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CD24Fc Administration to Decrease LDL and Inflammation in HIV Patients, Both as Markers of Efficacy and Cardiovascular Risk Reduction (CALIBER)

Protocol Number: HP-00086029

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OncoImmune, Inc.
Rockville, MD

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NIH Addendum

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NHLBI Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

STUDY TEAM

Principal Investigator: Shyamasundaran Kottilil, MD, PhD **Lead Associate Investigator**: Poonam Mathur, DO, MPH **Associate Investigators:** Joel Chua, MD Jennifer Hoffman, MSN, MPH, CRNP Jennifer Husson, MD, MHS Amy Nelson, RN, MS Angie Price, ANP-C, DNP Lydia Tang, MBChB **Study Sites**: Institute of Human Virology, University of Maryland, Baltimore, MD 725 West Lombard Street Baltimore, MD National Institutes of Health 10 Center Drive Bethesda, MD	**Protocol Statistician**: PPD **NIH Lead Investigator:** Henry Masur, MD (NIH/CCMD) **Collaborating Investigators**: Bhawna Poonia, PhD Tae-Wook Chun, PhD (NIH/NIAID) Nehal N. Mehta, MD, MSCE, FAHA (NIH/NHLBI) Amit Dey, MD (NIH/NHLBI) **Medical Monitor:** PPD **Pharmacist:** PPD **IRB of Record:** University of Maryland HRPO

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: CD24Fc Administration to Decrease LDL and Inflammation in HIV Patients, Both as Markers of Efficacy and Cardiovascular Risk Reduction (CALIBER)

Study Description: This is a phase 2, randomized, double-blinded, placebo-controlled clinical trial. The intervention drug will be CD24Fc (IV infusion). A cohort of 64 subjects with HIV on antiretroviral therapy will be randomized in a 1:1 fashion to be administered 3 doses of CD24Fc (240mg IV infusion) or placebo q2w during a 4-week window, followed by a 24-week follow-up window to assess safety and changes in LDL.

Objectives:

Primary Objectives:

1. To determine the safety and tolerability of CD24Fc during the 4-week dosing period and a 24-week follow-up period in a cohort of HIV patients.
2. To evaluate the change in LDL during a 4-week dosing period of CD24Fc and a 24-week follow-up period.

Secondary Objectives:

To evaluate the effect of CD24Fc on the following variables between the placebo and intervention arms in comparison with baseline values:

1. Levels of total cholesterol, HDL, and triglycerides
2. Markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14)
3. Size of HIV reservoirs
4. Myocardial damage (measured by Troponin I and T)
5. Hepatic steatosis, as determined by transient elastography
6. Leptin
7. Hemoglobin A1c
8. Presence of anti-drug antibody (ADA) and temporal correlation to any adverse events, and its effect on PK (For first 6 subjects).
9. The pharmacokinetics (PK) and pharmacodynamics (PD) of CD24Fc in the first 6 randomized subjects.

Exploratory Objectives:

1. To assess the effect of CD24Fc on aortic vascular inflammation as measured by standardized uptake value of arterial FDG by PET/CT. We will select 12 subjects with an LDL>125 to have the imaging study.
2. To assess the effect of CD24Fc on the inflammatory markers hs-CRP and GlycA.
3. To assess the effect of CD24Fc on the CEC and NMR lipoproteins.
4. To assess the effect of CD24Fc on endothelin-1.

Endpoints:

Primary Endpoints:

1. Incidence and severity of any adverse events (AEs) during the administration of drug and 24 weeks after completion. Safety will be evaluated by assessment of clinical laboratory tests, physical examination at various time points during the study, and by the documentation for AEs.
2. The percentage reduction in LDL level from the baseline (predosing) to 2 weeks after the last treatment.

Secondary Endpoints:

1. Percent change in levels of total cholesterol, HDL, and triglycerides from baseline to Weeks 6 and 28 between placebo and intervention arms.
2. Percent change in markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14) from baseline to Week 6 and 28 between placebo and intervention arms.
3. Change in proviral DNA from baseline to Week 6 and Week 28 between placebo and intervention arms.
4. Percent change from baseline to week 28 in Troponin I and T between placebo and intervention arms.
5. Change in percent of hepatic steatosis (by CAP measurement) and fibrosis (by KPA) as determined by transient elastography from baseline to week 28 between placebo and intervention arms.
6. Percent change in leptin from baseline to Week 6 and Week 28 between placebo and intervention arms.
7. Percent change in hemoglobin A1c from baseline to Week 6 and 28 between placebo and intervention arms.
8. PK and PD assessments (For 6 subjects)
9. Presence of ADA in all subject with temporal correlation to any adverse events, and its effect on PK (For first 6 subjects).
10. Changes in IL-6, apoB, Lp(a), urine albumin to creatinine ratio before and after treatment.

Exploratory Endpoints:

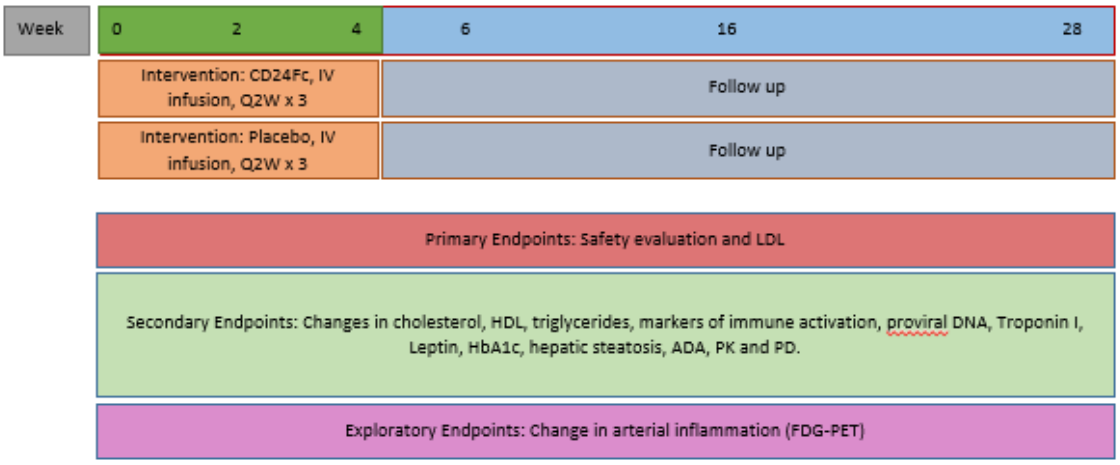
1. Change in vascular inflammation as evidenced by aortic FDG uptake by FDG-PET/CT will be assessed before and after therapy. The arterial uptake of FDG is measured by the standardized uptake value (SUV) max divided by the venous SUV mean yielding a target to background ratio (TBR).
2. Changes in hs-CRP and GlycA before and after treatment.
3. Changes in CEC and NMR lipoproteins before and after treatment.
4. Changes in endothelin-1 before and after treatment.

Study Population:

64 adults with HIV infection (age 50 and older) on antiretroviral therapy (ART) with HIV viral suppression for at least 2 years. Subjects will be recruited from the Baltimore, MD and Washington, DC regions.

Phase:	2
Description of Sites/Facilities Enrolling Participants:	University of Maryland Institute of Human Virology Clinical Research Unit (IHV/CRU) 725 West Lombard Street Baltimore MD 21201 National Institutes of Health Clinical Center Radiology (Bldg 10) 10 Center Dr. Bethesda, MD 20814
Description of Study Intervention:	Human CD24 (also known as cluster of differentiation 24 or heat stable antigen (HSA)) is an 80 amino acid glycosyl-phosphatidyl-inositol (GPI)-anchored glycoprotein expressed on the membrane surfaces of hematopoietic and non-hematopoietic cells. Recombinant fusion protein, CD24Fc, is composed of the extracellular domain (ECD) of human CD24 fused to the hinge and Fc region of human IgG. It has been used for the treatment of autoimmune diseases and Graft vs Host Disease. Doses of 240mg have been shown to be safe, well-tolerated, and effective in reducing LDL.
Study Duration:	2 years
Participant Duration:	28 weeks

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening+ Day -55 to -14	Day -55 to -1	Day -55 to -1#	Day 0	Wk 2*	Wk 4*	Wk 6^	Wk 16^	Wk 28^
Informed Consent	X								
Medical History & Physical Exam[1]	X			X			X	X	X
Height, Weight, and BMI	X								X
Vital Signs	X			X	X	X	X	X	X
Medication Reconciliation	X			X	X	X	X	X	X
Adverse Event Review and Evaluation				X	X	X	X	X	X
CMP, CBC with diff, PT/INR, Urinalysis	X			X	X	X	X	X	X
CD4 count and HIV VL	X			X	X	X	X	X	X
Hepatitis B panel (surface antigen, core antibody, surface antibody)	X								
Hepatitis C Ab with reflex RNA	X								
Hemoglobin A1c	X						X		X
Lipid panel (Fasting)	X		X	X	X	X	X	X	X
Troponin I and T	X						X		X
Leptin (Fasting)	X		X				X		X
ECG (once at Screening and Wk 6; pre-dose and 2 hrs post-dose during dosing visits)	X			X	X	X	X		
Serum hCG (women of child-bearing potential)	X								X
POC Urine hCG (women of child-bearing potential)				X	X	X	X	X	
PK of ART and CD24Fc before (and 2 hrs post-dose for Day 0 to Week 4)- first 6 subjects				X	X	X	X	X	X
Anti-drug antibody%				X			X		X
Immunology labs (for CD4:CD8, sCD14, proviral DNA), inflammatory cytokines	X			X	X	X	X	X	X
GlycA, CEC, NMR lipoproteins[2]				X			X		X
hsCRP, IL-6, apoB, Lp(a), UACR	X			X	X	X	X	X	X
Endothelin-1	X								X
CD24Fc Infusion				X	X	X			
Transient elastography with CAP	X		X						X
FDG PET/CT (NIH)[3]		X							X

+ Screening tests within the last 8 weeks prior to screening visit that have been done as part of routine medical care or at an outside facility can be used. Screening window of 8 weeks with more than 2 weeks between screening and Day 0.
*Study Visits for Weeks 2-4 include a window of +/-4 days
^Study Visit for Weeks 6, 16 and 28 include a window of +/- 1 week except for FDG PET/CT, which will include a window of +/-30 days
[1] Targeted history and exam will be performed as needed for symptoms or lab abnormalities
[2] Only for subjects completing the optional FDG-PET/CT testing
[3] See protocol section 8.1.1.2 for criteria leading to FDG PET/CT testing
If subject is not fasting at screening, may return for fasting labs and Transient Elastography prior to Day 0
% also done for suspected immune-related adverse events.

2 INTRODUCTION

2.1 STUDY RATIONALE

Infection with Human Immunodeficiency Virus (HIV) affects an estimated 36.7 million worldwide. In the United States, an estimated 1.1 million are infected, and as access to antiretroviral treatment (ART) has increased, the population of people infected with HIV ages. Patients with viral suppression have increased life expectancy, therefore, they are apt to develop comorbidities seen in age-matched individuals without HIV, including cardiovascular disease (CVD). Among people living with HIV, CVD and its risk factors are an important cause of morbidity and mortality[1]. With the use of antiretroviral therapy (ART), the life expectancy of people with HIV has increased, making management of these comorbidities an important focus in prevention of cardiovascular disease. Findings from the SMART[2] study showed the consequences of untreated HIV infection, including an increased relative risk for CVD by 60% in those who received episodic therapy, composed to those who received continuous ART[2].

HIV infection affects lipid metabolism by increasing triglycerides (TG) and low-density lipoprotein (LDL)[3,4]. In addition to HIV itself changing lipid concentrations[5], antiretroviral therapy can also be pro-arthrogenic[1], and chronic inflammation from HIV (even in virally suppressed patients) can alter lipid metabolism profiles[4]. Studies have shown that compared to uninfected controls, patients with HIV who were on ART have an increased risk of CVD[6,7]. ART regimens have been studied extensively to determine their risk on lipid metabolism, and some classes of medications, such as protease inhibitors and older nucleoside reverse transcriptase inhibitors, may have more impact on lipid metabolism than newer classes of medications, such as integrase inhibitors[7,8].

Persistent inflammation and chronic immune activation are seen in HIV even when ART use leads to viral suppression[4,9], increasing the risk for cardiovascular disease. The SMART study[2] found that plasma levels of interleukin-6 (IL-6), C-reactive protein (CRP), and D-dimer products of fibrinolysis are independent predictors of mortality in HIV, including CVD-related deaths, and this has been supported by other studies, including that by Duprez et al[10]. Also, chronic immune activation may increase LDL levels by altering how lipids are processed and transported and/or by modifying lipids through the activity of reactive oxygen species[11], rendering these lipids more inflammatory through their activation of monocytes and endothelial cells[12,13]. Oxidized LDL levels in HIV have been linked to markers of monocyte/macrophage activation[13], coronary calcium[14], noncalcified coronary artery plaques[15], and arterial inflammation in HIV-infected patients[16], indicating that oxidized LDL is an important contributor of blood vessel inflammation in HIV infection.

In an effort to decrease effects of dyslipidemia and inflammation on cardiovascular health, use of statins in HIV patients has become a method to prevent CVD[14,17]. However, studies show that use of statins in patients with HIV is underutilized[17,18], suggesting that there is a need for alternative lipid-lowering therapies in this population. In addition, delineating immune pathways that form the basis for abnormal lipid metabolism observed in HIV-infected patients seem to be vital in our efforts to reduce morbidity and mortality of this population.

2.2 BACKGROUND

Human CD24 (also known as cluster of differentiation 24 or heat stable antigen (HSA)) is an 80 amino acid glycosyl-phosphatidyl-inositol (GPI)-anchored glycoprotein expressed on the membrane surfaces of

hematopoietic and non-hematopoietic cells encoded by a coding sequence (CDS) of 240 base pairs. The first 26 amino acids constitute the signal peptide, while the last 23 serve as a signal for cleavage to allow for the attachment of the GPI tail. As a result, the mature human CD24 molecule has only 31 amino acids. CD24 is highly expressed in many cell types involved in the pathogenesis of Rheumatoid Arthritis (RA) and Multiple Sclerosis (MS). Furthermore, a single-nucleotide polymorphism of the CD24 gene results in replacement of alanine (CD24a) with valine (CD24v) in the mature protein and is an important genetic modifier for risk of several autoimmune diseases, including RA, MS and Systemic Lupus Erythematous.

OncoImmune, Inc. has developed a recombinant fusion protein, CD24Fc, composed of the extracellular domain (ECD) of human CD24 fused to the hinge and Fc region of human IgG1, for the treatment of autoimmune diseases and Graft vs Host Disease (GVHD). CD24 (and CD24Fc) is highly glycosylated and based on the structural analysis of the saccharides, we identified lectins as relevant CD24 ligands that regulate innate and adaptive immunity. Furthermore, OncoImmune, Inc. has demonstrated that CD24Fc reduces production of multiple cytokines involved in the pathogenesis of RA and is highly effective in treating experimental autoimmune encephalomyelitis (EAE), the mouse model of MS. CD24Fc has also been shown to be highly effective in preventing graft versus host disease (GVHD) in mice.

The nonclinical program has been designed to support the ongoing clinical program. A first-in-human (FIH), single ascending dose clinical trial in healthy subjects has been successfully completed. A second, single ascending dose (Phase IIa) clinical trial with CD24Fc for the prevention of acute GVHD following myeloablative allogeneic hematopoietic stem cell transplant was completed in December 2018. Additional clinical studies for a metabolic disorder in prediabetic patients is planned.

For more information on the background and development of CD24Fc, please see section 2 of the Investigator Brochure (IB).

2.2.1 PHARMACOLOGY AND TOXICOLOGY OF CD24FC

PK information from human studies is further described in section 2.2.3. In human studies, The C_{max} and AUCs of plasma CD24Fc increased proportionally to the doses administered, consistent with data in mouse and monkey. The plasma CD24Fc reached T_{max} between 1.01 and 1.34 hours. The $t_{½}$ of plasma CD24Fc ranged between 280.83 and 327.10 hours. More information is available in section 5 of the IB.

For information about nonclinical pharmacokinetics, please refer to sections 1.3 and 4.2 of the IB.

For more information about nonclinical pharmacology, please refer to section 4.1 of the IB.

For more information about toxicology in animals, please refer to section 4.3 of the IB.

For more information about safety pharmacology, please refer to section 4.4 of the IB.

2.2.2 SAFETY OF CD24FC IN ANIMAL STUDIES

In a multi-dose intravenous toxicity study of CD24Fc in mice, no adverse effects were noted at doses of 12.5, 35 or 125 mg/kg once weekly for 4 weeks with a 4-week recovery period. The no-observed-adverse-effect-level (NOAEL) was considered to be equal to or greater than 125 mg/kg. In a multi-dose

toxicity study in cynomolgus monkeys, CD24Fc administered via 1-hour intravenous infusion once weekly for 4 consecutive weeks at 12.5 mg/kg/week, 35 mg/kg/week, or 125 mg/kg/week was generally well tolerated in male and female cynomolgus monkeys through a 4-week dosing period with a 10-week recovery period. On Day 28, one male administered 35 mg/kg/week had an approximate 13% decrease in hemoglobin concentration. On Day 98 (76 days after the last dose), changes in hematology for this animal included a 21% decrease in hemoglobin, a 16% increase in red blood cell counts, a 21% decrease in mean cell volume (MCV), a 32% decrease in mean cell hemoglobin (MCH), a 14% decrease in mean cell hemoglobin concentration (MCHC), a 24% increase in red cell distribution width (RDW), and an approximately 2-fold increase in platelet and reticulocyte counts compared to prestudy (Day -2) levels. Day 98 blood smear analysis documented hypochromic red blood cells, microcytosis, anisocytosis, schistocytes, poikilocytes, and spherocytes, as well as an apparent increase in platelet numbers; these hematology changes are not considered typical findings in cynomolgus monkeys. However, no corresponding histopathology abnormalities were identified, and these hematology findings were not observed in any other animals in the study. Based on the hematology findings, the NOAEL for CD24Fc was considered to be 12.5 mg/kg/week under the conditions of this study when administered once weekly for four weeks.

