An Exploratory, Open-Label Study of Vedolizumab (anti-$\alpha4\beta7$ Monoclonal Antibody) in Subjects with HIV Infection Undergoing Analytical Treatment Interruption

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
cART	Combination Antiretroviral Therapy
CC	Clinical Center
CD	Crohn's Disease
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CLIA	Clinical Laboratory Improvement Amendment of 1988
COI	Conflict of Interest
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Form
CRIMSON	Clinical Research Information Management System of the NIAID
DCR	Division of Clinical Research
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GALT	Gut Associated Lymphoid Tissue
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	Intravenous
MAb	Monoclonal Antibody
MRI	Magnetic Resonance Imaging
N	Number (typically refers to number of subjects/sample size)
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
OHRP	Office for Human Research Protections
OHSRP	Office of Human Subjects Research Protections
PBMC	Peripheral Blood Mononuclear Cells
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SC	SubCutaneous
SIV	Simian Immunodeficiency Virus
SMC	Safety Monitoring Committee
UC	Ulcerative Colitis
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event

Protocol Summary

Full Title:	An Exploratory, Open-Label Study of Vedolizumab (anti-$\alpha\beta$ antibody) in Subjects with HIV Infection Undergoing Analytical Treatment Interruption
Short Title:	Therapeutic Vedolizumab
Clinical Phase:	1
IND Sponsor:	OCRPRO
Conducted by:	NIAID/LIR
Principal Investigator:	Michael C. Sneller, MD
Sample Size:	N= up to 20
Accrual Ceiling:	40
Study Population:	HIV-infected Adults (age 18-65 years) on cART with suppressed viremia
Accrual Period:	18 months
Study Design:	An exploratory, open-Label, single arm study of vedolizumab in subjects with HIV Infection undergoing analytical treatment interruption
Study Duration:	Start Date: April 2016 End Date: July 2018
Study Agent:	Vedolizumab 300 mg
Primary Objective:	To evaluate the safety and tolerability of vedolizumab in HIV-infected individuals prior to and following analytical treatment interruption (ATI).

Secondary Objective: To evaluate the effect of vedolizumab administration on plasma viral rebound in HIV-infected individuals following ATI

Endpoints:

1. The rate of occurrence of grade 2 or higher AEs, including SAEs, which are probably or definitely related to vedolizumab.
2. The number of subjects who experience rebound of plasma viremia following ATI and meet criteria to restart cART before week 48

Précis

While combination antiretroviral therapy (cART) has improved the clinical outcome for HIV-infected individuals, persistence of viral reservoirs in the peripheral blood and lymphoid tissues remains a hurdle to complete eradication of virus and cure of the infection. The concept that HIV preferentially infects discrete subsets of $CD4^+$ T cells underscores the need to develop therapeutics that exploit specific cell-virus interactions. T cells expressing integrin $\alpha4\beta7$ not only regulate migration into the gut-associated lymphoid tissue (GALT), but also concomitantly bind HIV, placing them in a prime position to disseminate HIV throughout the tissue. Previously, it has been shown that the HIV envelope protein gp120 binds to $\alpha4\beta7$ on $CD4^+$ T cells *in vitro*, $\alpha4\beta7^{high}$ $CD4^+$ T cells are highly susceptible to productive HIV infection *in vitro*, and the administration of anti-$\alpha4\beta7$ monoclonal antibody (mAb) prevents and/or delays transmission of SIV upon repeated challenges and preserves $CD4^+$ T cells in rhesus macaques. Furthermore, it has been demonstrated that administration of anti-$\alpha4\beta7$ mAb in SIV-infected rhesus macaques receiving cART suppresses plasma viremia for extended periods following discontinuation of cART, collectively suggesting that sustained virologic remission in the absence of cART may be achieved via direct targeting of $\alpha4\beta7$ integrin. It is well established that the vast majority of HIV-infected individuals treated with cART experience plasma viral rebound within weeks of cessation of therapy. Considering that current research on the treatment of HIV-infected individuals has been heavily focused on developing strategies aimed at achieving sustained virologic remission in the absence of cART, it is of great interest to investigate whether administration of anti-$\alpha4\beta7$ mAb can prevent plasma viral rebound and allow durable suppression of viral replication in HIV-infected individuals after discontinuation of cART. We propose to examine the effect of vedolizumab, an FDA-approved anti-$\alpha4\beta7$ mAb for the treatment of ulcerative colitis and Crohn's disease, on plasma viral rebound in HIV-infected individuals following analytical treatment interruption (ATI).

1 Background Information and Scientific Rationale

1.1 Background Information

Prolonged suppression of plasma viremia is now achievable in the majority of HIV-infected individuals receiving cART[1]. Complete eradication of virus, however, has not been possible with cART alone due to the persistence of viral reservoirs in a variety of tissues [2-5]. Previous studies have demonstrated that HIV persists in latently infected, $CD4^+$ T cells in the peripheral blood of virtually all infected individuals receiving clinically effective cART [6-8]. In addition, recent studies suggest that low levels of HIV replication may persist even in the absence of detectable viremia[5,9,10]. As plasma viremia appears to rebound in nearly all HIV-infected individuals upon cessation of cART regardless of duration and timing of therapy[11-13], alternative therapeutic strategies aimed at destroying or permanently suppressing persistently infected cells are needed to potentially eradicate HIV [14].

Despite the success of cART in suppressing plasma viremia and HIV replication, the burden of taking daily medication for life, long-term toxicity of cART regimens, and potential resistance to antiretroviral drugs, necessitates a continued search for effective alternatives for the control of HIV infection. Consequently, a major thrust of HIV research over the past several years has been to develop therapeutic strategies that target the persistent HIV reservoir and could induce a sustained virologic remission in infected individuals in the absence of cART. To this end, numerous attempts have been made to purge the persistent HIV reservoir in infected individuals receiving cART. These include the use of non-specific immune-activating agents, such as IL-2 [15] and an anti-CD3 antibody [16], as well as histone deacetylase inhibitors, such as valproic acid and vorinostat [17,18]. However, these reagents neither prevented plasma viral rebound following cessation of cART nor decreased the size of the persistent viral reservoir in HIV-infected individuals.

Other therapeutic strategies aimed at achieving eradication are under investigation. These include genetic manipulation of $CD4^+$ T cells [19] and stem-cell transplantation [20]. While it appears that eradication of HIV was achieved in one individual who underwent multiple rounds of chemotherapy and stem cell transplantation [20], this approach is currently impractical and unlikely to be safely applied to a substantial proportion of the HIV-infected population.

In recent years, research directed at the development of an effective HIV vaccine has provided insights into the nature of the immune response to HIV infection[21,22]. Antibody cloning technologies and B cell biology have led to the discovery of several highly potent and broadly neutralizing mAbs against HIV produced by B cells of some HIV-infected individuals [23-25]. Several studies have demonstrated that certain broadly neutralizing HIV-specific mAbs can prevent acquisition of the virus, suppress viral replication, prevent plasma viral rebound following treatment interruption in infected animals [26-28], and block cell-to-cell transmission of laboratory-adapted HIV in vitro [29]. However, durable suppression of virus has yet to be achieved via these modalities.

As mechanisms for viral entry are discovered, alternative methods of viral suppression may emerge. Recent investigations have revealed a potential access point via

engagement of the cell surface integrin $\alpha 4\beta 7$ by HIV gp120 on $CD4^+$ T cells[30,31]. The $\alpha 4\beta 7$ integrin is expressed on the surface of a discrete subset of T-lymphocytes that facilitates preferential migration into the gastrointestinal tract. Integrin $\alpha 4\beta 7$ mediates homing of T lymphocytes to the gut by binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), an adhesion molecule preferentially expressed on venules in gut associated lymphoid tissue (GALT).

In addition to preferentially migrating to GALT, $\alpha 4\beta 7^{high}$ $CD4^+$ T are highly susceptible to productive HIV infection *in vitro.* Furthermore, it has been shown that α4β7 integrin on $CD4^+$ T cells binds HIV gp120 leading to rapid activation of LFA-1, the integrin involved in the establishment of virologic synapses [30,31]. Thus, $\alpha 4\beta 7^{high}$ $CD4^+$ T cells are in a prime position to disseminate HIV between GALT and the periphery. Based on these observations, the efficacy of $\alpha 4\beta 7$-mAb therapy in preventing transmission was evaluated in a nonhuman primate model [32]. Initial results revealed that administration anti-$\alpha 4\beta 7$ mAb prior to and during acute infection protected rhesus macaques from transmission after repeated low-dose intravaginal challenges with SIVmac251. In the treated animals that became infected, GALT was protected from infection and $CD4^+$ T cells were maintained in both the periphery and GALT[32]. These results suggest that antibodies directed against $\alpha 4\beta 7$ might have potential as an immune-based therapy for HIV.

