg, consent forms, CRIMSON data abstracts) and pertinent hospital or clinical records, including CRIMSON, readily available for inspection by the local IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

14 Statistical Considerations

The primary safety outcome is the occurrence of Grade 3 or higher AEs or Grade 2 or higher autoimmune events requiring corticosteroid therapy.

Although this is a randomized controlled trial, the placebo arm will be used informally to interpret AEs in the pembrolizumab arm. For instance, concern over AEs in the pembrolizumab arm would be tempered if one or more people in the placebo arm experienced the same type of AE. Formal between-arm comparisons will also be made, but it is extremely difficult to show a statistically significant between-arm difference. For instance, if there are no AEs of a given type in the placebo arm, 9 or more people out of 15 in the pembrolizumab arm would have to experience the AE to declare a statistically significant difference using Fisher's exact test and two-tailed type 1 error rate 0.05. For this reason, we focus below on estimating the probability of AEs in the pembrolizumab arm rather than on power to compare arms.

An exact 95% confidence interval for the probability of AEs will be computed using the Clopper-Pearson method. Changes from baseline in continuous measurements will be analyzed using paired t-tests or, if data are skewed, then the Wilcoxon signed rank statistic. Secondary analyses will use mixed models to estimate the trajectories over time. Linear and quadratic terms will be incorporated, if warranted.

A sample size of 15 pembrolizumab-administered participants provides a 91.3% chance of observing at least one AE under the assumption of single participant AE rate of 15%. Table 3 shows the chance of observing at least one AE of given probability.

Table 3. Probability of Observing Adverse Events

Probability of Grade 3 or higher AE for a single participant	0.025	0.050	0.075	0.100	0.125	0.150
Probability of observing at least one AE with 15 participants	0.316	0.537	0.689	0.794	0.865	0.913

Time for PD-1 levels to return to baseline will be estimated and plotted using the Kaplan-Meier method. In addition, trajectories of PD-1 levels over time for different participants will be plotted, and an average trajectory will be estimated using a mixed model.

15 Ethics/Protection of Human Participants

15.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research participant and the researchers which begins before consent is given and continues until the end of the participant's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks, and benefits. Participants will be given the opportunity to ask questions and have them answered.

The participants will sign the informed consent document prior to undergoing any research procedures. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The researcher will document the signing of the consent form in the participant's medical record. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The consent form has been translated into Spanish due to the expected enrollment of Spanish-speaking subjects.

15.1.1 Ongoing Informed Consent

People who are unable to provide informed consent are excluded from enrolling in the protocol (Section 4.2). If a participant becomes decisionally impaired during the course of the study, then they will be removed from the study.

15.2 Participant Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. Records will be kept locked and 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 IRB, the FDA, NIAID, OHRP, the pharmaceutical supporter, or the sponsor's designee.

16 Data Handling and Record Keeping

16.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from participants during study visits and telephone calls or will be abstracted from participants' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. The investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

16.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP guidelines. Study records will be maintained by the PI for a minimum of 5 to 7 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID will be notified in writing and written OCRPRO/NIAID permission shall be obtained by the site prior to destruction or relocation of research records.

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Appendix A: Supportive Care Measures for Immune-mediated Adverse events and Infusion Reactions

Note: These recommendations provide guidance, but management should be individualized based on clinical evaluation of the patient.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with oral corticosteroids.
  - For **Grade 3-4 events**, immediately treat with IV corticosteroids followed by high-dose oral corticosteroids. Administer additional anti-inflammatory measures as needed.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, then fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with IV corticosteroids followed by high-dose oral corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (DM, if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **type 1 DM** or **Grade 3-4** hyperglycemia
    - Insulin replacement therapy is recommended for type I DM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate participants with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with oral corticosteroids.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time after the dose. Monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events and **Grade 2-4** hypothyroidism:
    - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 hours, followed by oral corticosteroids.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with oral corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after study drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to, IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening consequences; urgent intervention indicated.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics, oxygen, pressors, corticosteroids, epinephrine. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.
CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous(ly); NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.	

Appendix B: Schedule of Procedures and Evaluations

Evaluation	Study week (day window)														Early termination visit
	Screening[a] Week -6 to 0	**Baseline Day 0**	**1 (± 4)**	**2 (± 4)**	**3 (± 4)**	**4 (± 4)**	**6 (± 4)**	**9 (± 7)**	**12 (± 7)**	**16 (± 7)**	**24 (± 7)**	**36 (± 7)**	**48 (± 7)**	**60, 72, 84, 96 (all ± 14)**	
Informed consent	X														
Physical exam with vital signs	X		X	X	X	X	X	X	X	X	X	X	X		X[b]
Medical history/medication review	X		X	X	X	X	X	X	X	X	X	X	X	X[c]	X[d]
Counseling on use of birth control	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Blood draw for screening labs	X														
Urinalysis	X														
Urine Pregnancy t(for participants of childbearing potential only)	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG	X														
HLA typing	X														
Blood draw for storage	X														
Leukapheresis	X[e]				X[f,g]	X[f,g]			X[f]						

Evaluation	Study week (day window)														Early termination visit
	Screening[a] Week -6 to 0	**Baseline Day 0**	**1 (± 4)**	**2 (± 4)**	**3 (± 4)**	**4 (± 4)**	**6 (± 4)**	**9 (± 7)**	**12 (± 7)**	**16 (± 7)**	**24 (± 7)**	**36 (± 7)**	**48 (± 7)**	**60, 72, 84, 96 (all ± 14)**	
Administration of pembrolizumab[h] or placebo		X													
AE assessment			X	X	X	X	X	X	X	X	X	X	X	X[c]	X[d]
Blood draw for clinical/research labs, storage		X	X	X	X	X	X	X	X	X	X	X	X		X[b]

AE = adverse event; ECG = electrocardiogram; X = to be performed.

a Screening can be scheduled over multiple visits per convenience of the participant and study team.

b This assessment will only be conducted if the early termination visit is on or before week 48.

c This assessment will be conducted over the phone.

d This assessment will be conducted over the phone if the early termination visit is after week 48.

e Will be performed after confirmation of eligibility. If the participant cannot do this procedure (eg, poor venous access), then an extra 80 mL of blood will be collected for storage and research.

f This procedure is optional. If the participant declines to do it or cannot (eg, poor venous access), then an extra 80 mL of blood will be collected for storage and research.

g Leukapheresis will be done at either week 3 or 4, not both. Scheduling will depend on the convenience of the participant and study team.

h 200 mg via intravenous infusion for 30 minutes.