In the multi-dose studies, anti-drug antibodies (ADA) were raised in CD24Fc-treated mice and monkeys, respectively. However, ADA were not associated with accelerated drug clearance or with any toxicological findings.

In the tissue cross-reactivity study, cross-reactivity was determined using biotinylated CD24Fc and found to be widespread in tissues from normal human and cynomolgus monkeys. The staining intensity of CD24Fc binding and its distribution varied from minimal to marked, but the cytoplasmic staining pattern is consistent in all cell types with occasional membrane staining primarily in epithelial cells. Specific CD24Fc binding was detected in the similar tissues from human and monkeys, including lymphoid system, central nervous system, squamous cells of multiple tissues, epithelia of glands and goblet cells of digestive tract. Except the intensity of the specific staining is slightly stronger in cynomolgus monkey tissues, the cross-reactivity of CD24Fc with tissues from human and cynomolgus monkey tissues was considered similar under the study conditions.

2.2.3 CD24FC IN HUMAN STUDIES

FIRST IN-HUMAN STUDY (PHASE I)

A Phase I, randomized, double-blind, placebo-controlled, single ascending dose study was conducted to assess the safety, tolerability, and PK of CD24Fc in healthy male and female adult subjects. A total of 40 subjects in 5 cohorts of 8 subjects each were enrolled in this study. Six of the 8 subjects in each cohort received study drug and 2 subjects received placebo (0.9% sodium chloride, saline). The first cohort was dosed with 10 mg. Succeeding cohorts received 30 mg, 60 mg, 120 mg, and 240 mg of CD24Fc or matching placebo. Dosing was based on a fixed amount of CD24Fc and not based weight or BSA.

Safety:

In total, 18 (45.0%) subjects had a treatment-emergent adverse event (TEAE) during the study: 6 (60.0%) subjects in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 3 (50.0%) subjects in the CD24Fc 30 mg group, 2 (33.3%) subjects in the CD24Fc 60 mg group, 3 (50.0%) subjects in the CD24Fc 120 mg group, and 2 (33.3%) subjects in the CD24Fc 240 mg group. All TEAEs in the study were

considered mild or moderate in severity by the Investigator except for 1 subject in the placebo group who experienced a severe headache. The most common TEAEs were headache (6 [15.0%] subjects), burns, second degree (3 [7.5%] subjects), ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects).

Overall, 5 (12.5%) subjects had a study drug-related TEAE: 1 (10.0%) subject in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 1 (16.7%) subject in the CD24Fc 30 mg group, and 1 (16.7%) subject in the CD24Fc 60 mg group. The study drug-related TEAEs during the study were headache (4 [10.0%] subjects) and ventricular tachycardia (1 [2.5%] subject).

A drug-related SAE of non-sustained ventricular tachycardia was experienced by 1 (16.7%) subject in the CD24Fc 60 mg group approximately 4 hours post-dose. The SAE was considered mild in severity by the Investigator and did not lead to discontinuation of the subject from the study. The Investigator considered the event to be drug related due to its close temporal proximity to dosing, though similar short, isolated episodes of non-sustained ventricular tachycardia may be seen in up to 4% of normal, healthy populations undergoing continuous cardiac monitoring. The other episode of non-sustained ventricular tachycardia was not considered related to study drug administration, and occurred without symptoms the second night post-infusion.

No deaths or adverse events leading to discontinuation occurred during the study. No clinically meaningful changes from baseline in laboratory parameters, vital signs, or ECGs occurred.

Exploratory Pharmacodynamic Markers:
As surrogate markers for treatment-emergent changes in basal levels of inflammation, pre- and post-dose levels of interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) were analyzed. Changes in fasting low-density lipoprotein cholesterol (LDL-C) levels were also analyzed.
Interleukin-6 levels were determined from samples collected on Day -1; Day 1, 8 hours after dosing; Day 2; Day 7; and Day 42. The pre-dose levels of IL-6 were generally extremely low among the subjects, which did not allow for its use as a surrogate marker for CD24Fc anti-inflammatory activity in a normal, healthy population.

High-sensitivity C-reactive protein levels were determined from samples collected on Day -1, Day 7, and Day 42. Two additional time points (Day 1, 8 hours and Day 2) were added beginning with the last 6 subjects dosed in Cohort 2 (CD24Fc 30 mg group). The Day -1 hs-CRP levels were normal in all except 4 subjects. Overall, there were no significant treatment-emergent reductions in hs-CRP levels.
Fasting LDL-C levels were determined from samples collected on Day -1, Day 7, and Day 42 for Cohort 1 (CD24Fc 10 mg group). Beginning with Cohort 2 (CD24Fc 30 mg group), this lipid sampling was expanded to include Day 14. At Day 14, the CD24Fc 240 mg group had a statistically significant percent change decrease in LDL-C from baseline.

PK:
This study also characterized the single-dose PK of CD24Fc in healthy subjects. The mean plasma concentration of CD24Fc increased proportionally to the doses administered with $t_{½}$ of 280.83 to 327.10 hours.

Immunogenicity:
Anti-CD24Fc antibodies were detectable at Day 28 and Day 42 in 1 subject in each of the 5 dose cohorts; however, for the subject in the CD24Fc 120 mg group and the subject in the CD24Fc 240 mg group, anti-CD24Fc antibodies were also detectable pre-dose at levels higher than post-dose levels. Except for those subjects with significant pre-dose anti-CD24Fc antibody levels, all post-dose anti-CD24Fc antibody levels were modest. No deviations in PK were found in any subjects with detectable anti-CD24Fc antibody levels.

Conclusions:
This study showed that the single dose of IV administration of CD24Fc up to 240 mg was safe and well tolerated in healthy subjects. A drug-related SAE of non-sustained ventricular tachycardia was experienced by 1 subject in the CD24Fc 60 mg group. The SAE occurred at a rate comparable with normal populations, was considered mild by the Investigator, and did not lead to discontinuation from the study. There were no clinically meaningful changes from baseline in laboratory parameters, vital signs, ECGs, or physical exams during the study.

For more information, please see section 5.1 of the IB.

CD24FC FOR THE PREVENTION OF ACUTE GRAFT-VERSUS-HOST DISEASE FOLLOWING MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL (PHASE II)

A randomized, placebo-controlled Phase IIa dose escalation trial was conducted to evaluate the addition of CD24Fc to standard of care acute GVHD prophylaxis in cancer patients undergoing allogeneic myeloablative hematopoietic stem cell transplantation (HCT). The trial was designed to define the recommended phase II dose (RP2D) or Maximum Tolerated Dose (MTD) of CD24Fc for acute GVHD prophylaxis. The trial enrolled patients receiving transplants from matched unrelated donors undergoing allogeneic HCT according to institutional practice. This trial exclusively utilized myeloablative conditioning regimens and standard of care prophylaxis comprising tacrolimus and methotrexate since these patients experience the most severe tissue injury and drug will likely have the strongest biological effect in this setting.

The Phase IIa trial comprised two single ascending dose cohorts (240 mg and 480 mg) and a single multi-dose cohort of CD24Fc in addition to standard-of-care GVHD prophylaxis. In the single dose cohort, the study agent, CD24Fc, was administered intravenously on day -1 pre-transplant. In the multi-dosing cohort, patients received 3 biweekly administrations of CD24Fc of 480 mg (day -1), 240 mg (day +14) and 240 mg (day +28). Dosing was based on a fixed amount and not based on weight or BSA. Each dosing cohort enrolled 8 subjects using a randomized 3:1 ratio (6 CD24Fc subjects and 2 placebo) design for a total enrollment of 24 patients.

The primary objectives of the study were:

- To evaluate the safety and tolerability of CD24Fc in subjects undergoing myeloablative allogeneic hematopoietic cell transplantation (HCT)
- To determine the recommended Phase II dose (RP2D) or maximum tolerable dose (MTD) of CD24Fc in patients undergoing HCT

The secondary objectives of the study were:

- To estimate grade II-IV acute GVHD free survival (GFS) at day 180 following HCT.
- To estimate grade III-IV acute GVHD free survival (GFS) at day 180 following HCT.

- To describe incidence of chronic GVHD at one year following HCT
- To describe incidence of relapse at one year following HCT
- To describe incidence of transplant-related mortality (TRM) at one year following HCT
- To describe rates of infection at day 100 following HCT
- To evaluate overall survival (OS) and disease-free survival (DFS) at one year following HCT

The correlative and biologic study objectives of the study were:

- To assess the pharmacokinetic (PK) profile of single-dose CD24Fc and anti-drug antibodies in the target patient population
- To examine functional responses of antigen presenting cells and T cells before and after administration of CD24Fc
- To perform phenotyping of T cells, B cells, NK cells and other cellular immune subsets before and after donor cell infusion (HCT)
- To assess plasma concentrations of pro-inflammatory cytokines, damage-associated molecular patterns (DAMPs), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides, Total cholesterol and GVHD biomarkers before and after administration of CD24Fc
- To assess genetic polymorphism of *CD24* and *Siglec10* genes, and microRNAs such as mir29, in both donor and recipients

Efficacy:

Overall, treatment with CD24Fc resulted in trends toward a higher Grade III to IV acute GFS rate at Day 180 (94.4% and 50.0%, respectively) (hazard ratio = 0.1), higher DFS rate at 1 year post-HCT (83.3% and 50.0%, respectively) (hazard ratio = 0.2), better OS rate at 1 year post-HCT (83.3% and 50.0%, respectively) (hazard ratio = 0.2), and higher Grade III to IV acute GFS and relapse-free survival (GRFS) rate at Day 180 (83.3% and 33.3%, respectively) (hazard ratio = 0.2) compared to placebo.

Additionally, there were overall trends toward a lower cumulative incidence rate of relapse at 1 year post-HCT (11.1% and 33.3%, respectively) (hazard ratio = 0.3) and a lower cumulative incidence rate of TRM at Day 180 (0.0% and 16.7%, respectively) and 1 year (5.6% and 16.7%, respectively) (hazard ratio = 0.3) for the CD24Fc treatment group compared to the placebo group.

Overall, there was a trend toward a lower incidence of Grade III to IV acute GVHD by Day 180 in CD24Fc-treated patients when compared to patients receiving placebo (5.6% and 33.3%, respectively) (hazard ratio = 0.1) but a higher cumulative incidence of Grade II to IV acute GVHD by Day 100 for the CD24Fc treatment group compared to the placebo group (38.9% and 16.7%, respectively) (hazard ratio = 2.6). Overall, the Grade II to IV acute GFS rate at Day 180 was slightly higher in the CD24Fc treatment group compared to the placebo group (61.1% and 50.0%, respectively).

Overall, there was a trend toward a higher incidence of chronic GVHD at 1 year post-HCT in CD24Fc-treated patients when compared to patients receiving placebo (63.3% and 33.3%, respectively) (hazard ratio = 2.1) and a similar GRFS rate at 1 year post-HCT (32.4% and 33.3%, respectively) (hazard ratio = 0.7).

In total, 13 (72.2%) patients who received CD24Fc and 2 (33.3%) patients who received placebo had an infection through Day 100. The majority of the infections were bacterial or viral and occurred in the blood or urine. The majority of the bacteria recovered from blood culture were common skin inhabitants and low virulence pathogens (i.e., coagulase negative staphylococci).

In total, there was a reduced rate of cytomegalovirus (CMV) reactivation at Day 100 in the CD24Fc treatment group over the placebo group (22.2% and 50.0%, respectively) among high risk populations (pre-transplantation CMV status as D+/R+, D-/R+, or unknown D/R+). The CMV reactivation in the 2 patients in the CD24Fc group occurred after systemic steroid treatment. The 1 patient in the placebo group with CMV reactivation did not receive steroid treatment prior to CMV reactivation.

PK:
Following a single IV administration of CD24Fc (240 and 480 mg CD24Fc single dose cohorts), the geometric mean plasma exposure ($C_{max,-1d}$, AUC_{0-42d}, $AUC_{0-last,-1d}$, and AUC_{0-inf}) increased with increasing CD24Fc doses. The mean $t_{½}$ and λ_z were similar between the 240 and 480 mg doses of CD24Fc. The mean values of $t_{½}$ were 414.739 and 406.648 h and the mean values of λ_z were 0.0018 and 0.0017 h^{-1} for the 240 and 480 mg CD24Fc single dose cohorts, respectively. Additionally, there was an increase in the mean V_z and CL between the 240 and 480 mg doses of CD24Fc.

Following multiple IV administrations of CD24Fc (960 mg CD24Fc multiple dose cohort), the exposure of CD24Fc was sustained over time. Additionally, the mean plasma CD24Fc concentration on Day 100 was higher for the 480, 240, and 240 mg (ie, 960 mg) CD24Fc multiple dose cohort (850.84 ng/mL) compared to the single dose cohorts (216.38 ng/mL and 330.96 ng/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively). Furthermore, the geometric mean $AUC_{0-last,overall}$ value was higher for the 480, 240, and 240 mg (ie, 960 mg) CD24Fc multiple dose cohort (37,363,953.5 ng·h/mL) compared to the single dose cohorts ($AUC_{0-last,-1d}$ of 10,156,549.9 ng·h/mL and 15,522,686.2 ng·h/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively).

The median $t_{max,-1d}$ (2.10 h for both the 240 and 480 mg CD24Fc single dose cohorts and 2.13 h for the 960 mg CD24Fc multiple dose cohort) was similar across all of the CD24Fc doses. For the 960 mg CD24Fc multiple dose cohort, the median $t_{max,-1d}$ and $t_{max,28d}$ were similar (2.13 and 2.52 h, respectively).

Safety:
No patients experienced a DLT during the study. The MTD was not reached. The highest dose in this study, 960 mg CD24Fc multiple dose (ie, 480 mg, 240 mg, and 240 mg on Days -1, 14, and 28), is considered safe and recommended for future studies.

The incidence of TEAEs from Day -1 to 30/60 days after the last dosing was the same between all treatments: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 960 mg multiple dose cohort, and 6 (100.0%) patients who received placebo experienced TEAEs.

The most common TEAEs were stomatitis (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 960 mg CD24Fc multiple dose cohort, and 6 [100.0%] patients who received placebo); platelet count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 960 mg CD24Fc multiple dose cohort, and 5 [83.3%] patients who received placebo); and white blood cell count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 960 mg CD24Fc multiple dose cohort, and 4 [66.7%] patients who received placebo). Severe stomatitis (≥ Grade 3) occurred in 3 (50.0%) patients in the 240 mg CD24Fc single dose cohort,

4 (66.7%) patients in the 480 mg CD24Fc single dose cohort, 2 (33.3%) patients in the 960 mg CD24Fc multiple dose cohort, and 5 (83.3%) patients who received placebo, with a clear inverse correlation between CD24Fc doses and duration of severe stomatitis.

One (16.7%) patient in the 480 mg CD24Fc single dose cohort and 2 (33.3%) patients who received placebo experienced a study drug-related TEAE. The most common study drug-related TEAE was diarrhea (1 [16.7%] patient in the 480 mg CD24Fc single dose cohort and 2 [33.3%] patients who received placebo). No patients in other cohorts experienced a study drug-related TEAE.

The incidence of Grade 3/4/5 TEAEs was the same between all treatments: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 960 mg CD24Fc multiple dose cohort, and 6 (100.0%) patients who received placebo. One (16.7%) patient in the 480 mg CD24Fc single dose cohort experienced hyperglycemia that was considered a study drug-related Grade 3/4/5 TEAE.

In total, 1 (4.2%) patient died during the study due to TEAEs. Patient PPD received placebo and experienced Grade 4 pneumomediastinum and Grade 5 pneumonia TEAEs that resulted in death. Per the Investigator, it was considered unlikely that these TEAEs were related to study drug.

In total, 9 (37.5%) patients experienced a treatment-emergent serious adverse event (SAE): 2 (33.3%) patients in the 240 mg CD24Fc single dose cohort, 1 (16.7%) patient in the 480 mg CD24Fc single dose cohort, 4 (66.7%) patients in the 960 mg CD24Fc multiple dose cohort, and 2 (33.3%) patients who received placebo. Treatment-emergent SAEs reported for patients who received CD24Fc were nausea, stomatitis, abdominal pain, dehydration, decreased appetite, device related infection, arthritis, polymyalgia rheumatica, weight decrease, cognitive disorder, and pulmonary embolism.

No patients experienced a study drug-related treatment-emergent SAE.

In total, the incidence of TEAEs of alanine aminotransferase increase and blood alkaline phosphatase increase were similar between patients who received CD24Fc and patients who received placebo. The incidence of TEAEs of aspartate aminotransferase increase was higher for patients who received CD24Fc compared to patients who received placebo. Treatment-emergent adverse events of blood cholesterol increase were only reported by patients in the 960 mg CD24Fc multiple dose cohort (2 [33.3%] patients). Treatment-emergent adverse events of blood creatinine increase were only reported by patients who received placebo (2 [33.3%] patients). A TEAE of blood bilirubin increased was reported by 1 (16.7%) patient who received placebo.

In total, the incidence of TEAEs of white blood cell count decrease, lymphocyte count decrease, and neutrophil count decrease were higher in patients who received CD24Fc compared to patients who received placebo. The incidence of TEAEs of platelet count decrease was similar between patients who received CD24Fc and patients who received placebo.

No patient had a laboratory abnormality that was considered an SAE or resulted in discontinuation of study drug.

No patients who received either single or multiple dosing of CD24Fc had positive ADA results at any time point sampled pre- or post-infusion.