1.1.1 Description of the Study Agent

Vedolizumab is a humanized monoclonal antibody that specifically binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with MAdCAM-1, which in turn inhibits the migration of T-lymphocytes across the endothelium into GALT. Vedolizumab does not bind to or inhibit function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with vascular cell adhesion molecule-1 (VCAM-1).

Consistent with its specificity for α4β7, IV administration of vedolizumab did not elevate neutrophils, basophils, eosinophils, B helper and cytotoxic T lymphocytes, total memory T helper lymphocytes, monocytes or NK cells in the peripheral blood of healthy subjects or subjects with UC or CD (Vedolizumab Investigators Brochure, Dec. 2015). Vedolizumab did not affect immune surveillance and inflammation of the central nervous system (CNS) in experimental autoimmune encephalitis in nonhuman primates, a model of multiple sclerosis[33]. Consistent with these results, vedolizumab IV did not alter the ratio of $CD4^+/CD8^+$ T cells or the number of T cells in the CSF of healthy subjects[34]. Vedolizumab IV did not inhibit the adaptive immune response to intramuscular antigen challenge with hepatitis B vaccine in healthy subjects, but did inhibit an adaptive immune response to oral antigen challenge with killed cholera toxin vaccine[35]. These results support the conclusion that, unlike natalizumab (a duel α4β7 and α4β1 antagonist), vedolizumab selectively inhibits migration of T lymphocytes to the gut and does not inhibit central nervous system or systemic immune responses in humans.

Clinical Pharmacology

The single and multiple dose pharmacokinetics (PK) of vedolizumab IV have been investigated in completed studies in healthy subjects and in subjects with moderately to severely active UC or CD. Similar PK was observed in healthy subjects, as well as in subjects with UC or CD. Vedolizumab clearance depends on both linear and nonlinear

pathways; with linear PK observed at serum concentrations >1 µg/mL to 10 µg/mL. Population PK analyses indicate that the linear clearance was approximately 0.157 L/day, the serum terminal elimination half-life was approximately 25 days at the 300 mg dosage, and the volume of distribution at steady state was approximately 5 L. Vedolizumab was not detected in the CSF of 14 healthy subjects at 5 weeks after a single intravenous (IV) administration of 450 mg vedolizumab (1.5 times the recommended dosage).

Clinical Pharmacodynamics

Two pharmacodynamic markers (Act-1 and MAdCAM-1-Fc) were independently evaluated to assess the presence of $\alpha4\beta7$ integrin binding sites on cell surfaces and to determine the number of free $\alpha4\beta7$ receptor sites by vedolizumab. Vedolizumab inhibition of Act-1 and MAdCAM-1-Fc binding to the $\alpha4\beta7$ receptor indicated the extent of $\alpha4\beta7$ receptor saturation by vedolizumab[36].
Dose-dependent duration of $\alpha4\beta7$ receptor saturation was consistently observed following both single and multiple dosing in phase 1 studies. Rapid and near complete $\alpha4\beta7$ receptor saturation was achieved following dosing and the time to loss of $\alpha4\beta7$ receptor saturation was dose dependent. The serum concentrations of vedolizumab following 300 mg dosing every 4-8 weeks are expected to maintain >90% α4□7 receptor binding saturation over the dosing interval in >90% of subjects[36,37].

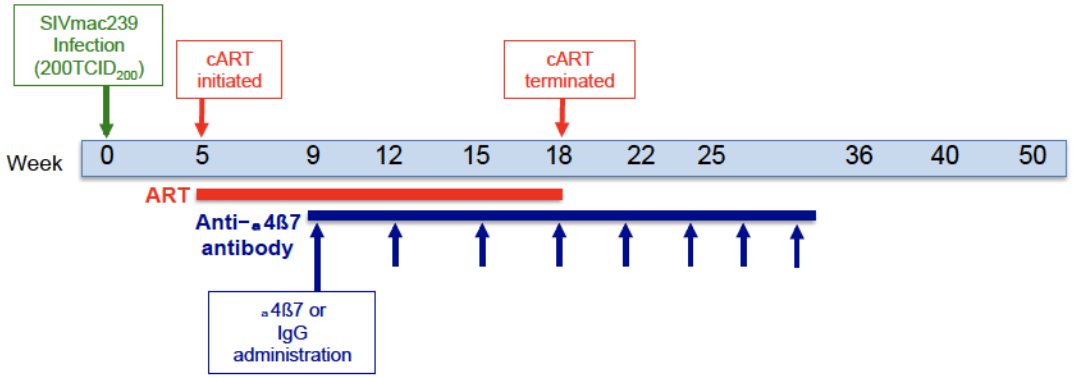
1.1.2 Summary of Pre-Clinical Nonhuman Primate Studies

Based on the results of the nonhuman primate studies demonstrating efficacy of anti-$\alpha4\beta7$ mAb in preventing SIV infection (see Section 1.1), a follow-up study was designed to investigate the potential therapeutic effects of anti-$\alpha4\beta7$ mAb in SIV infected macaques (A. Ansari unpublished data). The anti-$\alpha4\beta7$ mAb used in these studies contains the same antigen binding region as vedolizumab fused to a rhesus IgG1 Fc region[38]. In this study, 10 rhesus macaques were infected with SIVmac239 intravenously. When the animals reached steady state viremia, they were initiated on cART. Once viral levels were suppressed on cART, the monkeys were divided into two groups; the control group received 50 mg/kg IV of normal rhesus IgG, while group 2 received 50 mg/kg IV of anti-$\alpha4\beta7$ mAb. Infusions were administered every three weeks for a total of 8 infusions. After four infusions, cART was stopped in order to determine the effect of anti-$\alpha4\beta7$ mAb alone on the expected rebound of plasma viremia (Figure 1.1.2-1).

As expected, all five animals in the IgG control group experienced a rebound of viremia within 2 weeks of stopping cART. In contrast, 4/5 monkeys in the anti-$\alpha4\beta7$ mAb group exhibited intermittent or continued suppression of plasma viremia (Figure 1.1.2-1). In these animals, suppression of plasma viremia persisted, in the absence of cART through week 45 (12 weeks after the last anti-$\alpha4\beta7$ mAb). The single animal in the anti-$\alpha4\beta7$ mAb group (RNo13) that exhibited rebound viremia was shown to have developed antibodies against the $\alpha4\beta7$ mAb that became detectable after the third infusion.

A second study was designed in the same manner with the addition of 8 animals, 2 of which were added to the IgG control group and 6 of which received anti-α4β7 mAb.

Figure 1.1.2-1. Nonhuman Primate Trial Design



Both of the control monkeys experienced viral rebound within 2 weeks of stopping cART. Two of the monkeys in the treatment group developed antibodies against the α4β7 mAb and exhibited rebound viremia similar to the control animals (Figure 1.1.2-3). Of the remaining 5 animals in the treatment group, 2 showed sustained suppression of plasma viremia out to study week 40 (8 weeks after the last anti-α4β7 mAb infusion). The other 3 animals showed intermittent levels of plasma viremia.