A TEAE of weight increase was reported by 1 (16.7%) patient who received placebo and a TEAE of weight decrease was reported by 3 (16.7%) patients who received CD24Fc. A TEAE of ECG QT prolonged was reported by 1 (16.7%) patient who received placebo.

The mean percent change from baseline in the blast percentage in bone marrow at Day 100 was -57.11%, -12.50%, 1433.33%, and -51.33% for the 240 mg CD24Fc single dose cohort, 480 mg CD24Fc single dose cohort, 960 mg CD24Fc multiple dose cohort, and placebo group, respectively.

Engraftment:
In total, 18 (100.0%) patients who received CD24Fc and 6 (100.0%) patients who received placebo experienced neutrophil engraftment. In total, 18 (100.0%) patients who received CD24Fc and 5 (83.3%) patients who received placebo experienced platelet engraftment. The median times to neutrophil and platelet engraftment were similar between all treatment groups. No patients experienced primary engraftment failure.

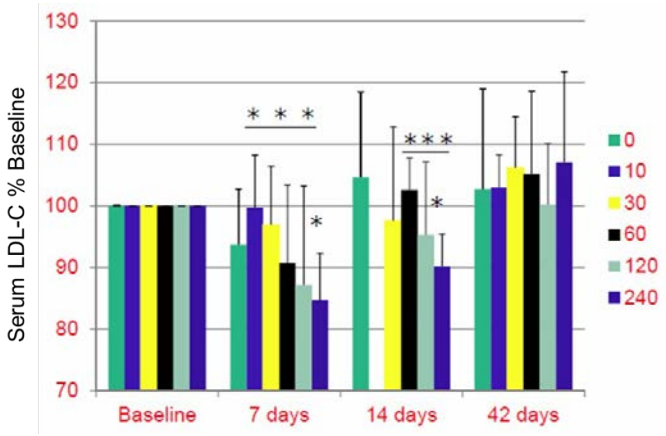
The mean CD3 and CD33 cell chimerism on Day 28/Day 30 was 73.0% donor cells and 100.0% donor cells, respectively, for patients who received CD24Fc and 77.4% donor cells and 100.0% donor cells, respectively, for patients who received placebo. The mean CD3 and CD33 cell chimerism on Day 100 was 80.9% donor cells and 99.4% donor cells, respectively, for patients who received CD24Fc and 73.8% donor cells and 96.6% donor cells, respectively, for patients who received placebo.

Conclusions:
- The safety profile of CD24Fc did not appear to be affected by increasing dose or multiple administrations.
- No patients experienced a dose-limiting toxicity (DLT) during the study. The MTD was not reached. The highest dose in this study, 960 mg CD24Fc multiple dose (ie, 480 mg, 240 mg, and 240 mg on Days -1, 14, and 28, respectively), is considered safe and recommended for future studies.
- Treatment with CD24Fc resulted in trends toward a higher Grade III to IV acute GFS rate at Day 180 (hazard ratio = 0.1), higher DFS rate at 1 year post-HCT (hazard ratio = 0.2), better OS rate at 1 year (hazard ratio = 0.2), and higher Grade III to IV acute GRFS rate at Day 180 (hazard ratio = 0.2) compared to treatment with placebo.
- There was a trend toward a lower incidence of Grade III to IV acute GVHD by Day 180 for the CD24Fc treatment group compared to the placebo group (hazard ratio = 0.1).
- There was a trend toward a higher cumulative incidence of Grade II to IV acute GVHD by Day 100 for the CD24Fc treatment group compared to the placebo group (hazard ratio = 2.6).
- The Grade II to IV acute GFS rate at Day 180 was slightly higher in the CD24Fc treatment group compared to the placebo group.
- Treatment with CD24Fc resulted in a trend toward a lower cumulative incidence rate of relapse at 1 year post-HCT compared to treatment with placebo (hazard ratio = 0.3).
- There was a lower rate of CMV reactivation among the at risk populations but a higher rate of infection with CD24Fc treatment compared to placebo.
- The majority of the bacteria recovered from blood culture were common skin inhabitants and low virulence pathogens.
- Multiple doses of CD24Fc induced more sustained exposure over time and resulted in higher mean plasma CD24Fc concentrations on Day 100 compared to the single dose cohorts.
- The median $t_{max,-1d}$ and $t_{max,28d}$ remained consistent across all of the CD24Fc doses.

- No patients who received either single or multiple dosing of CD24Fc had positive ADA results at any time point sampled pre- or post-infusion.

For more information, please see section 5.2 of the IB.

2.2.4 RATIONALE FOR USE OF CD24FC TO REDUCE LDL



During OncoImmune's Phase I trial, serum samples were taken and the level of LDL was measured over time; the 240mg dose significantly reduced LDL (see Figure) and IB section 2.4.2 for more information).

CD24Fc has also been used in Phase II testing for the prophylaxis of acute GVHD in cancer patients undergoing allogeneic myeloablative hematopoietic stem cell transplantation (HCT). In the Phase IIa portion of the trial (ClinicalTrials.gov Identifier: NCT02663622), patients were sequentially double-blind randomized into three cohorts with 2 placebo and 6 in CD24Fc treatment. The two single ascending dose cohorts (240 mg and 480 mg) and one multi-dose cohort (480 mg (day -1), 240 mg (day +14) and 240 mg (day +28)) were given CD24Fc in addition to standard of care GVHD prophylaxis with tacrolimus and methotrexate. The LDL levels were examined and recorded at pre-dosing baseline and Day 14 post-HCT. The D14 samples in the multi-dose cohort were taken before the D14 CD24Fc administration. The D14 results in the multi-dose cohort are combined with the 480mg single dose cohort as both groups of patients received 480mg at Day-1. In this Phase IIa clinical trial, HCT patients underwent myeloablative conditioning treatment with intensive chemotherapy before the HCT. Some patients had additional total body irradiation. The placebo group had an average 78+19% of the D14 LDL level to the pre-dosing level. The CD24Fc 240mg group had an average of 50+10% of the D14 LDL level to the pre-dosing level. The CD24Fc 480mg group (including the single dosing and multi-dosing groups) had an average of 60+20% of the D14 LDL level to the pre-dosing level. When compared with placebo control, both 240mg and 480mg of CD24Fc significantly reduced LDL-C at Day 14 post-HCT. These results suggest that LDL is significantly reduced with use of CD24Fc; this investigation aims to see if a similar reduction occurs in HIV positive patients who are virally suppressed, thus serving as a surrogate marker for CVD risk reduction. For more information, please see section 2.4.2 of the IB.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

To date, CD24Fc has been tested in a Phase I clinical study in healthy subjects, and in a Phase IIa trial for the prevention of acute GvHD following myeloablative allogeneic HSCT.

Phase I Study: The Phase I study was a randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, and PK of CD24Fc in healthy male and female adult subjects. A total of 40 subjects in 5 cohorts of 8 subjects each were enrolled in this study. Six of the 8 subjects in

each cohort received study drug and 2 subjects received placebo (0.9% sodium chloride, saline). The first cohort was dosed with 10 mg and succeeding cohorts received 30 mg, 60 mg, 120 mg, and 240 mg of CD24Fc or matching placebo and were dosed at least 3 weeks apart to allow for review of safety and tolerability data for each prior cohort.

The Phase I study showed that the single dose of CD24Fc up to 240 mg by IV administration was generally well tolerated in healthy subjects. The most common TEAEs reported by subjects included headache and second-degree burns. However, no statistically significant difference was observed between those who received placebo vs those who received CD24Fc. All TEAEs in the study were considered mild or moderate in severity by the Investigator except for 1 subject in the placebo group who experienced a severe headache. A drug-related SAE of ventricular tachycardia was experienced by 1 subject in the CD24Fc 60 mg group. The SAE was considered mild in severity by the Investigator and did not lead to discontinuation from the study, and occurred at a rate comparable with normal populations, was considered mild by the Investigator, and did not lead to discontinuation from the study. There were no infusion reactions or injection site reactions reported.

Phase II study: The Phase IIa GvHD study was also a randomized, double-blind, placebo-controlled trial that evaluated the safety and tolerability of the addition of CD24Fc to standard GVHD prophylaxis in healthy male and female adult subjects in subjects undergoing myeloablative allogeneic hematopoietic cell transplantation (HCT). The Phase IIa trial comprised two single ascending dose cohorts (240 mg and 480 mg) and a single multi-dose cohort (480/240/240 mg)of CD24Fc to define the recommended phase IIb dose (RP2D) or maximum tolerated dose (MTD). A total of 24 subjects in 3 cohorts of 8 subjects were enrolled in this study. Six of the 8 subjects in each cohort received study drug and 2 subjects received placebo (0.9% sodium chloride, saline).

The safety profile of CD24Fc did not appear to be affected by increasing dose or multiple administrations. No patients experienced a DLT during the study. The MTD was not reached. One patient in the 480 mg CD24Fc single dose cohort and 2 patients who received placebo experienced a study drug-related TEAE. The most common study drug-related TEAE was diarrhea. No patients in other cohorts experienced a study drug related TEAE. The highest dose in this study, 960 mg CD24Fc multiple dose (ie, 480 mg, 240 mg, and 240 mg on Days -1, 14, and 28, respectively), is considered safe and recommended for future studies. The most common adverse events (AEs) observed included hematologic AEs (i.e. anemia, thrombocytopenia, leukopenia, neutropenia), nausea and oral mucositis, which are expected based on the patient population and/or treatment procedure.

As with the FIH study and the Phase II GvHD study, the planned studies include many precautions that are being taken to ensure subject safety. The protocol has been designed to exclude subjects who are at heightened risk of adverse events (AE) and ensure that clinical sites are equipped to manage any toxicities.

Based on the known biology of the CD24-Siglec pathways and its importance in the immune system, immune-related adverse events (irAE) are the most likely class of toxicity that could be observed in humans. As in the FIH and Phase IIs GvHD study, potential risks, and plans to mitigate these risks are incorporated into the design of future studies.

Ventricular Tachycardia: An SAE of ventricular tachycardia was observed in one healthy subject that received CD24Fc in the Phase 1 trial. This SAE was considered mild in severity by the investigator and did not lead to discontinuation of the subject from the study. This SAE was considered to be drug related due to its close temporal proximity to dosing, though similar short, isolated episodes of non-sustained ventricular tachycardia may be seen in up to 4% of normal, healthy populations. No deaths or adverse events leading to discontinuation occurred during the study.

During the Phase IIa trial, all patients had 12-line EKG before and after each CD24Fc or placebo I.V. infusion. The 24 patients in Phase IIa trial did not have abnormal EKG when compared with baseline pre-dosing EKG.

Based on the mechanism of action and pre-clinical data, there is no reason to believe that CD24Fc administration would lead to ventricular tachycardia or any other cardiac-related adverse events. Inclusion criteria for the CD24Fc in preventing GVHD study includes having a Hematopoietic Cell Transplant-Co-morbidity Index (HCT-CI) of ≤ 4, which includes an assessment of arrhythmia and cardiac co-morbidities. Vital signs will be monitored before and during each infusion of CD24Fc in this trial, and an assessment of arrhythmia and cardiac co-morbidities will be done in the screening period.

Adverse Immune Suppression: Preclinical studies indicate that CD24Fc is not broadly immunosuppressive. Preclinical data have demonstrated that CD24 negatively regulates host inflammatory response to cellular Danger-Associated Molecular Patterns (DAMPs) that are released as a result of tissue injury and, through interaction with its receptor, Siglec G, CD24 provides a powerful negative regulation for host response to tissue injuries. This mechanism is particularly relevant to the lead indication, GVHD and extensive preclinical studies have demonstrated that CD24Fc prevents GVHD in a mouse model. Tissue injury is caused by hematopoietic stem cell transplantation conditioning regimens, including high-dose chemotherapy and/or total body irradiation (TBI), and is considered to be the first step in the development of acute GVHD. In contrast, host response to pathogen-associated molecular patterns (PAMPs) is unaffected by CD24-Siglec G interaction and thus the CD24-Siglec G interaction appears to play a critical role in discriminating DAMPs from PAMPs.

Importantly, the drug has advantages over conventional immunosuppressants as it does not cause general immune suppression and use of high doses of CD24Fc does not block antibody response in non-human primates. Furthermore, an important function of allogeneic stem cell transplantation is to use donor T cells to eliminate allogeneic leukemia cells. This effect is called GVL. Importantly, treatment of CD24Fc, which prevented GVHD had no effect of GVL in the mouse model. Finally, extensive studies in non-human primate demonstrate that CD24Fc does not suppress antigen-specific immune response, which suggest that CD24Fc will not likely increase risk of infection. Regardless, eligibility criteria in this study excludes subjects that are considered at risk for uncontrolled infections. Serum samples will be evaluated for autoantibodies as indicated in the SOA. In the Phase IIa trial, the rate of fungal, bacterial and viral infections was not significantly increased. Instead, there seemed to be a trend of reduced CMV reactivation.

In this trial, HIV patients with anti-retroviral treatment may have increased risk of infections. However, the eligibility criteria in the planned study exclude subjects that are considered at risk for uncontrolled infections.

Infusion Reactions: Infusion reactions have not been observed in the Phase 1 or Phase IIa clinical trials. However, the administration of any recombinant protein has the potential to elicit infusion reactions. CD24Fc includes the Fc portion of human IgG1. After target binding, CD24Fc may induce FcγR cross-linking, which has been associated with infusion reactions for some therapeutics.

Infusion reactions may include events such as changes in vital signs, fever, difficulty breathing, hypotension, generalized or facial edema, nausea, chills, mental status changes, urticaria or vomiting during or up to 2 hours following infusion. The Phase IIa Clinical Protocol incorporated generalized procedures designed to closely monitor, minimize and manage any potential infusion reactions and initially was administered only on an inpatient hospital unit. However, the protocol was amended to allow CD24Fc dosing to be administrated in outpatient clinics for the multi-dosing cohort of 8 patients.

in this study, patients will be monitored before, during, and for 2 hours post infusion to assess for infusion-related reactions.

Exacerbation of Immune Responses:

CD24 has wide-spread expression among both hematopoietic and non-hematopoietic cells and, as a rule, CD24 tends to express at higher levels among immature immune cells than their terminally differentiated products. Therefore, CD24 has been widely used as a marker to track the development of both T and B cells.

CD24 was initially identified as a costimulatory molecule on activated B cells by functional screening for monoclonal antibodies that inhibit T cell activation driven by activated B cells. One of the most potent antibodies was identified as recognizing CD24 on B cells. When expressed on CHO cells, CD24 can provide costimulatory activity for clonal expansion of naïve CD4 T cells. Enk and Katz demonstrated that the CD24 functions as a costimulatory molecule on Langerhans cells (Enk and Katz 1994) [19], as anti-CD24 blocks proliferation and induces clonal anergy of cloned Th1 cells. The function of CD24 in CD8 T cell priming was demonstrated in two models. First, CD24 was rapidly induced on macrophages following the phagocytosis of latex beads (De Bruijn et al 1996)[20]. The induction of CD24 was essential for the *in vitro* priming of naïve CD8 T cells, as such priming was completely abrogated by anti-CD24 antibodies. Second, transfection of CD24 into tumor cells resulted in enhanced priming of CD8 T cells *in vivo* (Want et al 1987)[21]. These results demonstrated that CD24 is a costimulatory molecule capable of promoting the priming of both CD4 and CD8 T cells. Therefore, there is a theoretical risk that CD24Fc could exacerbate immune responses.

Pre-clinical animal models of disease, including GVHD, did not show any exacerbation of immune responses. Clinical observations during the FIH study did not suggest an exacerbation of immune responses. The Phase IIa clinical trial provided evidence that CD24Fc suppresses the severe acute GVHD while preserving the graft vs leukemia effect. There was no increase of infection in this highly susceptible population. In the planned trial, serum samples will be collected evaluated for anti-drug antibodies, and the eligibility criteria exclude those that are at high risk for uncontrolled infections.

Other Risks:
The primary risks of phlebotomy include occasional bleeding or bruising of the skin at the site of needle puncture, and the sensation of transient lightheadedness, or rarely, fainting and infection. The amount of blood drawn will be within the limits allowed for adult subjects.

The risks of intravenous catheters used to give the study drug or placebo includes local bleeding, infection, or local inflammation of the skin and vein with pain and swelling.

After the ECG, subjects may experience mild skin irritation, slight redness or itching where the recording patches were placed. They may also need to have chest hair shaved for the procedure.

The risks with transient elastography are minimal since it is a non-invasive procedure. Patients may feel discomfort from the cold temperature of the gel that is applied for sonography, or from the pressure the probe transducer elicits against the skin with sound wave.

The study involves exposure to radiation from the radioactive sugar, but the radiation from 2 FDG PET/CT scans will be less than the radiation safety limit for research. There is no medical risk from lying in the scanner, although subjects may become uncomfortable or restless. Subjects will also have to fast 6 hours before the appointment due to the use of radioactive glucose, which may also cause discomfort.

In addition to any radiation concern, there could be psychological distress caused by an incidental finding of asymmetric FDG uptake that would likely necessitate additional investigation to exclude cancer. Additional minimal risks include bleeding or bruising at the venous site of FDG administration.

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefits of CD24Fc in patients with HIV infection included in the current study population are:

- Use of an agent as lipid-lowering therapy in the growing number of chronically infected HIV patients who have risk factors for cardiovascular disease and have underutilization of statins, resulting in sub-optimal cardiovascular disease risk modification
- Addressing the unmet medical need for decreasing immune activation and inflammation in patients infected with HIV, in order to reduce the risk of additional comorbidities and possibly lead to immune reconstitution

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There is no intravenous treatment available to patients with HIV which is able to lower LDL and reduce inflammation/immune activation. Statins remain the standard of care for dyslipidemia, but are underutilized and may be ineffective in some cases. Other approaches, including ezetimibe, fibrates, and PCSK9 inhibitors, are approved therapies to lower LDL. However, CD24Fc has been found to lower LDL through different molecular mechanisms than statins and other approved drugs. CD24Fc may modulate the antigen presenting cells and promote immune reconstitution in HIV patients undergoing ART treatment. If favorable changes in immune activation, inflammatory markers, and LDL can be achieved in patients who receive a 4-week regimen of CD24Fc, the anticipated value of lowering cardiovascular risk with a safe and tolerable regimen offers a favorable risk-benefit determination.

3 OBJECTIVES AND ENDPOINTS

3.1.1 PRIMARY OBJECTIVES

1. To determine the safety and tolerability of CD24Fc during the 4-week dosing period and a 24-week follow-up period in a cohort of HIV patients.
2. To evaluate the change in LDL during a 4-week dosing period of CD24Fc and a 24-week follow-up period.

3.1.2 SECONDARY OBJECTIVES

To evaluate the effect of CD24Fc on the following variables between the placebo and intervention arms in comparison with baseline values:

1. Levels of total cholesterol, HDL, and triglycerides
2. Markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14)
3. Size of HIV reservoirs
4. Myocardial damage (measured by Troponin I and T)
5. Hepatic steatosis, as determined by transient elastography
6. Leptin
7. Hemoglobin A1c

8. Presence of anti-drug antibody (ADA) and temporal correlation to any adverse events, and its effect on PK (For first 6 subjects).
9. The pharmacokinetics (PK) and pharmacodynamics (PD) of CD24Fc in the first 6 randomized subjects.
10. Changes in IL-6, apoB, Lp(a), urine albumin to creatinine ratio before and after treatment.

3.1.3 EXPLORATORY OBJECTIVES

1. To assess the effect of CD24Fc on aortic vascular inflammation as measured by standardized uptake value of arterial FDG by PET/CT. We will select 12 subjects with an LDL>125 to have the imaging study.
2. To assess the effect of CD24Fc on the inflammatory markers hs-CRP and GlycA.
3. To assess the effect of CD24Fc on the CEC and NMR lipoproteins.
4. To assess the effect of CD24Fc on endothelin-1.

3.1.4 PRIMARY ENDPOINTS

1. Incidence and severity of any adverse events (AEs) during the administration of drug and 24 weeks after completion. Safety will be evaluated by assessment of clinical laboratory tests, physical examination at various time points during the study, and by the documentation for AEs.
2. The percentage reduction in LDL level from the baseline (predosing) to 2 weeks after the last treatment.

3.1.5 SECONDARY ENPOINTS

1. Percent change in levels of total cholesterol, HDL, and triglycerides from baseline to Week 6 and 28 between placebo and intervention arms.
2. Percent change in markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14) from baseline to Week 6 and 28 between placebo and intervention arms.
3. Change in proviral DNA from baseline to Week 6 and Week 28 between placebo and intervention arms.
4. Percent change from baseline to week 28 in Troponin I and T between placebo and intervention arms.
5. Change in percent of hepatic steatosis (by CAP measurement) and fibrosis (by KPA) as determined by transient elastography from baseline to week 28 between placebo and intervention arms.
6. Percent change in leptin from baseline to Week 6 and Week 28 between placebo and intervention arms.
7. Percent change in hemoglobin A1c from baseline to Week 6 and week 28 between placebo and intervention arms.
8. PK and PD assessments (For 6 subjects)
9. Presence of ADA and its effect on PK in all subjects

3.1.6 EXPLORATORY ENDPOINT

1. Change in vascular inflammation as evidenced by aortic FDG uptake by FDG-PET/CT will be assessed before and after therapy. The arterial uptake of FDG is measured by the standardized uptake value (SUV) max divided by the venous SUV mean yielding a target to background ratio (TBR).
2. Changes in hs-CRP and GlycA before and after treatment.

3. Changes in CEC and NMR lipoproteins before and after treatment.
4. Changes in endothelin-1 before and after treatment.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a phase 2, randomized, placebo-control, double-blinded clinical trial to assess the safety and tolerability of CD24Fc among patients with HIV, and the effect of CD24Fc on change in low-density lipoprotein (LDL) among patients with HIV. We will also evaluate the effect of CD24Fc on total cholesterol and triglycerides, markers of immune activation (T cell activation, sCD14, and inflammatory cytokines), size of HIV reservoirs, HbA1c and leptin, and hepatic steatosis, among other inflammatory markers.

We hypothesize that therapy with CD24Fc will be safe and tolerable in HIV patients on ART and result in significant decreases in LDL. In addition, we hypothesize that CD24Fc will reduce cholesterol, leptin, HbA1c, hepatic steatosis and fibrosis, and markers of inflammation in patients with chronic HIV who are virally suppressed on ART.

In this phase 2 study, a cohort of 64 HIV patients virally suppressed on ART will be randomized in a 1:1 fashion to receive an intravenous infusion of 240mg of CD24Fc vs. placebo administered every 2 weeks during a 4-week treatment window, followed by a 24- week follow-up period. Patients will be followed for safety and adverse events as well as changes in lipid metabolism and inflammatory markers during a 24-week follow-up period. This investigation will take place at the University of Maryland and National Institutes of Health.

4.2 JUSTIFICATION FOR DOSE

This study will use the 240 mg dose as it has been proven to be safe in both healthy volunteers and GVHD patients. Importantly, 240 mg has been shown to significantly reduce LDL-C levels in clinical trials (see section 2.4.2 of IB). Since LDL-C is an important endpoint for the study, we believe this a safe and likely effective dose. In the Phase IIa CD24Fc in prevention of GVHD study, a multi-dosing cohort of 6 patients given 480 mg, 240 mg and 240 mg of CD24Fc with 2 week intervals, none of the patients showed drug-related adverse effects. Notably, multiple dosing studies in non-human primate involving 125 mg/kg showed no adverse effect. Since this is 30-40-fold higher than the proposed human dose (3-4 mg/kg), there is large window for safety for the proposed dosing (biologics of 50kD or more is normally translated directly using body weight).

The proposed dosing number (3 doses) and window (4 weeks) will be the same as the number of dosing in clinical trials (3 doses) and non-human primates (4 doses), all within 4 weeks of dosing. We believe this is well-justified, since total exposures in proposed trial will be less than the dosing schedule in the Phase IIa multi-dosing cohort (480-240-240 mg at Day -1, 14, and 28).

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

The target population is patients age 50 or older with chronic HIV infection who have achieved viral suppression with use of ART for at least 2 years. The study is designed to target a demographic of people in the United States who are at risk for cardiovascular disease but have different risk factors than that of the HIV-uninfected population.

Baltimore and Washington, DC are two geographic regions with high prevalence of HIV and risk of CVD. We recently performed a cross-sectional analysis of a retrospective cohort study on 100 patients from our Baltimore HIV clinic[22]. This cohort consists of 95% African American and 38% women with median age of 52 years old. The majority of patients had been diagnosed with HIV for over 10 years at study entry (86%) and 87% patients were receiving ART with 55% achieving viral suppression. The atherosclerotic vascular disease risk score was calculated using the Pooled Cohort Equation by calculating the 10-year risk of developing CVD according to 2013 AHA/ACC guideline[23]. The study findings confirm that there is an elevated risk of developing CVD in high risk demographic groups of the HIV epidemic at a relatively young age in the current HIV era.

Washington DC has a disproportionally high rate of HIV patients with a rate of 22.3[24] per 1,000 cases. Lifetime risk of HIV acquisition is 1 in 13[25], the highest in the United States. Also, in Washington DC, heart disease ranks first as the then leading cause of death, with 1,300, or 28%, of all deaths in 2010, attributed to CVD. CVD accounts for nearly 1 in 3 deaths in DC[26] and is an area in which CVD risk reduction methods must be targeted. Therefore, this study will recruit from both the Baltimore and Washington, DC areas.

There will be no racial, ethnic, religious, or gender discrimination. Persons in jail or prison are not eligible for this study. We will be enrolling participants from ongoing clinical trials with collaborators, as well as recruiting referrals. Adults will be recruited through Institutional Review Board (IRB)-approved advertising to HIV providers and screened to confirm eligibility requirements for participation.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. At least 50 years of age or older at screening
4. LDL-C > 70 mg/dL.

5. Has a median ACC/AHA ASCVD risk score ≥ 7.5%.
6. Available for clinical follow-up through Week 28 after enrollment
7. Chronic HIV infection based on documentation from a primary care physician that the patient has HIV and is on antiretroviral therapy
8. On a stable regimen of ART for more than 3 months. The subject is expected to continue on an accepted ART regimen for the duration of the study (through week 28).
    a. Accepted combinations
        - FTC/TAF [Descovy®], FTC/TDF [Truvada®], or ABC/3TC [Epzicom®]
          PLUS
            - Ritonavir © and darunavir (DRV), or
            - Raltegravir (RAL), or
            - Elvitegravir (EVG) ± Cobicistat©, or
            - Dolutegravir (DTG), or
            - Rilpivirine (RPV)
    b. Accepted fixed dose combinations
        - FTC/RPV/TAF [Odefsey®]
        - FTC/RPV/TDF [Complera®]
        - EVG/c/TAF/FTC [Genvoya®]
        - EVG/c/TDF/FTC [Stribild®]
        - DTG/ABC/3TC [Triumeq®]
        - BIC/TAF/FTC [Biktarvy®]
    c. Alternative ART regimens will be considered on an individual basis, based on available DDI data at the discretion of the principal investigator
9. At least 2 years of maintained HIV RNA < 50 copies/mL (or < LLOQ if the local laboratory assay's LLOQ is ≥50 copies/mL) prior to Screening and HIV RNA<50 at screening.
10. CD4 count ≥ 350 cells/mm^3 at Screening
11. Ability to communicate effectively with the study investigator and other key personnel
12. Subjects must have a primary care doctor for their medical management
13. Willing to donate blood for sample storage to be used for future research
14. Female study participants with childbearing potential (defined below) and male study participants with female partners of childbearing potential must be willing to practice either:

- Complete abstinence from sexual intercourse with a member of the opposite sex
  OR
- At least one form of effective contraception from the list below, in addition to correct use of either a male or female condom throughout dosing and for a defined period following the last dose (30 days for women, 14 days for men) of study medication.:
    i. Intrauterine device with a failure rate of <1% per year
    ii. Tubal sterilization
    iii. Bilateral tubal occlusion
    iv. Vasectomy in a male
    v. Female barrier method (diaphragm or cervical cap)
    vi. Hormonal methods
        1. Oral contraceptives
        2. Injectable progesterone
        3. Implants of levonorgestrel or etonorgestrel
        4. Transdermal contraceptive patch
        5. Contraceptive vaginal ring

a. Definition of Childbearing Potential: For the purposes of this study, a female subject is considered of childbearing potential from menarche until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women are considered to be in a post-menopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

15. Agreement to adhere to Lifestyle Considerations (see section 4.3) throughout study duration

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current or prior history of any of the following:
    a. Clinically significant illness (other than HIV) or any other major medical disorder that may, in the opinion of the investigator, interfere with the subject treatment, assessment of compliance with the protocol; subjects currently under evaluation for a clinically-significant illness (other than HIV) are also excluded
    b. Poor venous access interfering with required study blood collection
    c. Solid organ transplantation
    d. Significant pulmonary disease, significant cardiac disease, or porphyria
    e. Uncontrolled chronic hepatitis B infection (surface antigen positive with detectable HBV DNA as noted in patient's medical documentation from a treating physician)
    f. Chronic hepatitis C infection (current active only)
    g. Unstable psychiatric disease. (Subjects with psychiatric illness that is well-controlled on a stable treatment regimen or currently not requiring medication may be included.)
    h. Any malignancy or its treatment that in the opinion of the PI may cause ongoing interference with host immunity; subjects under evaluation for malignancy are not eligible.
2. Abnormal hematological and biochemical parameters at screening, unless the test has been repeated and at least one subsequent result is within the acceptable range prior to study drug administration, including:
    a. Neutrophil count <750 cells/mm^3
    b. Hemoglobin level <10 g/dL
    c. Platelet count ≤50,000 cells/mm^3
    d. Estimated glomerular filtration rate, calculated by the chronic kidney disease epidemiology collaboration formula: <30 mL/min/1.73 m^2
    e. ALT or AST level ≥5 times upper limit of normal (ULN)
    f. Total bilirubin level ≥2.0 times ULN, except in subjects with Gilbert's syndrome or other clinical explanation at the discretion of the PI
    g. Albumin level <3 g/dL
3. Poorly controlled diabetes as indicated by a screening glycosylated hemoglobin (HbA1c) >10
4. Need for the use of the following medications from 21 days prior to the start of study drugs through the end of treatment:
    a. Hematologic stimulating agents, erythropoiesis stimulating agents (ESAs), granulocyte colony stimulating factor (GCSF, thrombopoietin (TPO) mimetics

b. Chronic systemic antineoplastic or immunomodulatory treatment including supraphysiologic doses of immunosuppressants such as corticosteroids (e.g., prednisone equivalent >10 mg/day for >2 weeks), azathioprine or monoclonal antibodies (e.g., infliximab)
c. Investigational agents or devices for any indication

5. Hyperlipidemia (defined as an LDL≥190 mg/dL), that is not being treated per the 2018 ACC/AHA Cholesterol Clinical Practice guidelines with medications such as statins, Ezetimibe, and PCSK9 inhibitors, since these would be the standard of care for these patients., Patients with hyperlipidemia who are deemed ineligible to be on statin therapy by a treating physician will not be excluded.
6. Initiation of statin therapy or change in dose of already-prescribed statin therapy within the last 3 months.
7. Known history of cardiac arrhythmia or baseline ECG with arrhythmia including but not limited to atrial fibrillation (with or without rapid ventricular rate), supraventricular tachycardia or ventricular tachycardia.
8. Any medical, psychiatric, social condition, occupational reason or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a volunteer's ability to give informed consent.

Female-specific criteria:

9. Woman who is breast-feeding or planning to become pregnant during the first 24 weeks after study drug administration.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Abstain from alcohol for 24 hours before the start of each dosing session until after collection of the final PK and/or pharmacodynamic sample. If participants do not abstain from alcohol use, samples will not be collected for PK assessment. This will be pertinent for 6 subjects in the study.
- Fasting prior to blood draws for each study visit.
- If having FDG-PET/CT, nothing by mouth for 6 hours prior to the imaging study. This will be pertinent for 12 subjects in the study. Subjects should dress in warm, comfortable clothing with no zippers, snaps clips or metal of any kind. A high fat/low carbohydrate diet should be followed for 24 hours prior to the imaging study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography and the description of eligibility criteria failure.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an abnormal hematological or biochemical parameter, poorly controlled diabetes, or use of a restricted

medication (for example, exclusion criteria 4) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The study will be advertised and posted using flyers and the IHV website. All advertisements will be IRB approved before use. We will recruit patients from the University of Maryland Medical Center (UMMC) and from Unity Parkside Clinic in Washington DC (patients will only be seen at University of Maryland Medical Center). Recruitment of patients will take place largely from outpatient clinics at UMMC and Unity Parkside, where HIV patients are seen for primary care. A primary care physician may refer patients to the study team, in which case the study team will speak to the patient either in person or by phone to schedule a screening appointment at UMMC. Residents of DC will be provided transportation to UMMC via mileage reimbursement for Metro, train, Uber or driving as approved by the Sponsor or will be scheduled with transportation for the visit as needed.

Study retention will be promoted by visit reminders via phone calls. Participants will receive remuneration for their time and any inconvenience due to participating in the study (as outlined below).

An anticipated 110 subjects with HIV will be screened for this study (which includes screening failures and those lost to follow-up) in order to enroll 64 subjects.

This study will be limited to adults age 50 and older. This criterion has been included in order to study the effects of CD24Fc in a population with inherently higher CVD risk than those aged 18-49 years. Children and pregnant women will be excluded since the safety and efficacy of CD24Fc has not been studied in the pediatric population or during pregnancy. Any woman of child-bearing potential must have a negative serum pregnancy test prior to receiving the first dose of CD24Fc on Day 0 and use effective contraception throughout the study.

Subjects will not be excluded based on gender. This study is designed to target an underrepresented demographic of the HIV epidemic in the United States with poor representation in clinical trials, and in which current therapy is underutilized and has had poor results.

All remuneration made by the University of Maryland, Baltimore will be provided to participants for their time and inconvenience, as outlined below.

COMPENSATION SCHEDULE	
Screening Visit	$50
FDG-PET/CT (#1) if applicable*	($200 if applicable)
Fasting Labs & Fibroscan (if needed, not included in totals below)	($25 if needed)
Day 0 Study Drug or Placebo Infusion	$150 (+/- PK $25)
Week 2 Study Drug or Placebo Infusion	$150 (+/- PK $25)
Week 4 Study Drug or Placebo Infusion	$150 (+/- PK $25)
Week 6 Follow up	$50 (+/- PK $25)
Week 16 Follow Up	$50 (+/- PK $25)

Week 28 Follow Up	$50 (+/- PK $25)
FDG-PET/CT (#2) if applicable*	($200 if applicable)
TOTAL	**$650**
Additional for PK	$150
Additional for FDG-PET/CT x2 at NIH	$400
Additional if Fasting Screening labs / FibroScan Visit needed or when unexpected visits are required	$25

*Compensation due for Optional FDG-PET/CT will be provided to subjects upon next visit to IHV and not at the NIH visit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

CD24Fc (CD24 Ig) is a fusion protein consisting of the extracellular domain of mature human CD24 linked to the human immunoglobulin G1 (IgG1) Fc domain. The complete molecular formula of CD24Fc has not been determined at this time. The mature protein is 261 amino acids long and each CD24Fc molecule includes the 30 amino acid CD24 extracellular domain. CD24Fc forms a disulfide-linked homodimer with a predicted mass of 57.7 kilodaltons (kDa) based on the homodimer amino acid sequence. However, the apparent molecular weight of the intact dimer is approximately 80 KDa based on non-reduced SDS-PAGE. The CD24 domain is highly glycosylated with both N-linked and O-linked oligosaccharides, which comprise approximately 80% of the mass of the CD24 domain.