Figure 1.1.2-2. SIV Plasma Viremia in α4β7 mAb Treated Animals-Trial 1

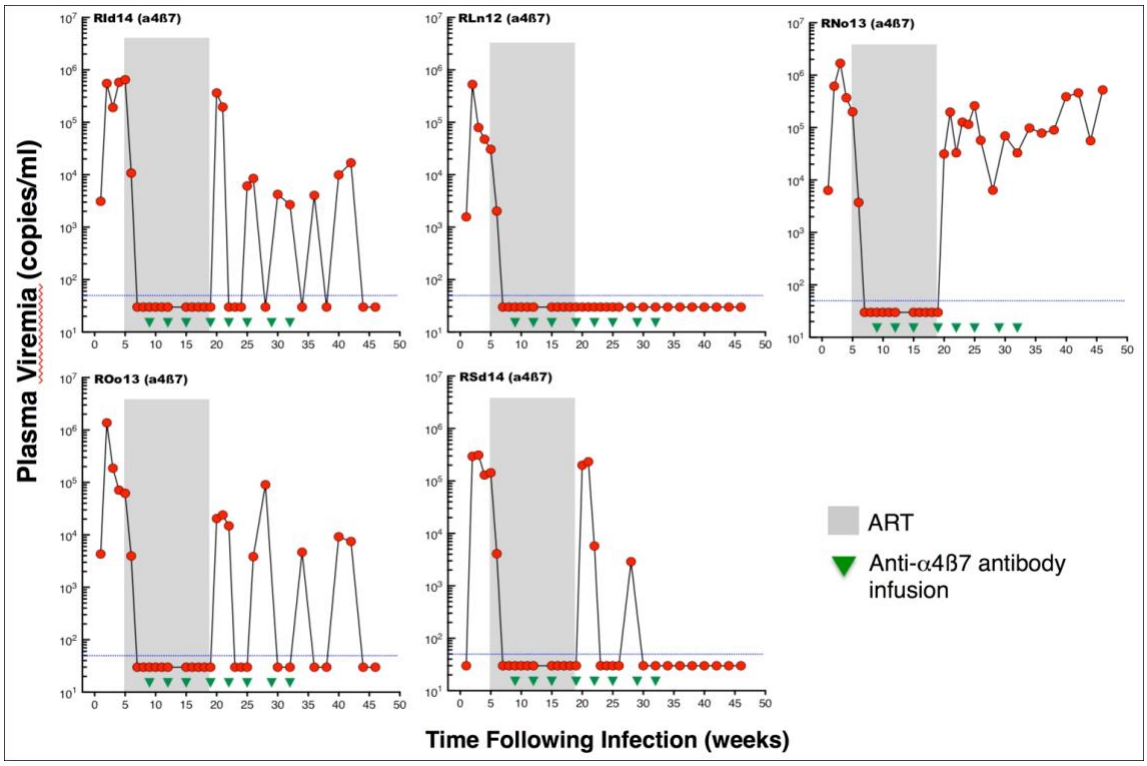
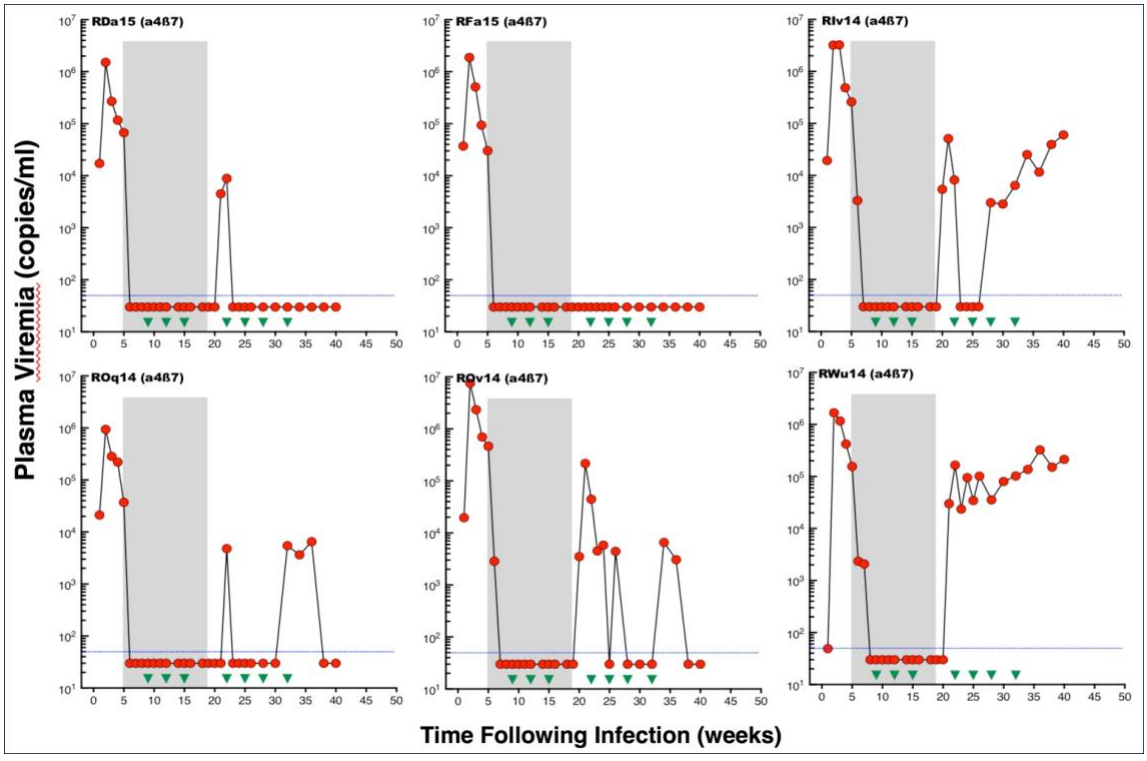


Figure 1.1.2-3. SIV Plasma Viremia in α4β7 mAb Treated Animals-Trial 2



1.1.3 Summary of Relevant Clinical Studies

Vedolizumab (ENTYVIO) is approved by the FDA for treatment of adult patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD) who have had an inadequate response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. The FDA approval was based largely on the results of 2 two integrated randomized controlled studies in UC[39] and 2 integrated randomized controlled studies in CD[40]. In these studies, the dose of vedolizumab was 300 mg IV.

Ulcerative Colitis (UC)
In a randomized, multicenter trial, 374 patients with active UC were assigned to vedolizumab or placebo for the induction of remission[39]. A significantly greater proportion of vedolizumab-treated patients achieved clinical response, remission, and mucosal healing at six weeks compared with placebo. In a trial of vedolizumab for the maintenance of remission, 373 patients with a clinical response to vedolizumab at six weeks, in either the induction trial or following open label treatment, were assigned to continue to receive vedolizumab every eight weeks, four weeks, or switch to placebo for up to 52 weeks. At week 52, remission rates were significantly higher in patients who received vedolizumab compared with placebo.

Crohn's Disease (CD)
A randomized trial enrolling 368 patients with moderately to severely active CD who had failed at least one conventional therapy were assigned to vedolizumab or placebo for induction therapy[40]. At week 6, rates of clinical remission were significantly higher in patients treated with vedolizumab as compared with placebo (14 versus 7 percent). This same trial also looked at the ability of vedolizumab to maintain remission. A total 461 patients who had had a prior clinical response to vedolizumab were randomly assigned to receive placebo or vedolizumab every 8 or 4 weeks until week 52. Subjects randomized to vedolizumab for maintenance therapy were more likely to be in remission at week 52.

Summary of Adverse Events in Inflammatory Bowel disease Trials
The data described in Table 1.1.3-1 reflect exposure to vedolizumab in patients participating in the four Phase 3 trials[39,40]. In these trials, 1,434 patients received vedolizumab 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had UC and 962 patients had CD. Patients were exposed for a mean duration of 259 days (UC) and 247 days (CD). In these studies, concomitant treatment with stable doses of prednisone and/or immunosuppressive agents were allowed. Adverse reactions were reported in 52% of patients treated with vedolizumab and 45% of patients treated with placebo. Serious adverse reactions were reported in 7% of patients treated with vedolizumab compared to 4% of patients treated with placebo.

The most common adverse reactions were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (Table 1.1.3-1).

Table 1.1.3-1. Adverse Reactions in ≥ 3% of Vedolizumab-treated Patients and ≥ 1% Higher than in Placebo

Adverse Reaction	Vedolizumab* (N=1434)	Placebo** (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

* Patients who received vedolizumab for up to 52 weeks
** Patients who received placebo for up to 52 weeks

Laboratory Abnormalities
No clinically important treatment group differences in patients with markedly abnormal values in laboratory tests (hematology, chemistry, or coagulation) were observed in any of the phase 3 studies.

Infusion-Related Reactions
Serious infusion-related reactions following vedolizumab administration have been reported in clinical trials. In the UC and CD phase III trials described above, a single case of anaphylaxis (1/1434 subjects-0.07%) was reported in a patient with CD following the second infusion of vedolizumab. In these same trials, other infusion-related reactions were reported in 4% of patients treated with vedolizumab and 3% of patients treated with placebo. The most common reactions were nausea, headache, pruritus, dizziness, fatigue, pyrexia, urticaria, and vomiting. These reactions generally occurred during the infusion, and resolved either with no treatment or following administration of antihistamine and/or hydrocortisone. Less than 1% of patients treated with vedolizumab developed infusion reactions assessed by the investigator as being severe.

Infections
In the Phase III UC and CD Trials, the rate of infections was 0.85 per patient-year in the patients treated with vedolizumab and 0.7 per patient-year in the patients treated with placebo. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued vedolizumab due to infections.

The rate of serious infections was 0.07 per patient-year in patients treated with vedolizumab and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in CD patients than UC patients, and anal abscesses were the most frequently reported serious infection in CD patients. Over 48 months, there was no increase in the rate of serious infections. Sepsis was reported in 4 of 1434 (0.3%) of patients treated with vedolizumab compared with 2 of 297 (0.7%). patients treated with placebo.

In controlled- and open-label long-term extension trials in adults treated with vedolizumab, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegalovirus colitis. No cases of PML were reported.