For more information on the description of CD24Fc, please see section 3 of the IB.

6.1.2 DOSING AND ADMINISTRATION

Dosing of CD24Fc (240mg) will occur intravenously and over the duration of 1 hour (at minimum). A pre-dose ECG will be completed prior to dosing. The IV rate may be reduced to prolong the duration of infusion at the discretion of the investigator and clinical team based upon symptoms suggestive of an infusion-related reaction. If an infusion reaction is deemed severe (e.g. severe hypotension, hypoxemia) the infusion will be stopped and assessment of AEs will proceed as outlined in section 8.

All enrolled subjects who have received CD24Fc will be evaluated for safety before and after dosing. Safety may be assessed by physical examination, vital signs, hematology, and/or chemistries (see section 8 for detailed study assessments and procedures per visit). Subjects do not have to be fasting to receive the infusion (but will be fasting to have lipid panel and leptin drawn, as specified in the SOA). Vital signs will include pulse, blood pressure, respiratory rate, and oxygen saturation. The severity of signs, symptoms, and AEs will be determined by using DAIDS toxicity table. Subjects will be monitored during the infusion and until 2 hours after the infusion has completed, with vital signs every 30 minutes (+/- 5

minutes with +/-10 minutes at 2 hours post) and a post-infusion ECG at two hours post dose (+/- 10 minutes). Laboratory results will be ascertained as needed based on reported symptoms. Please note that dose modifications will not be made.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The site will receive individual vials of CD24Fc (each shipment will consist of 8 vials of investigational product). Upon receipt of the investigational product, contents will be examined for damage or missing vials. The product will be immediately stored in the appropriate temperature-controlled conditions. Included in the shipment is a temperature monitoring device which will be used to verify the minimum and maximum temperatures reached. The Investigational Product Receipt Confirmation Form included with the shipment will be completed and returned to PPD to acknowledge receipt of the shipment. If the device shows an out-of-range value, the drug will be quarantined within the appropriate temperature-controlled environment and the Temperature Excursion Report Form will be submitted for approval.

Study agents will be distributed according to standard pharmacy procedures. All drug products will be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug products will not be stored in a container other than the container in which they are supplied. Consideration will be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions will be followed to avoid direct eye contact or exposure through inhalation when handling study drugs.

Records will be maintained indicating the receipt, dispensation, and destruction of all investigational product shipments. The responsible Pharmacist or designated staff at the investigational site must keep an accurate inventory of study product shipments received, the amount of study product administered, and all product returned or destroyed. This information is to be recorded on the Master Drug Accountability Log, as well as on the Investigational Product Overall Subject Accountability Log.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

CD24Fc is supplied as a sterile, clear, colorless, preservative-free aqueous solution for parenteral administration, in a clear borosilicate glass vials with chlorobutyl rubberstoppers and aluminum flip off seals. CD24Fc is formulated as single dose injection solution, at a concentration of 10 mg/mL at pH of 7.2. Each CD24Fc vial contains 120 mg of the fusion protein in 12 ± 0.2 mL injection solution. CD24Fc is stored at -20° C until use. CD24Fc should be thawed to room temperature prior to administration. New CD24Fc Drug Product has been manufactured as “Lot 0118-002”. Stability studies for Lot 0118-002 are ongoing and it has demonstrated to be stable for 12 months at the intended storage temperature, -20°C, for 6 months at 5°C and 1 month at 25°C. The area in which the investigational product is stored must be locked, with limited access only to unblinded study personnel and the temperature must be monitored.

Each study vial will be labeled according to Title 21 of the U.S. Code of Federal Regulations. Each vial product label will contain the following information:

- Product name (CD24Fc)
- Lot number
- "Caution: New Drug- Limited by Federal (or United States) law to investigational use"
- 120mg/vial, 10mg/mL in 12.0 mL
- Storage Condition: -20 degrees Celsius
- "DO NOT SHAKE OR DROP THE VIAL"
- OncoImmune, Inc.

6.2.3 PRODUCT STORAGE AND STABILITY

CD24Fc must be stored between -15ºC and -25ºC. If a temperature excursion should occur, the investigational product will be quarantined and the Temperature Excursion Report Form will be completed and sent to the Sponsor at PPD for approval prior to proceeding with use of the investigational product.
CD24Fc is stored at -20° C until use. CD24Fc should be thawed and equilibrated to room temperature prior to administration. Stability studies for Lot 0118-002 are ongoing and it has demonstrated to be stable for 12 months at the intended storage temperature, -20°C, for 6 months at 5°C and 1 month at 25°C.

6.2.4 PREPARATION

The constituted drug infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Determine the volume of CD24Fc solution: 240 mg per infusion with a volume of 24 ml from 2 vials.
2. Parenteral drug products should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.
3. Calculate the volume of sterile 0.9% Sodium Chloride Injection, USP, required: 76 ml in volume to reach a final volume of 100 ml.
4. Using an empty IV bag, add the above 76 ml volume of sterile 0.9% Sodium Chloride followed by the 24 ml volume of CD24Fc solution. Gently mix.
5. The CD24Fc infusion should begin within 6 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 60 minutes for dose of 240 mg. An infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less) must be used.
6. At the end of infusion, add a small amount of normal saline (25 ml) to the infusion bag to ensure the entire volume of study drug is infused.

For the placebo, the preparation will be as follows.

1. Calculate the volume of sterile 0.9% Sodium Chloride Injection, USP, required: 100 ml in volume to reach a final volume of 100 ml.
2. Using an empty IV bag, add the above 100 ml volume of sterile 0.9% Sodium Chloride.
3. The CD24Fc or placebo infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 60 minutes for dose of 240 mg. An infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less) must be used.

4. At the end of infusion, add a small amount of normal saline (25 ml) to the infusion bag to ensure the entire volume of study drug is infused.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a randomized, double-blinded, placebo-controlled trial. Subjects will be randomized using block randomization in a 1:1 ratio of CD24Fc:placebo. They will be block randomized in blocks of six (except for the last block of four). The first block of six will all have PK analyses and there will be a safety and efficacy review upon completion of dosing by this group of six without halting enrollment.

Every effort will be made to minimize the various known sources of bias. Breaking the blind will be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Any intentional or unintentional breaking of the blind will be reported to the sponsor and IRB, and explained at the end of the trial, irrespective of the reason for its occurrence.

6.4 STUDY INTERVENTION COMPLIANCE

Since the study drug will be administered intravenously by the clinical staff in an outpatient setting. Compliance with drug administration and adherence to the protocol will be documented by clinical staff in the study record.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported are concomitant prescription medications, over-the-counter medications and supplements.

Information about use of concomitant medications will be collected at the screening visit and subsequent visits as outlined in section 1.3. Use of these concomitant medications (which may affect study endpoints) that exclude a participant from enrolling in the study include those outlined in Section 4.2. Additionally, medications for disease conditions excluded from the protocol (e.g., active cancer, transplantation) are not allowed in the study. Should subjects have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

AEs are evaluated according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017. All adverse events will be reviewed by the Principal Investigator (PI) and the study team at team meetings. All Grade 3 events will be evaluated by the PI and the designated Medical Monitor. Grade 4 and Grade 5 events will be reported to the Sponsor and the Medical Monitor within 24 hours of notification of the event.

CD24Fc infusion will be paused for a single subject for any grade 4 event pending review by the Medical Monitor. The MM will include review of this event in a report issued to the DSMB every 12 weeks. Administration of medication will be paused for all subjects if 2 or more subjects have the same grade 4 adverse event deemed related to study drug. The MM will report these events to the DSMB and enrollment and dosing will be held for all pending review by the DSMB.

The study may be terminated after consultation with the Medical Monitor, DSMB and Sponsor, in the event that one or more of the following adverse reactions are not remediated within 2-4 hours, and in the opinion of the PI and Medical Monitor, are clinically relevant and constitute a substantial risk to the participants: cytokine release syndrome, hypotension, shortness of breath, disseminated intravascular coagulation, mental status changes.

Other criteria for study termination may include:

- the decision of the Medical Monitor or DSMB to stop further study visits
- the recommendation or decision for any reason of the PI that safety may be at risk or compromised by continuing the trial
- the decision of the Sponsor to terminate the study for any reason

The data to be collected at the time of study intervention discontinuation will include the following:

- Vital signs and physical examination
- Complete metabolic panel, complete blood count with differential, PT/INR
- Other laboratory tests that further evaluate a sign or symptom
- Procedures for further evaluation of lab abnormalities or symptoms

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator will discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy or breastfeeding
- Significant study intervention non-compliance
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation which occurs such that continued participation in the study would not be in the best interest of the participant (including malignancy)
- New or recurrent Centers for Disease Control and Prevention (CDC) category C AIDS-indicator condition.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive CD24Fc for 2 doses

- Development of life-threatening infection or clinical reason deemed to be life-threatening by the physician
- Request of the primary care provider or Investigator if s/he thinks the study is no longer in the best interest of the subject.
- If the subject is judged by the Investigator to be at significant risk
- The following laboratory abnormalities
    - HIV RNA>200 copies/mL (2 readings at least 2 weeks apart)
    - Decrease in eGFR to <30mL/min, confirmed by immediate repeat testing
    - Elevation of ALT >5x OR AST >5x Day 0, confirmed by immediate repeat testing
    - Abnormal elevation of ALT >3 x Day 0 *and* total bilirubin >2 x ULN, confirmed by immediate repeat testing
    - For participants with entry CD4+ T cell count between 350 - 500 cells/mm^3, confirmed absolute and percent CD4+ decline greater than 25% of baseline.
    - For participants with entry CD4+ T cell count between 501 to 800 cells/ mm^3, a confirmed absolute and percent CD4+ T cell decline greater than 33% of baseline.
    - For participants with entry CD4+ T cell count greater than 800 cells/ mm^3, a confirmed absolute and percent CD4+ T cell decline greater than 50% of baseline.
    - Occurrence of Grade 4 anemia/neutropenia or recurrence of Grade 3 anemia/neutropenia.

The reason for participant discontinuation or withdrawal from the study will be recorded in the study record. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Participants who prematurely discontinue the study agent due to toxicity will be followed closely for resolution of symptoms, until final outcome is known or until the end of the study follow-up period.

Subjects who discontinue the agent due to toxicity, as well as those who elect to discontinue study drugs prior to treatment completion for medical or personal reasons, will continue to follow the general study schedule of assessments unless unwilling to do so. The participant should have an end of treatment visit scheduled as soon as possible after all therapy is discontinued, if he/she is willing. Any subject continuing in the study will be followed closely for resolution of active laboratory abnormalities or adverse events that are considered related to the study agents.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 days for any visit through week 4 and within 1 visit for weeks 6, 16 and 28 visits, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY VISITS

Study visits, including screening, will occur at the IHV Clinical Research Unit at UMB. Drug doses may be infused +/-4 days to be considered in the study window (Day 0 to Week 4). Residents of DC may be provided transportation via Metro, train, or taxi, as needed.

All subjects will have a History and Physical during the screening process as part of final determination of protocol eligibility. Physical exams will be performed with study point visits at screening, Day 0, Week 6, Week 16 and Week 28. Directed physical exam will be done as needed at other study points. Subjects will be asked about their state of health and use of any concomitant medication since the previous study visit. They will also be questioned about adverse events and their adherence with study restrictions.

8.1.1.1 SCREENING

Each subject will provide informed consent of his/her free will prior to commencement of any study procedures according to ICH and Code of Federal Regulations (CFR). Each subject will be provided a copy of the signed informed consent form.

After a participant has provided informed consent, the Investigator and other study personnel will determine if they are eligible for participation in the study. Screening may begin up to 8 weeks prior to dosing with at least 14 days before Day 0.

Screening will include a review of the inclusion/exclusion criteria and completion of all screening procedures. Screening tests within the last 8 weeks prior to screening visit that have been done as part of routine medical care or at an outside facility can be used if within the acceptable time frame. Screening procedures do not need to be repeated within the 8-week screening window unless clinically indicated. Once the screening window has elapsed, subjects may be rescreened at the discretion of the PI.

At the screening visit, participants will have an H&P (including vital signs), height, weight and BMI assessment, and a medication reconciliation. Laboratory tests including CMP, CBC, HIV VL, CD4, PT/INR, hemoglobin A1c, Hepatitis B panel, Hepatitis C antibody and reflex RNA, and Troponin I and T will be collected. ECG will be done to assess for abnormalities. Females of child-bearing potential will have a serum hCG tested. Immunology labs looking at CD4 and CD8 by flow, sCD14, and inflammatory cytokines will also be done. If a subject is fasting, the procedures in section 8.1.1.3 including transient elastography may be done at this visit instead of at the "Fasting Lab Visit".

8.1.1.2 FDG-PET/CT VISIT

Twelve subjects will undergo FD -PET/CT to assess aortic inflammation at NIH. These participants will have an LDL>125. Subjects will have an FDG-PET/CT after screening, but prior to Day 0 and at week 28. Subjects will be provided transportation to and from the NIH if needed.

8.1.1.3 FASTING LAB VISIT, IF NEEDED

If subjects were not fasting at screening, they may return for fasting serum lipid and leptin levels along with transient elastography to assess for hepatic steatosis and fibrosis.

8.1.1.4 DAY 0 (FIRST INFUSION)

The participant will be started on CD24Fc or placebo on Day 0. For the first 6 subjects, prior to drug infusion and 2 hours after, blood samples for PK will be obtained. A window of +/- 10 minutes will be given around each post-infusion draw time point. Blood samples for anti-drug antibody will also be drawn before drug dosing for all subjects. For all subjects, an H&P will be performed, as well as a medication reconciliation prior to infusion. ECG should be done prior to infusion and two hours post infusion (+/- 10 minutes). Laboratory tests prior to drug infusion include: a CMP, CBC with diff, urinalysis, HIV VL, PT/INR, CD4, lipid panel, and point of care urine hCG (for females of child-bearing potential), Hs-CRP, along with research immunology and inflammation labs. Subjects participating in the FDG-PET/CT will also have GlycA, CEC, and NMR lipoprotein collected. All subjects must be fasting prior to blood draw. Adverse events will be documented.

8.1.1.5 WEEK 2 VISIT

At this visit, a medication reconciliation will be done, as well as documentation and review of adverse events. The first 6 subjects who had PK samples done at Day 0 will also have PK blood samples obtained before and 2 hours after dosing of study drug. A window of +/- 10 minutes will be given around each post-infusion draw time point. ECG should be done prior to infusion and two hours post-infusion (+/- 10 minutes). The following laboratory tests will be done prior to drug dosing: CMP, CBC, urinalysis, HIV VL, CD4, PT/INR, lipid panel, urine hCG (for females of child-bearing potential), and research immunology and inflammation labs. A dose of CD24Fc, 240mg vs placebo, will be infused intravenously, pending no laboratory abnormalities or adverse events which warrant holding the study drug. He/she must be fasting prior to blood draw.

8.1.1.6 WEEK 4 VISIT

At this visit, there will be a medication reconciliation and documentation and review of adverse events. The first 6 subjects who had PK samples done at Day 0 and Week 2 will also have PK blood samples obtained before and 2 hours after dosing of study drug. A window of +/- 10 minutes will be given around each post-infusion draw time point. ECG should be done prior to infusion and two hours post- infusion (+/- 10 minutes). The following laboratory tests will be done prior to drug dosing: CBC, urinalysis, HIV VL, CD4, PT/INR, lipid panel, urine hCG (for females of child-bearing potential), and research immunology and inflammation labs. A dose of CD24Fc, 240mg vs placebo, will be infused intravenously, pending no laboratory abnormalities or adverse events which warrant holding the study drug. He/she must be fasting prior to blood draw.

8.1.1.7 WEEK 6 VISIT

At this visit, there will be vital signs, a medication reconciliation and documentation and review of adverse events. The first 6 subjects who had PK samples done at Day 0, Week 2, and Week 4 will also have PK blood samples obtained. The following laboratory tests will be done prior to drug dosing: CMP,

CBC, urinalysis, HIV VL, CD4, PT/INR, lipid panel, urine hCG (for females of child-bearing potential), HbA1c, immunology labs, IL-6, apoB, Lp(a), urine albumin:creatinine ratio, Hs-CRP. Subjects participating in the FDG-PET/CT will also have GlycA, CEC, and NMR lipoprotein collected. He/she must be fasting prior to blood draw.

8.1.1.8 WEEK 16 VISIT

At this visit, vital signs, H&P and medication reconciliation will be done, as well as documentation and review of adverse events. The first 6 subjects who had PK samples done at Day 0, Week 2, Week 4, Week 6 will also have PK blood samples obtained. The following laboratory tests will be done: CMP, CBC, urinalysis, HIV VL, CD4, PT/INR, hemoglobin A1c, lipid panel, leptin, troponin I, urine hCG (for females of child-bearing potential), , IL-6, apoB, Lp(a), urine albumin:creatinine ratio, anti-drug antibody, and research immunology and inflammation labs.. He/she must be fasting prior to blood draw.

8.1.1.9 WEEK 28 VISIT

At this visit, vital signs, height, weight and BMI, H&P and medication reconciliation will be done, as well as documentation and review of adverse events. The first 6 subjects who had PK samples done at Day 0, Week 2, Week 4, Week 6, Week 16 will also have PK blood samples obtained. The following laboratory tests will be done: CMP, CBC, urinalysis, HIV VL, CD4, PT/INR, lipid panel, leptin, HbA1c, serum hCG (for females of child-bearing potential), Troponin I and T, anti-drug antibody, immunology labs, IL-6, apoB, Lp)a, urine albumin:creatinine ratio. Hs-CRP will also be drawn along with research immunology and inflammation labs. Subjects participating in the FDG-PET/CT will also have GlycA, CEC, and NMR lipoprotein collected. He/she must be fasting prior to blood draw. Transient elastography will be performed to assess for any change seen in hepatic steatosis post-dosing as immediate change within the four-week dosing period would not be expected.

Last, those who had a FDG-PET/CT prior to Day 0 will have a follow-up FDG-PET/CT done at the NIH. Again, this timing allows for potential vascular inflammatory changes to occur over the six month follow up period. Subjects will be provided transportation to and from the NIH if needed.

8.2 ASSAYS

Assays will be performed at one of the following locations:

1. NIAID (National Institute of Allergy and Infectious Diseases) Immunopathogenesis section, Building 10
2. NHLBI (National Heart, Lung and Blood Institute), Cardiovascular and Pulmonary Branch, Building 10
3. Laboratory Corp of America (LabCorp)
4. University of Maryland Marlene and Stewart Greenebaum Comprehensive Care Center- Shared Services Core Lab
5. Institute of Human Virology Research Lab

- CMP- comprehensive metabolic panel, serum. This assay will be done through LabCorp. The CMP includes Alanine aminotransferase (ALT/SGPT); albumin:globulin (A:G) ratio; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, total; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide, total; chloride, serum; creatinine, serum; eGFR calculation; globulin, total; glucose, serum; potassium, serum; protein, total, serum; sodium, serum.

- CBC- Complete Blood Count with Differential, whole blood. This assay will be done through LabCorp. The CBC includes Hematocrit; hemoglobin; mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); red cell distribution width (RDW); percentage and absolute differential counts; platelet count (RBC); red cell count; white blood cell count (WBC).

- Urinalysis- complete, with microscopic examination. This test will be done by LabCorp. This includes color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, biliriubin, urobilinogen, microscopic examination of urine sediment.

- HIV VL (viral load)- Human immunodeficiency virus 1 (HIV-1), quantitative, real-time PCR (nongraphical), plasma.

- CD4- Helper T-lymphocyte marker CD4, whole blood. This assay will be done through LabCorp. This test includes percentage of $CD4^+$; absolute $CD4^+$ (helper/inducer); absolute lymphocyte count.

- PT/INR- Prothromibin Time and Partial Thromboplastin Time, whole blood, plasma. This assay will be done through LabCorp. This test includes Activated partial thromboplastin time (aPTT); international normalized ratio (INR); prothrombin time (PT)

- Hemoglobin A1c- whole blood. This assay will be done through LabCorp.

- Lipid Panel- serum (fasting). This assay will be done through LabCorp. This test includes Cholesterol, total; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol (calculation); triglycerides; very low-density lipoprotein (VLDL) cholesterol (calculation).

- Hepatitis B panel- HBV Evaluation Panel, serum or plasma. This assay will be done through LabCorp. This test includes Hepatitis B core antibody, total; hepatitis B surface antibody, qualitative; hepatitis B surface antigen

- Hepatitis C Ab with reflex RNA- Hepatitis C Virus (HCV) Antibody with reflex to quantitative real-time PCR, serum or plasma. This assay will be done through LabCorp.

- Serum hCG- human chorionic gonadotropin, beta-subunit, qualitative, serum. This assay will be done through LabCorp. A serum hCG will be done for females of child-bearing potential, at the screening visit.

- Urine hCG- human chorionic gonadotropin, beta-subunit, qualitative, urine. This will be a point-of care assay. A urine hCG will be done for females of child-bearing potential before drug dosing, using a point-of-care urine hCG assay.

- Troponin I and T- In conjunction of cardiovascular inflammation measurement, we will also assess myocardial damage using a validated, sensitive cardiac troponin I and T assays (through LabCorp) will be used for all subjects run as batched samples.

- Leptin- serum or plasma (fasting). Used as a marker for lipodystrophy.
- hsCRP (high-sensitivity CRP), serum or plasma. This assay will be done through LabCorp.
- IL-6 (Interleukin- 6), serum or plasma.
- Apo B (apoliprotein B), serum. This assay will be done through LabCorp.
- Lp(a) (Lipoprotein a), serum. This assay will be done through LabCorp.
- Urine albumin /creatinine ratio, random urine. This assay will be done through LabCorp.
- Pharmacokinetic analyses- done for the first 6 subjects receiving CD24Fc.
  For PK analysis, blood samples will be collected prior to drug infusion at weeks 0, 2, 4, 6, 16, 28 before and 2 hours post dosing of CD24Fc as applicable. A +-/10-minute window around each draw point will be allowed. At weeks 6 and 28, a blood sample for PK will also be collected in order to demonstrate a decrease in drug concentration after dosing completion on week 4.

  Anti-drug antibody: For ADA analysis, blood samples on day 0 (predosing), week 6, and week 28 visits will be collected. ADA will be measured using a validated assay in a GLP-compliant laboratory that performed these analyses for the phase I and phase IIa CD24Fc studies. Pharmacokinetic parameters will be calculated using actual collection times. In those with pre-existing or induced ADA also completing the PK analysis, effects of ADA on the PK of the drug will be evaluated, although the results from the phase I study demonstrated that a small number of subjects with either pre-existing or induced ADA have similar PK to subjects without ADA.

  If ADA is positive, the ADA titration will be done and samples will be saved for neutralizing antibodies when the assay for neutralizing antibodies is available.

  When suspected immune related adverse events occur that are potentially related to CD24Fc, the unscheduled samples for ADA analysis will be collected and temporal correlation with a positive binding antibody results will be analyzed and recorded.

  All patients with treatment-emergent ADA titer greater than 1:64 should be followed until the ADA titers drop to 1:64 or lower. A titer of 1:64 is equivalent to 5 μg/ml of reference mouse anti-human CD24 monoclonal antibodies. This threshold is selected based on our phase I data that the patient this titer (the highest in our phase I cohort, and happened to be predosing) experienced neither adverse events nor aberrant CD24Fc PK.

  We will follow the recommendation from the White Paper by Shankar [27]. The treatment emergent ADA response will be defined as ADA is negative in pre-dosing but have positive ADA titers in samples from week 6 or week 28. Persistent ADA response is defined as the ADA titers remain unchanged from Week 6 and Week 28. Transient ADA response is defined the ADA is positive in one time point only.

RNAseq analysis provides an accurate and comprehensive profiling of gene expression. In addition to the immunological approaches, we will use RNAseq data to identify biomarkers for clinical response and PD-markers of drug efficacy. RNA-seq will be used to create a participant profile. RNA sample preparation will have two key steps: (a) RNA will be poly-A selected so that only mRNA is obtained for sequencing and (b) sample from CD24Fc and placebo-treated groups will be multiplexed across lanes and plates to mitigate batch effects from lane and plate bias. Illumina HiSeq sequencer will be used to generate 2x100bp sequencing reads. 3 replicates will be generated per sample, and samples will be multiplexed to obtain ~30M reads per sample; these specifications are common best practices for accurately quantifying mRNA expression.

A local computing cluster will analyze the RNA-seq data using the well-knownSAT-StringTie-Ballgown pipeline [28]. This pipeline produces (a) FPKM (fragments per kilobase per million reads), a measure of mRNA abundance, for each gene in a sample and (b) differentially-expressed genes and log-fold change between samples. The performance of this pipeline improves with replicates, so it matches well with this experimental design. Statistical analysis of RNA-seq pipeline outputs will be performed using log transformed intensities and measurements of correlation between the quantified proteome and transcriptome changes in the R software environment. To reduce dimensionality and avoid overfitting, correlations will use only differentially-expressed genes. DAVID [29] will be used to annotate our results with categorical annotation, including Gene Ontology and KEGG pathways for pathway analysis. Enrichment for these categories will be evaluated by Fisher exact test.

- sCD14
  Preliminary studies demonstrate that CD24Fc suppresses production of multiple inflammatory cytokines associated with HIV infections. To test the impact of CD24Fc on the systemic inflammatory responses, soluble factors that have been previously demonstrated with negative HIV outcomes (e.g. sCD14) and a larger array of inflammatory factors in the serum (IFNs, TNF etc.) will be quantified. The Luminex platform allows evaluation of over 60 soluble factors and performs bioinformatics analysis to identify factors/patterns of cytokine expression associated with changes in HIV latency.

- HIV Reservoirs (Proviral DNA)
  Although CD24Fc is not expected to have anti-viral activity, preliminary studies in humanized mice and non-human primate models [30], showed that CD24Fc significantly reduced viral burden in vivo, including proviral burden in the PBL of SIV-infected Macaques rhesus, perhaps by preventing T cell over-activation and its associated exhaustion immunity[30]. This hypothesis will be tested in ART-treated HIV infected subjects by longitudinal analysis of proviral titers. Established methods for quantification of proviral DNA (droplet digital PCR) will be used as described[31,32]. Droplet digital PCR will be conducted to quantitate the frequency of cells carrying HIV proviral DNA and cell-associated HIV RNA with single copy sensitivity. The level of replication-competent/infectious HIV in the $CD4^+$ T cell compartment will be determined by quantitative coculture assays.

- Inflammatory cytokines
  Peripheral blood mononuclear cells will be isolated using Ficoll-Hypaque density gradient technique and used for immunophenotyping. Cells will be washed and stained using appropriate panels of monoclonal antibodies that distinguish cell type (B, T NK, monocyte etc.), cellular

activation states (CD14, CD38, HLA DR, CD25, etc.) and their ability to secrete inflammatory cytokines (IFN, TNF) using intracellular cytokine staining using a 12 color flowcytometry analysis with FlowJo software, at the University of Maryland.

- CD4 and CD8 T cell counts and ratio
  T cell immunophenotyping will be performed as a clinical laboratory test using flow cytometry at the University of Maryland.

- GlycA, plasma. This is a heterogeneous nuclear magnetic resonance signal originating from mobile glycan residues on plasma glycoproteins, used as a novel composite biomarker of systemic inflammation. This assay will be done at the NIH for those subjects completing the optional FDG-PET/CT.

- CEC- cholesterol efflux capacity, plasma. This is an assay assessing HDL function using the macrophage J774 efflux system. This assay will be done at the NIH for those subjects completing the optional FDG-PET/CT.

- NMR lipoproteins, plasma. This is an assay looking at lipoprotein particle size and number using NMR spectroscopy. This assay will be done at the NIH for those subjects completing the optional FDG-PET/CT.

- Endothelin-1, plasma. An ELISA test will be done for subjects at screening and week 28 to look for changes in endothelin-1, which may indicate changes in pulmonary arterial pressure.

- Vascular inflammation, as measured by FDG-PET/CT
  A major challenge in pilot studies attending to study impact of interventions on CVD risk is the requirement of large sample sizes. Recent studies demonstrated that arterial inflammation may be a valuable surrogate marker for CDV risk [33-36]. ^{18}F-fluorodeoxyglucose (FDG) uptake is a sensitive and reliable marker of atherosclerotic inflammation, and this test will be done at the NIH. Measurements will be performed with the ascending aortic root 18F-FDG standardized uptake values (SUVs) as the maximal SUVs using regions of interest. At the same time, blood-pool SUV in the same superior vena cava will also be measured. The maximal SUV will be divided by the blood-pool SUV, yielding a target-to-background ratio (TBR). The average value will be calculated, and the degree of inflammation will be defined based on the TBR value. For our studies, TBR for 12 HIV subjects with LDL levels greater than 125 mg/dL will be imaged before day 0. These subjects will have a repeat FDG PET/CT at week 24 This allows us to compare the mean TBR score using unpaired t tests at the end of the trial as well as progression of TBR in the two groups using paired t test.

Results of subject's laboratory values and radiologic assessments will be discussed at the completion of study or during the study, in the event of laboratory or imaging abnormalities which require follow-up.

8.3 SAFETY AND OTHER ASSESSMENTS

Safety oversight will be conducted by collaboration between the Principal Investigator (PI), lead Study Coordinator (SC), the DSMB, and the Medical Monitor. A Medical Monitor (MM) has been appointed for

oversight of safety in this clinical study. If at any point in the trial halting rules are met, the study team (PI and SC) will arrange a (tele)conference so that the event can be reviewed and the discussion documented. At the end of each MM review meeting, the MM will be asked to provide a formal recommendation as to whether or not the protocol should be halted. A written summary of each MM review meeting will be provided to the MM and appropriate individuals. Participants on the MM teleconferences will include the MM, the PI and appropriate study team members. The MM will provide a written report to the DSMB as per Appendix A, Data Safety and Monitoring Plan (DSMP).

An independent DSMB has been established for oversight of safety in this clinical study, responsible to the NHLBI. This DSMB will be independent of regulatory agencies, IRB/EC, OncoImmune, Inc, and investigators. See Appendix A for the Data Safety Monitoring Plan.

Subject safety will be monitored by the PI and study team. Clinical data and safety data will be monitored at least every 2 weeks (or less frequently, based on the SOA). An evaluation of safety and efficacy data will be obtained when the first 6 subjects complete 4 weeks of therapy by the appointed Medical Monitor. The Medical Monitor will not be part of the clinical staff caring for subjects during study visits, so blinding will be maintained. If concerns about the safety or efficacy arise, the Medical Monitor will refer concerns to the Sponsor and DSMB and review of adverse events will proceed per section 8 and the DSMP. Thereafter, safety and data analysis will be performed every 12 weeks through completion of the study. Additionally, the PI will be responsible for submitting the IRB Continuing Review package and will provide the necessary safety data for the FDA IND Annual Report.

All enrolled subjects who have received CD24Fc will be evaluated for safety with the laboratory assays done at each visit as outlined in section 8.2. Safety will be assessed by physical examination, vital signs, hematology, and chemistries. Vital signs will include pulse, blood pressure, respiratory rate, and oxygen saturation. The severity of signs, symptoms, and AEs will be determined by using DAIDS toxicity table, version 2.1, July 2017. The CD24Fc infusion will be administered over a minimum of 1 hour. Subjects will be monitored during and after infusion is completed for 2 hours every 30 minutes and repeat vital signs and laboratory results will be ascertained as needed based on reported symptoms.

In the event of abnormal laboratory tests, the tests will be repeated immediately if they are inconsistent with the subject's screening (baseline) laboratory results. If considered abnormal and deviating from baseline, they will be repeated and may be referred for physician sub-specialty consultation. These laboratory results will be repeated until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded in the subject's study record.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

The investigator will grade the severity of each AE according to the "Division of AIDS Table For Grading The Severity Of Adult and Pediatric Adverse Events", version 2.1, July 2017.
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Grade 1-Mild –** Causing no or minimal interference with usual social and functional activities with intervention not indicated.
- **Grade 2-Moderate** – Causing greater than minimal interference with usual social and functional activities with intervention indicated.
- **Grade 3-Severe** – Causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- **Grade 4-Potentially Life Threatening –** Causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability or death.
- **Grade 5-Death**

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured in the study record. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. AEs and SAEs will be collected between Day 0 and Week 28 (completion of study).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI or study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All enrolled subjects who have received CD24Fc will be evaluated for safety with the laboratory assays done at each visit as outlined in section 8.2. Safety will be assessed by physical examination, vital signs, hematology, and chemistries. Vital signs will include pulse, blood pressure, respiratory rate, and oxygen saturation. The severity of signs, symptoms, and AEs will be determined by using DAIDS toxicity table, version 2.1. The CD24Fc infusion will be administered over a minimum of 1 hour. Subjects will be monitored after infusion is completed for 2 hours and repeat vital signs and laboratory results will be ascertained as needed based on reported symptoms.

In the event of abnormal laboratory tests, the tests will be repeated immediately if they are inconsistent with the screening (baseline) laboratory results. If considered abnormal and deviating from baseline, they will be repeated and subjects may be referred for physician sub-specialty consultation. These laboratory results will be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded in the subject's study record.

8.4.5 ADVERSE EVENT REPORTING

All AEs occurring from the time of ingesting one dose of the medications through the end of study will be documented, recorded, and reported. The Investigator will evaluate all AEs with respect to **Severity** (intensity or grade) and **Causality** (relationship to study agent and relationship to research). The investigator will record nonserious adverse events and report them to the sponsor within 30 days of the event occurrence.

Laboratory abnormalities that are gradable per the DAIDS toxicity table (version 2.1, July 2017) will be recorded as AEs or SAEs. All other laboratory abnormalities without clinical significance will not be recorded as AEs or SAEs. Laboratory abnormalities that require medical or surgical intervention or lead to study drug interruption, modification or discontinuation must be recorded as an AE or SAE if applicable. Laboratory assessments that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition. If a diagnosis is clinically evident, the diagnosis, rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of study drug up until study completion. Summaries (number and percentage of subjects) of treatment-emergent adverse events will be provided at study completion.

At each contact with the subject as outlined above in the study activities table, information regarding AEs will be elicited by appropriate questioning and examinations and will be immediately documented in the subject's medical record. Medical records will be reviewed in a timely manner by the research team. The onset date, the end date, the severity of each reportable event, and the Investigator's judgment of the AEs relationship to CD24Fc will also be recorded.

8.4.6 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events that occur following initiation of investigational agent on day 0 will be followed at a minimum until a final outcome is known (resolution of the AE or a return to baseline laboratory value) or until the end of the study follow-up period (Week 28).

SAEs that occur after the study follow-up period that are reported to and are assessed by the Investigator to be possibly, probably, or definitely related must be reported to the Medical Monitor.