Liver Injury
In the UC and CD phase III trials there were reports of elevations in hepatic transaminases and/or bilirubin. Three patients in the UC and CD trials reported SAE related to hepatitis. Based on case report information, it is unclear if these SAE were related to concomitant medications (e.g. 6-mercaptopurine) or autoimmune processes (sclerosing cholangitis). All patients recovered. In controlled trials, ALT/AST elevations ≥3 X upper limit of normal were seen in <2% of patients in both the placebo and vedolizumab groups.

Immunogenicity
In the completed 52-week controlled studies in subjects with UC or CD, vedolizumab IV showed an immunogenicity rate of 4%; 56 of 1434 subjects who received continuous treatment with vedolizumab IV tested positive for anti-vedolizumab antibodies at any time during treatment. Nine of these 56 subjects were persistently positive (positive at ≥2 study visits) and 33 subjects developed neutralizing antibodies. As with all therapeutic proteins, there is potential for immunogenicity. In UC Trials I and II and CD Trials I and III, in patients who received vedolizumab, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose).

Overall, there was no apparent correlation of anti-vedolizumab antibodies, clinical response, or treatment related AE. However, the number of subjects who developed antibodies was too limited to make a definitive assessment.

Post Marketing Experience
Based on drug shipment data as of 19 May 2015, the post marketing patient exposure to vedolizumab IV globally is estimated to be approximately 11,943 patient-years.
The post marketing safety profile of vedolizumab IV is consistent with what was seen in the clinical studies and no new safety signals have been identified (vedolizumab Investigators Brochure, Dec. 2015).

1.2 Rationale

Vedolizumab as a Potential Treatment for HIV Infection

The results in the nonhuman primate SIV study described in Section 1.1.2, suggest that blockade of $\alpha4\beta7$ with vedolizumab in virologically suppressed patients with HIV infection has the potential to induce sustained suppression of viremia after discontinuation of cART and anti-$\alpha4\beta7$ mAb administration. The purpose of this study is to test this hypothesis and evaluate the safety of vedolizumab in an exploratory open label study.

Use of Analytical Treatment Interruption (ATI)

Various assays measuring HIV-specific immune responses and the frequency of $CD4^+$ T cells carrying infectious HIV have been used to assess efficacy of immune-based therapies. To date, none of the assays are clinically validated to predict actual antiviral efficacy. Thus, ATI has been used to evaluate the anti-viral efficacy of immune-based therapies by testing the ability of these interventions to blunt or prevent the viral rebound that occurs following interruption of cART. The use of ATI in the design of this study is the only way to determine if administration of vedolizumab results in clinically significant antiviral activity, as evidenced by a blunted or absent plasma viral rebound following ATI.

2 Study Objectives

2.1 Primary Objective

- To evaluate the safety and tolerability of vedolizumab in HIV-infected individuals prior to and following analytical treatment interruption (ATI)

2.2 Secondary Objective

- To evaluate the effect of vedolizumab administration on plasma viral rebound in HIV-infected individuals following ATI

2.3 Exploratory Objectives

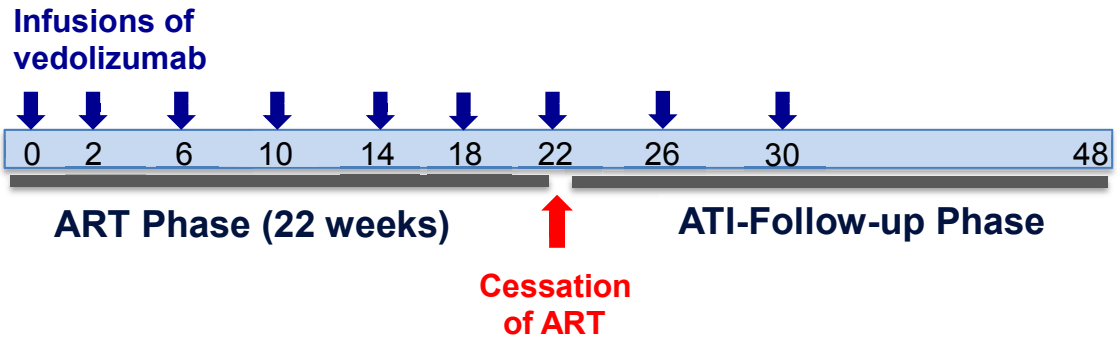
- To determine the effect of vedolizumab on the size of persistent HIV reservoirs
- To examine the impact of vedolizumab on continuing/residual HIV replication prior to discontinuation of cART

3 Study Design

3.1 Description of the Study Design

The proposed trial will be a single arm, open label study to examine the effect of vedolizumab on plasma viral rebound in HIV-infected individuals following an analytical treatment interruption (ATI). Fifteen HIV-infected individuals with suppressed viremia on cART will be studied. All study participants will receive a total of 9 IV infusions of vedolizumab 300 mg (Figure 1.1.3-1).

Figure 1.1.3-1. Study Design



At study week 22, all subjects will discontinue cART and enter the ATI phase of the study. Individuals taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) will switch to a protease inhibitor or an integrase inhibitor-based regimen at least 2 weeks prior to week 22 to ensure that the washout period of antiretroviral agents is roughly equal. HIV plasma viral levels and $CD4^+$ T cell counts will be monitored every 2 weeks during the ATI phase. If a subject meets any of the following criteria between study weeks 22-30, they will discontinue vedolizumab infusions, re-start ART, and enter the follow-up phase. Subjects who meet any of the criteria for restarting cART after week 30, will restart cART and enter the follow-up phase.

Criteria to Restart cART

- A confirmed >30% decline in baseline $CD4^+$ T cell count or an absolute $CD4^+$ T cell count <350 cells/mm^3 in the setting of detectable (>40 copies/ml) HIV viremia.
- A sustained (>4 weeks) HIV RNA level of >1,000 copies/mL
- Any HIV-related symptoms (e.g. acute retroviral syndrome, opportunistic infection) or pregnancy

3.2 Study Endpoints

3.2.1 Primary Endpoint

The rate of occurrence of grade 2 or higher AEs, including SAEs, which, are probably or definitely related (as defined in Section 11.3.2) to vedolizumab.

3.2.2 Secondary Endpoints

Number of subjects who experience rebound of plasma viremia following ATI and meet criteria to restart cART before week 48.

4 Study Population

4.1 Recruitment Plan

Subjects will be recruited from existing cohorts of individuals participating in NIAID protocols 09-I-0030 and 02-I-0202 who meet the Inclusion/Exclusion Criteria. Additional local and regional recruitment will be done using direct mailing to infectious disease physicians, internet ad campaigns, social media outlets, print ads, and from local clinics via the NIAID patient recruitment contract with Matthews Media Group.

4.2 Subject Inclusion Criteria

1. Age, 18-65 years
2. Documented HIV-1 infection and clinically stable
3. In general good health, with an identified primary health care provider for medical management of HIV infection and willing to maintain a relationship with a primary health care provider for medical management of HIV infection while participating in the study
4. $CD4^+$ T cell count >450 cells/mm^3 at screening
5. Documentation of continuous cART treatment with suppression of plasma viral level below the limit of detection for ≥2 years. Subjects with "blips" (i.e., detectable viral levels on cART) prior to screening may be included provided they satisfy the following criteria:
    a. The "blips" are <400 copies/mL, and
    b. Succeeding viral levels return to levels below the limit of detection on subsequent testing
6. Willingness to undergo ATI
7. Laboratory values within pre-defined limits at screening:
    - Absolute neutrophil count >1,000/mm^3
    - Hemoglobin (Hgb) levels >10.0 g/dL for men and >9.0 g/dL for women
    - Platelet count >100,000/mm^3
    - Prothrombin time (PT) and partial thromboplastin time (PTT) <1.5 upper limit of normal (ULN)
    - Estimated glomerular filtration rate (eGFR) of ≥50 mL/min as determined by the NIH Clinical Center laboratory
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of <1.1 x ULN. Total bilirubin <1.1 x ULN (unless subject is taking atazanavir or has Gilbert's Syndrome)
8. Willingness to have samples stored for future research

Participation of Women:

Contraception: The effects of vedolizumab on the developing human fetus are unknown. For this reason, men and women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