8.4.7 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the Medical Monitor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the Medical Monitor. The University of Maryland Medical Monitor will in turn notify the ClinDatrix Medical Safety Medical Monitor via email.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

The Medical Monitor will advise the Sponsor regarding the safety of the study participants as well as the continuing safety and scientific validity of the trial. The Medical Monitor may also review the results of any planned analysis, if applicable. If the data analysis shows significant findings with regards to safety, the Medical Monitor may recommend modification of the protocol, Informed Consent, and/or monitoring of the study. In these cases, the regulatory authorities and local review committees may be notified. The Medical Monitor may also stop the study for reasons of safety and/or futility. The Medical Monitor will also perform a quarterly review of the safety data. This review may include the designated reviews as described above based on the timing of the reviews.

8.4.8 REPORTING OF PREGNANCY

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information of all pregnancies will be reported to the MM via HIPAA-compliant fax or email within 3 business days from site awareness of the pregnancy. Study drug must be stopped immediately. The participant will be advised to notify her obstetrician of study agent exposure.

Pregnancy outcome data (e.g., delivery outcome, spontaneous, or elective termination of the pregnancy, presence of absence of birth defects, congenital abnormalities, or other complications) will be reported to the MM within 3 business days of the site's awareness via HIPAA-compliant fax or email.

8.4.9 PAUSING AND HALTING RULES

See Appendix A (Safety Monitoring Plan).

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor within 3 days of the investigator becoming aware of the event.

- Any other UP will be reported to the IRB and to the study sponsor within 15 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The objectives of this phase II trial are to (1) determine the safety and tolerability of CD24Fc during the 4-week dosing period and a 24-week follow-up period in a cohort of HIV subjects and (2) evaluate the change in LDL during a 4-week dosing period of CD24Fc and a 24-week follow-up period. The primary efficacy endpoint is the reduction of LDL levels when compared with placebo control at week 6. The hypothesis of superiority of CD24Fc 240mg compared to Placebo will be tested for the reduction of LDL levels.

Primary Efficacy Endpoints:

1. Incidence and severity of any adverse events (AEs) during the administration of drug and 24 weeks after completion. Safety will be evaluated by assessment of clinical laboratory tests, physical examination at various time points during the study, and by the documentation for AEs.
2. The percentage reduction in LDL level from the baseline (predosing) to 2 weeks after the last treatment.
3.

Secondary Efficacy Endpoint(s):

1. Percent change in levels of total cholesterol, HDL, and triglycerides from baseline to Weeks 6 and 28 between placebo and intervention arms.
2. Percent change in markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14) from baseline to Week 6 and 28 between placebo and intervention arms.
3. Change in proviral DNA from baseline to Week 6 and 28 between placebo and intervention arms.
4. Percent change from baseline to week 28 in Troponin I and T between placebo and intervention arms.
5. Change in percent of hepatic steatosis (by CAP measurement) and fibrosis (by KPA) as determined by transient elastography from baseline to week 28 between placebo and intervention arms.
6. Percent change in leptin from baseline to Week 6 and 28 between placebo and intervention arms.
7. Percent change in hemoglobin A1c from baseline to Week 6 and 28 between placebo and intervention arms.
8. PK and PD assessments (For 6 subjects)
9. Presence of ADA in all subjects with temporal correlation to any adverse events, and its effect on PK (For first 6 subjects).
10. Changes in IL-6, apoB, Lp(a), urine albumin:creatinine ratio before and after treatment.

Exploratory Endpoints:

1. Change in vascular inflammation as evidenced by aortic FDG uptake by FDG-PET/CT will be assessed before and after therapy. The arterial uptake of FDG is measured by the standardized uptake value (SUV) max divided by the venous SUV mean yielding a target to background ratio (TBR).
2. Changes in hs-CRP and GlycA before and after treatment.
3. Changes in CEC and NMR lipoproteins before and after treatment.
4. Changes in endothelin-1 before and after treatment.

9.2 SAMPLE SIZE DETERMINATION

We anticipate enrolling 64 subjects with HIV who have achieved viral suppression for 2 years while on ART. The primary efficacy endpoint is the reduction of LDL levels when compared with placebo control at week 6. We expect a 15% reduction of LDL levels. For better comparison, we define the predosing LDL level of each subject as baseline and compare the LDL levels at 6 weeks (2 weeks after the last treatment) to determine percentage reduction. The mean variations of the placebo groups will be subtracted when used to determine whether the 15% endpoints haven been met. From our previous Phase 1 and Phase 2a human studies, the estimate of standard deviation is about 20% for both placebo and treatment groups. A sample size of 28 completed subjects per treatment group (56 subjects in total) will provide 80% power to detect 15% reduction difference between treatment and placebo groups at a 2-sided significance level of 0.05. Accounting for 11% attrition, it is expected that a total of 64 subjects will be enrolled.

9.3 POPULATIONS FOR ANALYSES

The following analysis sets will be used in this trial:

- Intention-to-Treat (ITT) Analysis Dataset - this includes all randomized subjects
- Modified Intention-to-Treat Analysis Dataset (mITT) - this includes all randomized subjects with at least one application of study drug
- Safety Analysis Dataset- this includes all randomized subjects with at least one application of study drug
- Per-Protocol Analysis Dataset - this includes a subset of the subjects in the ITT analysis set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., subjects who took at least 80% of study intervention treatment for at least 80% of the initial 4 weeks).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

For descriptive statistics categorical data will be presented as frequencies and percentages.

Percentages will be based on the number of subjects with non-missing values for the corresponding categorical variable. Continuous data will be presented as number of subjects with non-missing values, mean standard deviation, median, minimum and maximum, as well as the 25th and 75th percentile.

All statistical tests as well as the confidence intervals will be two-sided. The type I error probability for the confirmatory analysis is set to 5%. 95% confidence intervals are to be calculated, if feasible. Covariates for the primary analyses will be pre-specified. For secondary analyses these will be specified later in the SAP.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY AND SECONDARY ENDPOINTS

The primary efficacy and secondary analysis will be based on the mITT set. Most of primary and secondary variables such as T cell surface markers and plasma cytokine levels, and change and percent change from baseline to week 28 on markers of vascular inflammation and myocardial damages will be viewed as continuous variables and transformed as necessary. Each of efficacy variables will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment as the fixed effect and other potential risk factors such as baseline value, clinical measures and demographic information as covariates. Differences between treatment groups and 95% confidence intervals will be estimated within the framework of ANCOVA. The statistical test for each of those variables will be a two-sided test at a significance level of 0.05 and no multiplicity adjustment will be done.

Specific details will be provided in the full statistical analysis plan (SAP) for the study.

9.4.3 SAFETY ANALYSES

Safety and tolerability will be summarized by treatment arm, including Treatment Emergent Adverse events (TEAEs), and laboratory evaluations. No inferential analysis is planned for safety data. Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as new or worsening AEs after the first dose of study medication, and will be summarized by system organ class, and preferred term. A list of subjects who have Severe Adverse Events (SAEs) and who discontinue from the study due to an adverse event will be provided.

Summary statistics for laboratory values will be provided at baseline, post baseline, and for changes from baseline to post baseline. Vital signs will also be summarized in the same way. Occurrence of significant laboratory abnormalities will be tabulated. Values of potential clinical concern will be pre-specified in the SAP. All medications administered during the study period must be documented on the Concomitant Medication electronic case report form (eCRF). These medications will be coded using the most current version of the World Health Organization Drug Dictionary. A listing of all medications including the reported term, dictionary term, start and stop dates, and other relevant data will be provided. The Safety Analysis Set (SAF) will include all subjects who received at least 1 dose of study medication and the subjects will be analyzed as treated. The safety and efficacy analyses will be summarized based on the SAF.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Subjects will also sign an NIH specific consent form for any procedures taking place at the NIH.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. 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. Only participants who can consent for themselves will be consented.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the principal investigator, funding agency (NHLBI), the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Institute of Human Virology and the Department of Epidemiology (University of Maryland School of Medicine). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. The PI and study team will have access to the password-protected database. At the end of the study, all study databases will be de-identified and archived at the University of Maryland Medical School of Medicine.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Institute of Human Virology (University of Maryland). After the study is completed, the de-identified, archived data will be retained at the Institute of Human Virology (IHV) for use by other researchers including those outside of the study. Permission to retain the data at the IHV will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the IHV. These samples could be used to research the causes of cardiovascular disease in HIV, its complications and other conditions for which individuals with

HIV are at increased risk, and to improve treatment. IHV researchers will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant. Genetic testing will not be performed.

When the study is completed, access to study data and/or samples will be provided through the IHV.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
Shyamasundaran Kottilil MD, PhD	PPD
Institute of Human Virology, University of Maryland	
725 W. Lombard St. Baltimore, MD 21201	
PPD	
PPD	

The National Institutes of Health, Bethesda, MD

The National Institutes of Health, Bethesda, MD campus will provide access to advanced cardiac imaging and other clinical research resources not available at the clinical sites. Henry Masur, MD and Nehal Mehta, MD are the NIH Intramural site Investigators. Drs. Masur and Mehta will oversee the protocol and all the individuals working on it at the NIH Clinical Center and provide expertise on study design and implementation. These individuals are listed in the UMB Protocol as Sub-Investigators and may include federal employees, special volunteers, and/or contractors. Drs. Mehta, Amit Dey and Henry Masur will be authorized to obtain informed consent, have access to identifiable data, and participate in data analysis and manuscript preparation/review. Drs. Mehta and Dey are experts in cardiometabolic evaluation of FDG-PET/CT and will provide interpretation of the results of these imaging studies which will strengthen evaluations to characterize the biologic effects of CD24Fc. The lab of Tae-Wook Chun, PhD will be processing research samples for the study at the NIH through a NIAID funded laboratory.

Shyam Kottilil, Poonam Mathur and Amy Nelson are UMB sub-investigators who are also special volunteers at NIH and are fully credentialed and able to see research patients at the NIH. They are authorized to obtain informed consent, have access to identifiable data, see patients at NIH and participate in data analysis and manuscript preparation/review.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the Medical Monitor, PPD. The Medical Monitor will be independent from the study conduct and free of conflict of interest. The Medical Monitor will meet at least quarterly with the PI and study team to assess safety and efficacy data on each arm of the study. The Medical Monitor will provide its input to the study sponsor quarterly and the NHLBI as needed.

An independent DSMB has also been established for oversight of safety in this clinical study, responsible to the NHLBI. This DSMB will be independent of regulatory agencies, IRB/EC, OncoImmune, Inc, and investigators. The DSMP can be found in Appendix A at the end of this protocol.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring of the site will be conducted in accordance to the current procedures in place at the Institute of Human Virology, University of Maryland School of Medicine.
- Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee or the Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection. The Investigator agrees to allow access to the required participant and study records during an audit. The Investigator will provide the Sponsor with copies of all correspondence with the regulatory authority which may affect the review of the current study or their qualification as an Investigator in studies conducted by the Sponsor. The Sponsor reserves the right to be present during an inspection by the regulatory agency.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Data quality control (QC) checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Medical Monitor and the DSMB will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

During the study, the Sponsor or designee will conduct periodic monitoring visits to ensure that the protocol and ICH GCP guidelines are being followed. The monitors may review source documents to confirm that the data recorded is accurate. The Investigator and institution will allow the Sponsor monitor or designee and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be participant to review by the IRB, and/or quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or inspection by appropriate regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data will be recorded in an electronic case report form (eCRF) using a secure electronic database. The data system includes password protection. The data entered will include but not be limited to clinical findings and observations, laboratory and test data, hospital medical records, physician or office charts, physician or nursing notes, recorded data from automated instruments, x-rays, etc.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team, in accordance with findings from previous trials as outlined in the IB. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Deaths related to the natural history of HIV will be reported at the time of continuing review.

It is the responsibility of the site investigator to use continuous vigilance to identify and report unanticipated deviations within 7 working days of identification of the protocol deviation, or within 7

working days of the scheduled protocol-required activity. All unanticipated deviations must be addressed in study source documents, reported to the NHLBI Program Official and sponsor.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The PI and study team share de-identified or identified data generated in this study with all collaborators and will have access to all data collected from all sites. The NIH will share cardiac imaging results and analysis as well as research lab data with the study team. All NIH data will be subject to a certificate of confidentiality whether it stays at the NIH or is shared with others.

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the study Sponsor.

At the conclusion of the study, the Sponsor will support the writing and publication of scientific reports, journal papers and oral presentations by the study principal investigator and others making scientific contribution to the research effort. Any reports, papers, and/or presentations must be reviewed and approved by prior to submitting for publication. All reports generated by this study will be in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983.

All publications relating to the study will comply with the guidelines set forth by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals drawn up by the International Committee of Medical Journal Editors.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all

reported dualities of interest. All NIH Investigators have been cleared of actual or perceived influence by the Deputy Ethics Counselors of the NIH Clinical Center

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

ABBREVIATION	TERM
ADA	Anti-Drug Antibody
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CD24	Cluster of Differentiation 24
CDC	Centers for Disease Control
CEC	Cholesterol Efflux Capacity
CFR	Code of Federal Regulations
ChRM	Chinese Rhesus Macaques
CMP	Complete Metabolic Panel
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computed Tomography
CVD	Cardiovascular Disease
DAMPs	Danger Associated Molecular Patterns
DSMB	Data and Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ECD	Extracellular Domain
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
ESA	Erythropoietin Stimulating Agent
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GVHD	Graft Versus Host Disease
HDL	High Density Lipoprotein

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency virus
HSA	Heat Stable Antigen
Hs-CRP	High Sensitivity CRP
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFN	Interferon
IL-6	Interleukin 6
IND	Investigational New Drug Application
Institute of Human Virology	IHV
IRB	Institutional Review Board
ITT	Intention-to-treat
LDL	Low Density Lipoprotein
MM	Medical Monitor
MS	Multiple Sclerosis
NCT	National Clinical Trial
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NMR	Nuclear Magnetic Resonance
PD	Pharmacodynamics
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
OHRP	Office for Human Research Protections
RA	Rheumatoid Arthritis
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Study Coordinator
sCD14	Soluble Cluster of differentiation 14
SIV	Simian Immunodeficiency Virus
SOA	Schedule of Activities
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TNF	Tumor Necrosis Factor
TnI	Troponin I
TnT	Troponin T
TPO	Thrombopoietin
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2	July 2019	Decrease dosing to 4 weeks, addition of further clinical laboratory testing and inclusion criteria strengthening, change to include CT with FDG PET	In response to FDA recommendations, CT added at request of NIH collaborator
3	February 2020	Revisions to clarify NIH Lead Investigator, roles, compensation for visits occurring at NIH, sharing of data. Addition of NIH Protocol Addendum to this protocol.	In response to NIH review to allow protocol to occur at their site
4	June 2020	Add DSMP appendix to protocol and clarify DSMB language in protocol	Per grant requirements, a DSMB was required
5	November 2020	Addition of endothelin-1 research testing and endpoints, clarification of screening window in SofA. Clarification of timing windows in post-infusion monitoring. Clarification of payment for unscheduled visits. Correction to inclusion criteria for drug components of Biktarvy. Clarification for discontinuation based on CD4 changes to include both change in absolute value and CD4%.	SofA changed for consistency, researchers desired to follow endothelin changes with the study. Windows added for allowable timepoints for monitoring. Payment changes to inform subjects of unscheduled visit payment and need to collect SS# for possible 1099. Biktarvy change as mistake noted. Absolute changes in CD4 undergo daily variation, so correlating absolute CD4 with CD4% will be more useful to determine if there is a clinically significant decline.

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Abbreviated Title: CALIBER

Protocol #: *iRIS assigned number- 20CC0038;* UMB HP-00086029; IND Sponsor - Oncolmmune Inc. CD24Fc-003; Radiation Safety #2757 Approved 10/24/2019

UMB Version Date: October 16, 2019

NIH Version Date: 01/13/2020

Title: CD24Fc Administration to Decrease LDL and Inflammation in HIV Patients, Both as Markers of Efficacy and Cardiovascular Risk Reduction (CALIBER)
(Phase II, randomized, double-blind, placebo-controlled clinical trial)

NIH Principal Investigator: Henry Masur, MD
Critical Care Medicine Branch
The NIH Clinical Center
Building 10, Rm 2C145
9000 Rockville Pike
Bethesda, MD 20892
PPD
PPD

Investigational Agents: None (not at the NIH)
Commercial Agents: Fludeoxyglucose F 18 Injection

Precis:

This study is a phase 2, randomized, placebo-control, double-blinded clinical trial to assess the safety and tolerability of CD24Fc among patients with HIV, and the effect of CD24Fc on change in low-density lipoprotein (LDL) among patients with HIV. We will also evaluate the effect of CD24Fc on total cholesterol and triglycerides, markers of immune activation (T cell activation, sCD14, and inflammatory cytokines), size of HIV reservoirs, HbA1c and leptin, and hepatic steatosis, among other inflammatory markers.

We hypothesize that therapy with CD24Fc will be safe and tolerable in HIV patients on ART and result in significant decreases in LDL. In addition, we hypothesize that CD24Fc will reduce cholesterol, leptin, HbA1c, hepatic steatosis and fibrosis, and markers of inflammation in patients with chronic HIV who are virally suppressed on ART.

In this phase 2 study, a cohort of 64 HIV patients virally suppressed on ART will be randomized in a 1:1 fashion to receive an intravenous infusion of 240mg of CD24Fc vs. placebo administered every 2 weeks during a 4-week treatment window, followed by a 24- week follow-up period. Patients will be followed for safety and adverse events as well as changes in lipid metabolism and inflammatory markers during a 24-week follow-up period. This investigation will take place at the University of Maryland and National Institutes of Health.

The research being completed at the National Institutes of Health Clinical Center as part of the University of Maryland study is to assess the effect of CD24Fc on aortic vascular inflammation as measured by standardized uptake value of arterial FDG by PET/CT. Twelve subjects with an LDL>125 (a high level of low-density lipoproteins (LDL), also known as "bad cholesterol") will be selected to have an

optional FDG PET/CT scan. Change in vascular inflammation as evidenced by aortic FDG uptake by FDG-PET/CT will be assessed before and after therapy. The arterial uptake of FDG is measured by the standardized uptake value (SUV) max divided by the venous SUV mean yielding a target to background ratio (TBR).