4.3 Subject Exclusion Criteria

1. Chronic hepatitis B, as evidenced by a positive test for hepatitis B surface antigen (HBsAg), or chronic hepatitis C virus (HCV) infection, as evidenced by a positive test for HCV RNA. Subjects with a positive test for HCV antibody and a negative test for HCV RNA are eligible.
2. Documented nadir $CD4^+$ T cell count <200 cells /mm^3
3. Documented multiclass antiretroviral drug resistance that, in the judgment of the investigator, would pose a risk of virologic failure should additional mutations develop during the study
4. HIV immunotherapy or vaccine(s) received within 1 year prior to screening
5. Any licensed or experimental non-HIV vaccination (e.g., hepatitis B, influenza, pneumococcal polysaccharide) received within 2 weeks prior to study enrollment
6. Receipt of other investigational study agent within 28 days of enrollment
7. Any active malignancy that may require systemic chemotherapy or radiation therapy
8. Systemic immunosuppressive medications received within 3 months prior to enrollment. The following are not excluded: [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; and [3] oral/parenteral corticosteroids administered for non-chronic conditions not expected to recur (length of therapy ≤10 days, with completion in ≥30 days prior to enrollment)
9. History or other clinical evidence of:
    - Significant or unstable cardiac disease (e.g., angina, congestive heart failure, recent myocardial infarction)
    - Severe illness, chronic liver disease, malignancy, immunodeficiency other than HIV, active systemic infection other than HIV, or any other condition that, in the opinion of the investigator, would make the subject unsuitable for the study
    - Active or latent tuberculosis, regardless of treatment history
10. Neurologic or neuropsychiatric disorder, the symptoms of which mimic PML and could interfere with the assessment of safety (e.g. history of encephalitis with motor sequela, stroke with sequela, severe major depressive disorder, severe bipolar disorder, seizure disorder)

11. Active drug or alcohol abuse or any other pattern of behavior that, in the opinion of the investigator, would interfere with adherence to study requirements
12. Pregnancy or breast-feeding

Routine Vaccination Assessment: During screening, subjects' vaccination history will be assessed. If subjects are not up to date on routine vaccinations (as recommended in *DHHS Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*), they will be offered vaccination prior to initiating treatment with vedolizumab.

Co-enrollment Guidelines: Co-enrollment in other trials is restricted, other than enrollment on observational studies. Study staff should be notified of co-enrollment as it will require the approval of the Principal Investigator.

4.4 Justification for Exclusion of Women, Minorities, and Children (Special Populations)

Exclusion of Children:

Because there are insufficient data regarding dosing or adverse events available in adults to judge the potential risk in children, children are excluded from this study.

5 Study Agent/Interventions

5.1 Disposition and Dispensation

Study agent will be distributed via the NIH Central Pharmacy according to standard pharmacy procedures.

5.1.1 Formulation, Packaging and Labeling

Vedolizumab is supplied in sterile 20 mL single-use glass vials, containing 300 mg of vedolizumab as a white to off-white cake. Refrigerate each unopened 300mg single dose vial in an individual carton at 2° to 8□C (36º to 46ºF). Retain in original package to protect from light.

5.2 Study Agent Storage and Stability

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance for the storage device to the PI and the IND Sponsor. The product must be quarantined in a separate area. The IND Sponsor's authorized representative will notify the site pharmacist if continued clinical use of the product is acceptable.

5.3 Preparation, Administration, and Dosage of Study Agent

Reconstitution Instructions

Reconstitute vedolizumab at room temperature. Vedolizumab will be reconstituted and prepared by the NIH Pharmacy using aseptic technique by the following procedure:

1. Remove the flip-off cap from the single-dose vial and wipe with alcohol swab. Reconstitute vedolizumab vial containing lyophilized powder with 4.8 mL of sterile water for injection, using a syringe with a 21 to 25 gauge needle.

2. Insert the syringe needle into the vial through the center of the stopper and direct the stream of sterile water for injection to the glass wall of the vial to avoid excessive foaming.

3. Gently swirl the vial for at least 15 seconds to dissolve the lyophilized powder. Do not vigorously shake or invert.

4. Allow the solution to sit for up to 20 minutes at room temperature to allow for reconstitution and for any foam to settle; the vial can be swirled and inspected for dissolution during this time. If not fully dissolved after 20 minutes, allow another 10 minutes for dissolution. Do not use the vial if the drug product is not dissolved within 30 minutes.

5. Visually inspect the reconstituted vedolizumab solution for particulate matter and discoloration prior to administration. Solution should be clear or opalescent, colorless to light brownish yellow, and free of visible particulates. Do not administer reconstituted solution showing uncharacteristic color or containing particulates.

6. Prior to withdrawing the reconstituted vedolizumab solution from the vial, gently invert vial 3 times.

7. Withdraw 5 mL (300 mg) of reconstituted vedolizumab solution using a syringe using a 21 to 25 gauge needle. Discard any remaining portion of the reconstituted solution in the vial.

Dilution Instructions
Add the 5 mL (300 mg) of reconstituted vedolizumab solution to 250 mL of sterile 0.9% sodium chloride and gently mix the infusion bag. Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Once reconstituted and diluted, use the infusion solution as soon as possible.

Storage
If necessary, the infusion solution may be stored for up to four hours at 2° to 8°C (36º to 46ºF). Do not freeze. Discard any unused portion of the infusion solution.

The dose of vedolizumab for this study is 300 mg in 250 mL normal saline.

The investigational study product solution will be administered by IV infusion over at least 30 minutes using a volumetric pump. The total time needed to administer the dose may be longer than 30 minutes based on factors such as subject tolerance. After the infusion is complete, the IV line will be flushed with 30 ml of normal saline.

For women of childbearing potential, study agent administration may not proceed unless a negative pregnancy test has been obtained within the previous 24 hours. Prior to each administration, temperature, blood pressure, heart rate (pulse) and weight will be recorded. Vital signs (temperature, blood pressure, heart rate) will be measured 15 minutes into the infusion and at the end of the infusion. Following completion of the first infusion, the subject will be monitored for 2 hours before leaving the clinic. For subsequent infusions, the subject will be monitored for 1 hour after completion of the infusion.

5.3.1 Dose Adjustments and Modifications

Should mild-moderate infusion-related symptoms (Grade I-II) develop, they will be managed by temporarily stopping the infusion until symptoms have resolved. For symptoms such as fever, myalgia, or urticaria, symptomatic treatment with standard doses of acetaminophen or antihistamines may be given. Once symptoms have resolved, the infusion will be restarted at half the initial rate. If symptoms recur following a reduced infusion rate and symptomatic treatment, the infusion will again be stopped until symptoms resolved and restarted at a lower rate. If the infusion cannot be completed within a 3-hour time frame because of recurrent symptoms, the infusion will be discontinued for that visit.

5.3.2 Duration of Therapy

The planned total duration of vedolizumab therapy is 30 weeks.

5.4 Concomitant Medications and Procedures

All concomitant prescription medications taken during study participation will be recorded in CRIMSON. 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 in CRIMSON are concomitant prescription medications, over-the-counter medications and non-prescription medications taken at the time of adverse events (all grades).

5.5 Prohibited Medications and Procedures

Treatment with immunosuppressive medications during the study is prohibited. Prohibited immunosuppressive medications do not include [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; or [3] oral/parenteral corticosteroids given for non-chronic conditions not expected to recur.

6 Study Schedule

For all the study visits, unless otherwise specified, subjects will come to the NIH Clinical Center to undergo the procedures. Unless otherwise specified, the visit window for the post-entry study visits is ± 5 days.

6.1 Screening

Screening may occur over the course of several contacts/visits. All inclusion and exclusion criteria must be assessed within 8 weeks before enrollment, unless otherwise specified in the eligibility criteria.

After signing informed consent, subjects will undergo the following procedures:

- Medical history and a physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant.
- Assessment of concomitant medications.
- Blood collection for:
    - Hepatitis B Surface Antibody, HBsAg, Anti-HAV, and Hepatitis C antibody serology
    - QuantiFERON® TB test
    - Complete blood count (CBC) with differential, PT, activated PTT
    - Chemistry panel to include: ALT, AST, alkaline phosphatase, creatinine, total and direct bilirubin, and serum albumin levels
    - Flow cytometry panel (includes $CD4^+$ T cell count)
    - Plasma HIV and HCV viral RNA levels
    - Serum and plasma for storage
- Urinalysis
- Serum or urine pregnancy test (for women of child-bearing potential)
- Electrocardiogram (ECG)

6.2 Enrollment/Baseline

The enrollment visit may take place over 2 visits to accommodate the baseline pretreatment apheresis procedure. The first dose of vedolizumab will be administered at this visit, and enrollment is defined as the day and time of receipt of the first dose of vedolizumab.