This scan is completed twice, once before starting the study drug, and again 24 weeks after completing the study drug. The FDG PET/CT scans will help to determine if there are any changes to the levels of inflammation in the blood vessels after taking the study drug, or placebo.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 NUMBER OF PATIENTS TO BE ENROLLED AT THE NIH

12 subjects will come to the NIH for the optional FDG PET/CT scans.

2 NIH PATIENT REGISTRATION

2.1 REGISTRATION PROCEDURES

2.1.1 REGISTRATION PROCESS AT NIH

Screening and enrollment into this study was performed at the University of Maryland in accordance with the sponsor protocol section **7.1 Study Visits and 7.1.1.1 Screening**. After the subjects meets the eligibility and signs the consent document, 12 subjects will be selected to travel to the NIH CC for the optional FDG PET/CT scans. Authorized member of the research team will make a request in the Admission Travel Voucher (ATV) system and have a medical record number assigned. Subject will then be registered in NIH Clinical Research Information System (CRIS). Both ATV and CRIS systems are password protected with access granted only to authorized personnel.

3 CRITERIA FOR REMOVAL FROM SPONSOR PROTOCOL

Per sponsor protocol section **6.2 Participant Discontinuation/Withdrawal from the Study**, study participation could be discontinued due to the following reasons:

- Pregnancy or breastfeeding
- Significant study intervention non-compliance
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation which occurs such that continued participation in the study would not be in the best interest of the participant (including malignancy)
- New or recurrent Centers for Disease Control and Prevention (CDC) category C AIDS-indicator condition.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive CD24Fc for 2 doses
- Development of life-threatening infection or clinical reason deemed to be life-threatening by the physician
- Request of the primary care provider or Investigator if s/he thinks the study is no longer in the best interest of the subject.
- If the subject is judged by the Investigator to be at significant risk
- The following laboratory abnormalities
    - HIV RNA>200 copies/mL (2 readings at least 2 weeks apart)
    - Decrease in eGFR to <30mL/min, confirmed by immediate repeat testing

- Elevation of ALT >5x OR AST >5x Day 0, confirmed by immediate repeat testing
- Abnormal elevation of ALT >3 x Day 0 *and* total bilirubin >2 x ULN, confirmed by immediate repeat testing
- For participants with entry CD4+ T cell count between 350 - 500 cells/mm^3, confirmed CD4+ decline greater than 25% of baseline.
- For participants with entry CD4+ T cell count between 501 to 800 cells/ mm^3, a confirmed CD4+ T cell decline greater than 33% of baseline.
- For participants with entry CD4+ T cell count greater than 800 cells/ mm^3, a confirmed CD4+ T cell decline greater than 50% of baseline.
- Occurrence of Grade 4 anemia/neutropenia or recurrence of Grade 3 anemia/neutropenia.

4 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN (THIS REPORTING SECTION OUTLINES THE REPORTING REQUIREMENTS THAT ARE REQUIRED TO THE NIH AND ARE IN ADDITION TO THE REPORTING REQUIREMENTS FOR THE UMB IRB.)

4.1 NIH DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found *here*.

4.2 NIH IRB AND CLINICAL DIRECTOR REPORTING

4.2.1 NIH INTRAMURAL IRB

Please refer to the reporting requirements in Policy 801: Reporting Research Events *here*.

4.2.2 REPORTING TO NIH INTRAMURAL IRB

Please refer to the reporting requirements in Policy 801: Reporting Research Events *here*.

4.2.3 NIH CC CLINICAL DIRECTOR REPORTING

All serious adverse events (SAEs) that meet the definition per Policy 801: must be reported to NIH CC Clinical Director via PPD .

4.3 DATA AND SAFETY MONITORING PLAN

4.3.1 PRINCIPAL INVESTIGATOR/RESEARCH TEAM

Drs. Masur and Mehta will oversee the NIH portion of the protocol (FDG by PET/CT) and all the individuals working on it at the NIH Clinical Center.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The PI will be responsible for overseeing collection and maintenance of source documents and data entry into eCRFs in accordance with the sponsor protocol section **9.1.9 Data Handling and Record Keeping.**
End of study procedures: Data will be stored according to applicable regulations, policies and requirements as well as NIH Intramural Records Retention Schedule as applicable.
Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified as above.

5.2 FUTURE USE OF STORED DATA/SAMPLES

FDG PET/CT scans will be kept indefinitely at the NIH and they may be used in the future. We will also receive blood in EDTA tubes from subjects seen at UMB. The samples will be coded and we will not know the identity of the subjects. We will be conducting measurements of HIV reservoir size (HIV DNA PCR, cell-associated RNA PCR) and soluble factors in plasma such as D-dimer, CRP, IL-2, IL-4, IFNg, TNF-a and other cytokines. Any remaining samples will be stored temporarily at NIAID but will be shipped back to UMB upon conclusion of our assays. No one else at NIH will have access to specimens coming from UMB.

6 HUMAN SUBJECTS PROTECTIONS

6.1 RATIONALE FOR SUBJECT SELECTION

Subjects for this study will include all subjects who meet the eligibility criteria outlined in the sponsor protocol sections **5.1 Inclusion Criteria** and **5.2 Exclusion Criteria**. No gender, racial, or ethnic groups will be excluded from participation in this trial.

6.2 RISK/BENEFIT ASSESSMENT

6.2.1 KNOWN POTENTIAL RISKS

^{18}FDG PET CT:
The study involves exposure to radiation from the radioactive sugar, but the radiation from 2 FDG PET/CT scans will be less than the radiation safety limit for research. There is no medical risk from lying in the scanner, although subjects may become uncomfortable or restless. Subjects will also have to fast 6 hours before the appointment due to the use of radioactive glucose, which may also cause discomfort. In addition to any radiation concern, there could be psychological distress caused by an incidental finding of asymmetric FDG uptake that would likely necessitate additional investigation to exclude cancer. Additional minimal risks include bleeding or bruising at the venous site of FDG administration.

6.4.2 Known Potential Benefits
This research involves no prospect of direct benefit to individual subjects but is likely to yield generalizable knowledge about the subject's disorder or condition.

7 COLLABORATIVE AGREEMENTS

7.1 AGREEMENT TYPE

NHLBI is in the process of putting together a Research Collaborative Agreement. Once the agreement is executed, more details will be provided.
Transfers that are associated with correlative studies conducted under an approved protocol: Dr. Chun will be receiving coded samples from the University of Maryland Baltimore. He will be conducting measurements of HIV reservoir size (HIV DNA PCR, cell-associated RNA PCR) and soluble factors in plasma such as D-dimer, CRP, IL-2, IL-4, IFNg, TNF-a and other cytokines.
Investigators in the NIH intramural program may participate in multi-site clinical trials (either as a site or as the coordinating center) under which human materials are transferred from the intramural program to another site for correlative studies that are part of the approved protocol. In such a situation, the protocol clearly documents the tests conducted under the correlative studies, and each institution participating in the clinical study is bound by the terms of their Protocol and their obligations under the statutes and regulations. In addition, intramural protocols are cleared by the IC Clinical Director. In such situations, use of an HM-MTA is not necessary for these transfers.

8 CERTIFICATE OF CONFIDENTIALITY

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy of participants.

9 INSURANCE BILLING

The NIH will not bill any insurance companies or participants for any research or related clinical care as the NIH is not a HIPPA-covered entity,

10 COMPENSATION, REIMBURSEMENT, AND PAYMENT

If a participant requires it, transportation to the NIH will be arranged by the UMB study staff. Participants will receive $200 cash after they have completed each FDG PET/CT from the UMB study staff.

If a participant is unable to finish the optional study after they arrive at the NIH for some reason, they will receive $100 from the UMB study staff.

All compensation will be given to the participant by a UMB study team member at their next visit to UMB.

This study does not offer reimbursement for or payment of travel, lodging or meals.

APPENDIX A: SAFETY MONITORING BOARD AND PLAN

Full Title: CD24Fc Administration to Decrease LDL and Inflammation in HIV Patients, Both as Markers of Efficacy and Cardiovascular Risk Reduction

Short Title: CALIBER

Clinical Phase: II

IND Sponsor: OncoImmune, Inc.

Principal Investigator: Shyam Kottilil, MD PhD

Sample Size: n = 64

Accrual Ceiling: 110

Study Population: Adults age 50 or older with chronic HIV infection who have achieved viral suppression with use of ART for at least 2 years

Accrual Period: 18 months

Study Design: This is a double blind, placebo controlled, randomized trial to evaluate the safety of CD24Fc in adults with HIV. Patients will be randomized to two arms: (1) CD24Fc (IV) for 3 doses over 6 weeks vs (2) Placebo (IV) for 3 doses over 6 weeks

Study Duration: Start Date: January 2020
End Date: December 2021

Study Agent: CD24Fc 240mg IV Infusion

Primary Objectives:

1. To determine the safety and tolerability of CD24Fc during the 4-week dosing period and a 24-week follow-up period in a cohort of HIV patients.
2. To evaluate the change in LDL during a 4-week dosing period of CD24Fc and a 24-week follow-up period.

Secondary Objectives:

1. Levels of total cholesterol, HDL, and triglycerides
2. Markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14)
3. Size of HIV reservoirs
4. Myocardial damage (measured by Troponin I and T)
5. Hepatic steatosis, as determined by transient elastography
6. Leptin
7. Hemoglobin A1c
8. Presence of anti-drug antibody (ADA) and temporal correlation to any adverse events, and its effect on PK (For first 6 subjects).
9. The pharmacokinetics (PK) and pharmacodynamics (PD) of CD24Fc in the first 6 randomized subjects.
10. Changes in IL-6, apoB, Lp(a), urine albumin to creatinine ratio before and after treatment.

Exploratory Objectives:

1. To assess the effect of CD24Fc on aortic vascular inflammation as measured by standardized uptake value of arterial FDG by PET/CT. We will select 12 subjects with an LDL>125 to have the imaging study.
2. To assess the effect of CD24Fc on the inflammatory markers hs-CRP and GlycA.
3. To assess the effect of CD24Fc on the CEC and NMR lipoproteins.
4. To assess the effect of CD24 Fc on endothelin-1.

Primary Endpoints:

1. Incidence and severity of any adverse events (AEs) during the administration of drug and 24 weeks after completion. Safety will be evaluated by assessment of clinical laboratory tests, physical examination at various time points during the study, and by the documentation for AEs.
2. The percentage reduction in LDL level from the baseline (predosing) to 2 weeks after the last treatment.

Secondary Endpoints:

1. Percent change in levels of total cholesterol, HDL, and triglycerides from baseline to Week 6 and 28 between placebo and intervention arms.
2. Percent change in markers of immune activation (CD4 and CD8 T cells, IFN, TNF, sCD14) from baseline to Week 6 and 28 between placebo and intervention arms.
3. Change in proviral DNA from baseline to Week 6 and Week 28 between placebo and intervention arms.
4. Percent change from baseline to week 28 in Troponin I and T between placebo and intervention arms.
5. Change in percent of hepatic steatosis (by CAP measurement) and fibrosis (by KPA) as determined by transient elastography from baseline to week 28 between placebo and intervention arms.
6. Percent change in leptin from baseline to Week 6 and Week 28 between placebo and intervention arms.
7. Percent change in hemoglobin A1c from baseline to Week 6 and week 28 between placebo and intervention arms.
8. PK and PD assessments (For 6 subjects; presence of ADA and its effect on PK in all subjects

Exploratory Endpoints:

1. Change in vascular inflammation as evidenced by aortic FDG uptake by FDG-PET/CT will be assessed before and after therapy. The arterial uptake of FDG is measured by the standardized uptake value (SUV) max divided by the venous SUV mean yielding a target to background ratio (TBR).
2. Changes in hs-CRP and GlycA before and after treatment.
3. Changes in CEC and NMR lipoproteins before and after treatment.

4. Changes in endothelin-1 before and after treatment.

Adverse Events, Serious Adverse Events, and Unanticipated Problems

The investigator will grade the severity of each adverse event (AE) according to the "Division of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events", version 2.1, July 2017. *https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf*

For AEs not included in the protocol defined grading system, severity will be determined using the guidelines outlined in the protocol. All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories outlined in the protocol. The investigator will record nonserious adverse events and report them to the sponsor within 30 days of the event occurrence.

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. All AEs will be followed to adequate resolution. AEs will be collected between Day 0 and Week 28 (completion of study).

The PI or study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of study drug up until study completion. Summaries (number and percentage of subjects) of treatment-emergent adverse events will be provided at study completion.

Serious Adverse Events (SAEs)

SAEs that occur after the study follow-up period that are reported to and are assessed by the Investigator to be possibly, probably, or definitely related must be reported to the Medical Monitor.

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be collected between Day 0 and Week 28 and followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

Unanticipated Problems

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor within 3 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 15 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

Pausing and Halting Rules

Enrollment and dosing will be paused for an individual subject who has a Grade 4 AE. After review by the Medical Monitor (MM) and reporting to the DSMB in the regularly scheduled report every 12 weeks, the MM will evaluate whether study participation for the subject should continue. During MM review, enrollment and dosing will not be paused for other study subjects.

If two subjects experience the same Grade 4 AE related to the study drug, all enrollment will be paused and all doses for enrolled subjects will be held. The MM will report to the DSMB within 24 hours and study dosing will halt until DSMB determination regarding continuation of study enrollment and dosing.

If one or more subjects experiences changes in mental status, DIC, dyspnea, cytokine release syndrome and/or hypotension related to the study drug, without remediation in 2-4 hours, the MM will report to the DSMB within 24 hours and the DSMB will review the report for possible study termination. During this review, enrollment and dosing will be halted for all subjects.

Safety and Efficacy Analyses

The primary safety endpoint will be assessed by Incidence and severity of any adverse events (AEs) during the administration of drug and 24 weeks after completion. Safety will be evaluated by assessment of clinical laboratory tests, physical examination at various time points during the study, and by the documentation for AEs. A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

Safety and tolerability will be summarized by treatment arm, including Treatment Emergent Adverse events (TEAEs), and laboratory evaluations. No inferential analysis is planned for safety data. Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities

(MedDRA). TEAEs are defined as new or worsening AEs after the first dose of study medication, and will be summarized by system organ class, and preferred term. A list of subjects who have Severe Adverse Events (SAEs) and who discontinue from the study due to an adverse event will be provided.

Summary statistics for laboratory values will be provided at baseline, post baseline, and for changes from baseline to post baseline. Vital signs will also be summarized in the same way. Occurrence of significant laboratory abnormalities will be tabulated. All medications administered during the study period must be documented on the Concomitant Medication electronic case report form (eCRF). These medications will be coded using the most current version of the World Health Organization Drug Dictionary. A listing of all medications including the reported term, dictionary term, start and stop dates, and other relevant data will be provided. The Safety Analysis Set (SAF) will include all subjects who received at least 1 dose of study medication and the subjects will be analyzed as treated. The safety and efficacy analyses will be summarized based on the SAF.

The following analysis sets will be used in this trial:

- Intention-to-Treat (ITT) Analysis Dataset - this includes all randomized subjects
- Modified Intention-to-Treat Analysis Dataset (mITT) - this includes all randomized subjects with at least one application of study drug
- Safety Analysis Dataset- this includes all randomized subjects with at least one application of study drug
- Per-Protocol Analysis Dataset - this includes a subset of the subjects in the ITT analysis set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., subjects who took at least 80% of study intervention treatment for at least 80% of the initial 4 weeks).

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods. For descriptive statistics categorical data will be presented as frequencies and percentages. Percentages will be based on the number of subjects with non-missing values for the corresponding categorical variable. Continuous data will be presented as number of subjects with non-missing values, mean standard deviation, median, minimum and maximum, as well as the 25th and 75th percentile.

All statistical tests as well as the confidence intervals will be two-sided. The type I error probability for the confirmatory analysis is set to 5%. 95% confidence intervals are to be calculated, if feasible. Covariates for the primary analyses will be pre-specified. For secondary analyses these will be specified later in the SAP.

The primary efficacy and secondary analysis will be based on the mITT set. Most of primary and secondary variables such as T cell surface markers and plasma cytokine levels, and change and percent change from baseline to week 36 on markers of vascular inflammation and myocardial damages will be viewed as continuous variables and transformed as necessary. Each of efficacy variables will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment as the fixed effect and other potential risk factors such as baseline value, clinical measures and demographic information as covariates. Differences between treatment groups and 95% confidence intervals will be estimated within the framework of ANCOVA. The statistical test for each of those variables will be a two-sided test at a significance level of 0.05 and no multiplicity adjustment will be done.

Timing of DSMB Meetings

Timeline	*Type of Data*
Prior to study dosing	Review charter, Review protocol, Select roles of DSMB members
Every Six Months	Enrollment summary, adverse events listings and tables for primary endpoints available.
Medical Monitor report every 12 weeks	Review for determination of need for additional DSMB review prior to next meeting
If two subjects have same G4 event related to study drug	AE reviews, response to continue or revert enrollment and dosing hold
If one or more subjects have mental status changes, DIC, dyspnea, cytokine release syndrome or hypotension not remediated within 2-4 hours and categorized as clinically relevant by PI and Medical Monitor with risk to participants	Review of events with determination of study termination or continuance
Unanticipated Problem or non-SAE	Review for determination of need for additional DSMB review prior to next meeting
Upon completion or termination of study	Enrollment summary, adverse events listings and tables for primary endpoints available.

Study Termination

This study may be terminated under a variety of circumstances including, but not limited to, termination for overwhelming effectiveness, futility, or safety issues per protocol or DSMB monitoring guidelines. Responsibilities of the DSMB with regard to closeout will be to review the final study report to ensure study integrity. The DSMB may recommend continuing action items based upon the final review.