Subjects will undergo the following procedures (prior to the first dose of study drug):

- Medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant
- PML checklist (Appendix C)
- Baseline neurologic evaluation by a neurologist –screen for signs and symptoms of PML
- Assessment of concomitant medications
- HIV transmission risk behavior assessment and counseling
- Leukapheresis for research studies
- Blood collection for:

  - Flow cytometry panel (includes $CD4^+$ T cell count)
  - Plasma HIV viral RNA level
  - HLA typing (if not already on file)
  - Storage of plasma, serum and peripheral blood mononuclear cells (PBMCs). Optional collection of PAXgene® Blood RNA Tube for storage.
  - CBC with differential
  - Chemistry panels, to include: ALT, AST, alkaline phosphatase, creatinine, total and direct bilirubin, and serum albumin levels
- Serum or urine pregnancy test (for women of child-bearing potential-obtained within 24 hours prior to infusion)

6.3 Study Phase (Figure 1.1.2-1)

Vedolizumab will be administered on study day 0. Subsequent infusions of vedolizumab (300 mg) will be given at weeks 2, 6, 10, 14, 18, 22, 26, and 30; for a total of 9 infusions. After the final infusion at week 30, all subjects will continue to be seen every 4 weeks until they restart cART. At infusion visits and the monthly visits following week 30, the following will be performed:

- Medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation
- Assessment of concomitant medications
- Assessment of any new or unresolved AEs/intercurrent illnesses
- PML checklist (done prior to infusion at infusion visits only)
- Neurologic examination- screen for signs and symptoms of PML. Any subjects that develop signs or symptoms suggestive of PML will be evaluated by a neurologist. No further vedolizumab doses will be administered until appropriate workup (e.g. MRI) has been done to exclude a diagnosis of PML.
- Blood collection:
  - CBC with differential.
  - Chemistry panels, to include: ALT, AST, alkaline phosphatase, creatinine, total and direct bilirubin, and serum albumin levels.
  - Flow cytometry panel (includes $CD4^+$ T cell count).
  - Plasma HIV viral RNA level
- Serum or urine pregnancy test (for women of child-bearing potential); results must be reviewed prior to infusion
- Storage of plasma, PBMCs, and serum. Optional collection of plasma, serum, and PAXgene® Blood RNA Tube for storage on day 3 (+/- 2 days) and week 1 visits (+/- 3 days). Optional collection of PAXgene® Blood RNA Tube for storage on week 2 and week 6 visits.

- Leukapheresis for research studies will be done within 14 days after the study week 10 and 22 visits (prior to beginning ATI)
- HIV transmission risk behavior assessment and counseling

Analytical Treatment Interruption

Following the study week 22 visit, all subjects will discontinue cART. During the ATI, additional $CD4^+$ T cell count, storage of plasma, and plasma HIV RNA levels will be obtained such that subjects will have these parameters monitored every 2 weeks during the ATI. Genotypic analysis for drug resistance mutations will be performed on all plasma samples with HIV viral levels ≥1,000 copies/ml. For select subjects residing outside the local (Bethesda, MD) area, blood samples for $CD4^+$ T cell counts, and HIV viral levels, may be collected at their local clinics or Quest Diagnostics and sent to the NIH Clinical Center for testing. Samples collected at clinics or at Quest may be labeled with a coded identifier, gender, and date of birth, as required by the local facility.

If a subject develops one or more criteria for ending ATI (see section 3.1) he/she will be asked to return for assessment and confirmation of the laboratory/clinical abnormality. If the criteria for ending ATI are met, no further vedolizumab infusions will be given, and the subject will be instructed to restart cART. He/she will then undergo the schedule of procedures described in Section 6.4. At week 48, any subject who has not met criteria to end the ATI but has detectable viremia (>40 copies/ml) will be instructed to restart cART. All subjects will be followed for 6 months after restarting cART. If a subject does not have detectable (>40 copies/ml) viremia at week 48, they may elect to remain off cART and will be followed until viremia becomes detectable. For such subjects, laboratory studies will be continued per the schedule outlined in Section 6.3 (except for the collection of serum for storage) until viremia is detected; at which time they will be instructed to restart cART and be followed as outlined in Section 6.4.

6.4 Follow-up

Upon restarting cART, subject will enter the follow-up phase of the study. After restarting cART, subjects will be seen every 4 weeks for 24 weeks. At these visits, subjects will undergo the following procedures:

- Medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant
- Assessment of concomitant medications
- Assessment of any new or unresolved AEs or intercurrent illnesses
- Neurological evaluation screen for signs and symptoms of PML. Any subjects that develop signs or symptoms suggestive of PML will be evaluated by a neurologist and undergo brain MRI and other workup as clinically indicated.
- Blood collection for:
    - CBC with differential

- Chemistry panels, to include: ALT, AST, alkaline phosphatase, creatinine, total and direct bilirubin, and serum albumin levels
- Flow cytometry panel (includes $CD4^+$ T cell count)
- Plasma HIV viral load
- HIV genotype (performed on all samples with viral levels ≥1,000 copies/ml)
- Storage of plasma and PBMCs

Management of cART during the follow-up period will be according to standard guidelines (http://aidsinfo.nih.gov/guidelines)

7 Study Evaluations

7.1 Clinical Evaluations

- Medical history and physical examination
- Phlebotomy: Blood will be collected for routine serologic, hematologic, and clinical chemistry evaluations as described in Section 6

7.2 Laboratory Evaluations

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

- HIV viral RNA levels
- Flow cytometry with $CD4^+$ T cell count
- Serum for levels of vedolizumab and antibody to vedolizumab

Leukapheresis: Leukapheresis will be performed for research studies including, but not limited to, measurements of the frequency of $CD4^+$ T cells carrying replication-competent HIV by quantitative co-culture assays. These studies will address the exploratory endpoints. If leukapheresis cannot be performed for technical reasons (e.g. poor venous access), 80 ml of blood will be drawn instead.
Other research evaluations measuring the effect of vedolizumab on the HIV pathogenesis may include:

- Frequency of $CD4^+$ T cells carrying HIV pro-viral DNA and cell-associated HIV RNA
- Frequency of HIV-specific $CD4^+$ and $CD8^+$ T cells
- T-cell activation and soluble markers of inflammation

- Residual (1-40 copies/mL) plasma viremia
- Gene expression profiling of T cells
- Immunophenotypic profiling of PBMCs

8 Potential Risks and Benefits

8.1 Potential Risks

Vedolizumab
The identified and potential risks of vedolizumab IV treatment listed in this section have been assessed during the course of controlled and open label clinical studies.

Identified Risks

Infusion-Related Reactions
In the completed 52-week controlled studies in subjects with UC or CD, 4% of vedolizumab treated subjects and 3% of placebo-treated subjects experienced infusion-related reactions as defined by the investigator[39,40]. The majority of reactions were mild or moderate in intensity and <1% resulted in discontinuation of study treatment. Observed infusion-related reactions generally resolved with no or minimal intervention following the infusion. Most reactions were not serious and occurred during the infusion or within the first hour after infusion was completed.

Upper Respiratory Tract Infections
Nasopharyngitis and upper respiratory tract infections are some of the most common infectious treatment emergent AE seen across the clinical studies of vedolizumab. In the Phase III studies[39,40], there was an overall rate of upper respiratory tract infection of 24% in vedolizumab-treated subjects compared with 17% in the placebo-treated subjects (see Section 1.1.3). The most commonly reported diagnosis included nasopharyngitis, upper respiratory tract infection, pharyngitis, and sinusitis.

Potential Risks of Vedolizumab Treatment

Serious Infections, Including Opportunistic Infections
In the completed 52-week controlled studies in subjects with UC or CD, the rate of infections was 0.85 per patient-year in vedolizumab-treated subjects and 0.70 per patient-year in placebo treated subjects. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most subjects continued on vedolizumab after the infection resolved. In the completed 52-week controlled studies[39,40], the rate of serious infections was 0.07 per patient year in vedolizumab-treated subjects and 0.06 per patient-year in placebo-treated subjects. Over time, there was no significant increase in the rate of serious infections.

In controlled and open-label studies in adults treated with vedolizumab, serious

infections have been reported, which include tuberculosis, sepsis, salmonella sepsis, Listeria meningitis, and cytomegaloviral colitis.

Natalizumab, another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the CNS[41]. PML is caused by the John Cunningham virus (JCV) and typically only occurs in patients who are immunocompromised. Natalizumab is a pan-α4 integrin antagonist that binds to both the α4β1 and α4β7 integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1[42]. In contrast, vedolizumab binds to the α4β7 integrin only and inhibits adhesion to MAdCAM-1, but not VCAM-1[43]. Although no cases of PML have been reported in clinical studies or post-marketing experience with vedolizumab to date (over 11,943 patient-years), a risk of PML cannot be ruled out.

Analytical treatment interruption

The risks from an ATI, performed under close virologic and immunological monitoring are minimal in this subject population. There is a theoretical risk that ATI could lead to the development of HIV drug resistance. This may be a particular concern for individuals taking NNRTIs. However, this potential risk with NNRTIs is essentially eliminated by undertaking the procedures described in Section 3.1[44]. Given the study population, the frequency of immunological and virologic monitoring, and strict criteria for restarting cART, it is extremely unlikely that the ATI will lead to the development of any opportunistic infections or AIDS-defining conditions.

During the ATI phase, subjects may transmit HIV infection if they do not adhere to safe sex practices.

Phlebotomy/Insertion of IV Catheter
This may be associated with discomfort, bruising, local hematoma formation and, on rare occasions, infections, lightheadedness, and fainting.

The amount of blood drawn for research purposes will be within the limits allowed for adult subjects by the NIH Clinical Center (CC) (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

HLA typing
Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic disorders, or a faster progression to AIDS. HLA typing will be performed on samples collected from all the enrolled subjects. Results from the HLA typing will become part of each subject's medical record at the NIH. Medical records containing this information are maintained in a secure place.

8.2 Potential Benefits

The possibility of vedolizumab-induced sustained control of HIV viremia in the absence of daily cART is a potential benefit from study participation. In addition,

others may benefit from knowledge gained in this study that may aid in the development better HIV treatments.

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

- **Intended Use:** Stored blood samples and data collected under this protocol may be used to study the effect of vedolizumab on the virologic and immunologic parameters listed in Section 7.2.1. Samples may be used to study other aspects of the immunopathogenesis of HIV infection or measure serum levels of vedolizumab and antiretroviral agents. Coded samples and demographic data will be sent to Takeda-Millennium Pharmaceuticals and its vendor, QPS for PK and immunogenicity studies.
- **Storage:** Access to stored samples will be limited using a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Samples will be tracked utilizing the NCI at Frederick Central Repository. Data will be stored and maintained in the NIAID CRIMSON database.
- **Disposition at the Completion of the Protocol:** At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.
- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**
    - Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of Protocol Deviation and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIAID IRB.
    - Subjects may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH *(If applicable).*

10 Remuneration Plan for Subjects

Eligible subjects will be compensated for travel according to the NIAID/NIH travel policy. Subjects will receive financial compensation for time and inconvenience according to the NIH CC volunteer guidelines: screening ($50), 2-pass leukapheresis ($200 for a procedure; $50 for unsuccessful apheresis attempts), research blood draw ($40), clinic visits ($30), vedolizumab infusion ($80). If subject does not qualify or declines leukapheresis, an additional 80 mL research blood will be drawn and subject may be compensated an additional $25 for inconvenience.

11 Assessment of Safety

11.1 Documenting, Recording, and Reporting Adverse Events

At designated visits with the subject, information regarding AEs will be elicited by appropriate questioning and examinations, and it will be:

- Immediately documented in the electronic database and medical record.
- Reported as outlined below (e.g., IND sponsor, IRB, Food and Drug Administration [FDA]).

11.2 Definitions

Adverse event (AE)

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse reaction (AR)

An adverse reaction (AR) is an AE that is caused by an investigational agent (drug or biologic).

Suspected adverse reaction (SAR)

A suspected AR (SAR) is an AE for which there is a reasonable possibility that the investigational agent caused the AE. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about the causality than an AR, which implies a high degree of certainty.

Serious adverse event (SAE)

An SAE is an AE that results in one or more of the following outcomes:

- Death
- A life-threatening (i.e., an immediate threat to life) event
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A medically important event*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected adverse event

An AE is unexpected if it is not listed in the investigator's brochure or package insert (for marketed products), or it is not listed at the specificity or severity that has been observed. It is the responsibility of the IND sponsor to make this determination.

Serious and unexpected suspected adverse reaction
A serious and unexpected suspected AR (SUSAR) is a SAR that is both serious and unexpected.

Unanticipated problem
An unanticipated problem (UP) is an event, incident, experience, or outcome that is—

1. Unexpected in terms of nature, severity, or frequency in relation to—
   a. The research risks that are described in the IRB-approved research protocol and informed consent document; investigator's brochure, or other study documents; and
   b. The characteristics of the subject population being studied; and
2. Related or possibly to participation in the research; and
3. Suggests the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (per the IND sponsor, an AE with a serious outcome will be considered increased risk).

Unanticipated problem that is not an adverse event
An unanticipated problem that is not an AE is an incident, experience, or outcome that is not associated with an AE, which meets the 3 criteria of a UP. Examples include breaches of confidentiality, accidental destruction of study records, and unaccounted-for study drug.

Protocol Deviation
Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

- Those that occur because a member of the research team deviates from the protocol
- Those that are identified before they occur, but cannot be prevented
- Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: Non-compliance that
   a. Increases risks, or causes harm, to participants
   b. Decreases potential benefits to participants
   c. Compromises the integrity of the NIH-HRPP
   d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

Protocol specified events
Protocol specified events are AEs specified in the protocol that the principal investigator, IND sponsor, or medical monitor would like to review in real time rather than weeks or months later, when they would otherwise appear in various line listings. These events may or may not also be SAEs.

11.3 Investigator Assessment of Adverse Events

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

All AEs occurring from the time when the first infusion is administered through the specified study follow-up period will be documented, recorded, and reported. The principal investigator will evaluate all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

11.3.1 Severity

The principal 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 2.0, November, 2014, which can be found at http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf

11.3.2 Causality

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

Definitely related
- Reasonable temporal relationship
- Follows a known response pattern
- Clear evidence to suggest a causal relationship
- There is no alternative etiology

Probably related
- Reasonable temporal relationship
- Follows a suspected response pattern (based on similar agents)
- No evidence of a more likely alternative etiology

Possibly related
- Reasonable temporal relationship
- Little evidence for a more likely alternative etiology

Unlikely related
- Does not have a reasonable temporal relationship
  OR
- Good evidence for a more likely alternative etiology

Not related

- Does not have a temporal relationship
  OR
- Definitely due to an alternative etiology

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

11.4 Investigator Reporting Responsibilities to the Sponsor

11.4.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND sponsor per the Safety Review and Communications Plan (SRCP – see below), or as needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

11.4.2 Serious Adverse Events

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

Sponsor clinical safety office contact information:
OCRPRO Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

11.4.3 Unanticipated Problems

Non-serious AEs that are UPs must also be reported on the SAE/UP report form and sent to the CSO by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the sponsor CSO.

11.4.4 Protocol Specified Events

Opportunistic infections are AEs of special interest. These protocol specified events must be reported to the CSO on a SAE/UP report form within 3 business days of site awareness.

11.4.5 Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information for all pregnancies, including pregnancies disclosed by the subject as occurring in a partner of a male subject, will be reported to the CSO via fax or e-mail within 3 business days from the site awareness of the pregnancy.

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site awareness on a protocol-specified form. In the event of pregnancy, the following steps will be taken:

- Discontinuation of the study agents
- Withdraw from the study but continue following for safety
- Report to Medical Monitor and the IRB
- Advise research subject to notify the obstetrician of study agent exposure

11.5 Investigator Reporting Responsibilities to the NIAID IRB

11.5.1 Expedited Reporting to the NIAID IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. SAEs that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator awareness, regardless of expectedness.

12.5.1.1. Waiver of Reporting Anticipated Protocol Deviations, Expected UP nonAEs and Deaths to the NIAID IRB

Anticipated deviations in the conduct of the protocol will not be subject to expedited reporting to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in HIV(+) population. 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.

11.5.2 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of continuing review:

- Serious and non-serious unanticipated problems
- Expected serious adverse events that are possibly, probably, or definitely related to the research
- Serious adverse events that are not related to the research
- All adverse events, except expected AEs and deaths granted a waiver of reporting

- Serious and Non-Serious Protocol deviations. 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
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

11.6 Follow-up of Adverse Events and Serious Adverse Events

AEs that occur following enrollment of subjects (i.e., after the first dose of vedolizumab) are followed until the final outcome is known or until the end of the study follow-up period.

SAEs that that are assessed by the investigator to be possibly, probably, or definitely related to vedolizumab and that have not resolved by the end of the follow-up period will be followed until the final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g. the subject is lost to follow up), the reason a final outcome could not be obtained will be recorded by the investigator on the SAE/UP report form.

SAEs that occur after study completion that are reported to and are assessed by the investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

11.7 Sponsor's Reporting Responsibilities

SUSARs as defined in 21 Code of Federal Regulations (CFR) 312.32 and determined by the IND sponsor will be reported to the FDA and all participating investigators as IND safety reports.

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

11.8 Halting Criteria for the Protocol

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

The halting criteria (as determined by the study PI and IND sponsor secondary to aggregate data review) for this study include:

- Any SAE or grade 4 AE that is possibly, probably, definitely related to the study agent; OR
- Any safety issue that the study principal investigator or IND sponsor determines should halt the study.
- Pre-defined futility criteria for virologic failure are met (see Section 13).

Any related AE that is ≥ grade 3 (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, chills) will be reviewed within 48 hours of site awareness, by the PI and IND sponsor medical monitor,

to consider the need for halting the protocol.

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

11.8.1 Reporting of Study Halting

If a halting rule is met, a description of the adverse event(s) or safety issue must be reported by the PI, within one business day, to the CSO and to the IRB by fax or email. The sponsor will notify the FDA as soon as possible that the study has been halted.

11.8.2 Resumption of a Halted Study

The IND Sponsor, in collaboration with the PI will determine if it is safe to resume the study. The PI will notify the IRB of the decision on resumption of the study. The sponsor will notify the FDA as soon as possible that the study has been resumed after a halt.

11.9 Pausing Criteria for a Subject

The decision to suspend administration of the study agent for a single subject requires discontinuation of the study agent administrated for the study subject until a decision is made whether or not to continue study agent administration.

The pausing criteria for a single subject in this study include:

- A subject experiences an SAE or grade 3 or greater AE (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, chills, or total bilirubin in subjects taking atazanavir) that is (as determined by the IND sponsor) possibly, probably, or definitely related to the study agent;

OR

- Any safety issue that the PI determines should pause administration of the study agent to a single subject.

The CSO, in collaboration with the PI, may also pause for an individual subject or the entire group if a safety concern is identified during routine aggregate data analysis.

11.9.1 Reporting of Pause

If a pausing requirement is met, a description of the AE(s) or safety issue must be reported by the PI by fax or e-mail within 1 business day to the sponsor CSO, principal investigator, IRB, and the Medical Monitor. The sponsor will notify the FDA as soon as possible that the study agent has been halted for an individual subject.

11.9.2 Resumption of Pausing for a Subject or Group

The CSO in collaboration with the PI will determine whether or not it is safe to resume administration of the study agent to the subject. The principal investigator will notify the IRB of the decision to resume administration of the study agent prior to resumption. The sponsor will notify the FDA as soon as possible that the study agent has been resumed for an individual subject.

A subject who does not resume study agent will continue to be followed for safety.

11.10 Withdrawal Criteria for an Individual Subject

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

- An individual subject's decision. (The PI will attempt to determine the reason for the subject's decision, and will strongly suggest a follow-up plan to help ensure the subject safely returns to baseline or better, if possible).
- Co-enrollment in a study with an investigational research agent (rare exception granted by the PI).
- Any SAE or grade 4 systemic infusion related symptom(s) or AE that is considered to be related to the study agent.
- Clinically significant type 1 hypersensitivity reaction associated with the study agent. In the event of a type 1 hypersensitivity reaction that is NOT considered to be clinically significant, (e.g., brief, mild, and self-limited skin reaction without other symptoms), the PI may consider possible additional infusions of the study agent with appropriate precautions.
- Any clinical AE, laboratory abnormality, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Subjects will be followed for the duration of the study for indicated safety assessments.
- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- Pregnancy.
- Participant misses more than 2 study infusions.

If possible, all subjects who discontinue the study treatment prematurely will be followed for 6 months for all the study evaluations.

11.11 Replacement for Withdrawn Subjects

Any subject who withdraws from the study, or who discontinues the study agent, prematurely, and whose reasons for withdrawing from the study or discontinuing study agent administration are unrelated to any real or perceived effect of the study agent or their administration, will be replaced.

11.12 Safety Oversight

11.12.1 Safety Review and Communications Plan (SRCP)

A Safety Review and Communications Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the principal investigator and the IND sponsor CSO, which delineates the safety oversight responsibilities of the principal investigator, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

11.12.2 Sponsor Medical Monitor

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

12 Clinical Monitoring Structure

12.1 Site Monitoring Plan

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

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

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

13 Statistical Considerations

The primary safety outcome is the occurrence of grade 2 or higher adverse events. An exact 95% confidence interval for the probability of adverse events will be computed using the Clopper-Pearson method. The primary efficacy outcome is rebound of plasma viremia requiring a restart of cART. An exact 95% confidence interval will be computed for the rebound probability using the Clopper-Pearson method. Changes from baseline in continuous measurements will be analyzed using paired t-tests or, if data are skewed, the Wilcoxon signed rank statistic.

In terms of safety, a sample size of 20 patients provides a 96.1% chance of observing an adverse event of probability 15% or greater. Table 1.1.3-1 shows the chance of observing at least one adverse event of given probability.

Table 13-1. The second row is the probability of observing at least one adverse event of probability given in the first row.

0.025	0.050	0.075	0.100	0.125	0.150
.397	.642	.790	.878	.931	.961

The sample size for this study is 20 subjects with suppressed HIV viremia on cART. In the absence of a therapeutic intervention, it is expected that 100% of such subjects would experience a rebound in plasma HIV viremia; with a median time to rebound of 2-4 weeks[11-13]. Based on the pre-clinical primate studies described above, we would expect treatment with vedolizumab to significantly reduce the rate of viral rebound after discontinuation of cART. Table 13-2 shows the confidence interval for the probability of rebound for a sample size of 15 subjects. Row 1 is the number of rebounds out of 15, and row 2 is the confidence interval.

Table 13-2. The second row gives exact 95% confidence intervals for rebound probability given the observed number of rebounders in row 1 among the 20 patients.

0	2	4	6	8	10	12	14	16	18	20
.000-.168	.012-.317	.057-.437	.119-.543	.191-.640	.272-.728	.360-809	.457-.881	.563-.943	.683-.988	.832-1.00

For example, if there are 6 rebounds, we can be quite confident that the true rebound probability is between .119 and .543.

Futility guidelines are based on the numbers of patients meeting virologic criteria to restart cART prior to study week 30. We use Bayesian methodology whereby we quantify our prior opinion about the 42 day probability with monoclonal antibodies as roughly equivalent to having observed 4 people, 2 of whom meet virologic criteria to restart cART by 30 weeks. This translates to a beta (2,2) prior distribution for p, the probability of meeting virologic criteria of failure by 30 weeks. Futility is declared if the posterior probability that p exceeds 0.70, given the observed results, is 90% or greater. The futility boundary is shown in Table 13-3. For example, the boundary is crossed if the first 9 patients rebound by 30 weeks. Likewise, futility can be declared if 12 of the first 13 rebound by 30 weeks, etc.

Table 13-3 Futility is declared if the number of patients rebounding by week 30, among the number tested in row 1, is at least as large as the figure in row 2

9	10	11	12	13	14	15	16	17	18	19	20
9	10	11	12	12	13	14	15	16	16	17	18

The probabilities of crossing this futility boundary are shown in Table 13-4 for different true probabilities.

Table 13-4. Row 2 shows the probability of crossing the futility threshold if the true 30-week rebound probability is as shown in row 1.

.50	.60	.70	.80	.90	.95
.003	.021	.099	.339	.775	.953

For instance, if the true 30-week probability of having plasma viral level >1,000 is 0.50, the probability of crossing the futility boundary is only 0.003. On the other hand, if the true 30-week rebound probability is 0.95, the probability of crossing the futility boundary is 0.953.

14 Ethics/Protection of Human Subjects

14.1 Informed Consent Process

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

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the subjects 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.

14.1.1 Non-English–Speaking Participants

If a non-English speaking participant is unexpectedly eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for

Non-English Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record (CRIMSON), including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

Illiterate English Speaking Participants

As the majority of the patient populations from which the study participants are drawn are literate, written consent will typically be provided. However, this population does have a significant rate of illiteracy, and oral consent will be obtained for illiterate participants as consistent with NIH Medical Administrative Services (MAS) Policy M77-2 without separate IRB approval for each specific use. At Continuing Reviews, the NIAID IRB will be informed of the number of illiterate participants who provided consent verbally.

14.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be stored in a locked area, and all computer entry and networking programs will use coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, FDA, NIAID, OHRP, Takeda, or the sponsor's designee.

15 Data Handling and Record Keeping

15.1 Data Capture and Management

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

15.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. Study records will be maintained by the PI for a minimum of 3 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from NIAID/RCHSPB.

Appendix A: Scientific References

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Appendix B: Schedule of Procedures/Evaluations

	Screening and Baseline			ART Phase												
Study Time Point	Screen	Apheresis	Baseline	Opt. Day 3	Opt. Week 1	Week 2	Week 6	Week 10	Apheresis	Week 14	Week 18	Apheresis	Week 22	Week 24	Week 26	Week 28	Week 30
ASSESSMENTS																	
Consent	X																
Vital Signs	X		X			X	X	X		X	X		X		X		X
H & P	X		X			X	X	X		X	X		X		X		X
HIV Counseling			X			X	X	X		X	X		X		X		X
PML Checklist			X			X	X	X		X	X		X		X		X
Neurologic Exam			X			X	X	X		X	X		X		X		X
MEDICATIONS																	
Last Dose of cART													X				
vedolizumab Infusion			X			X	X	X		X	X		X		X		X
Restart cART														PRN	PRN	PRN	PRN
PROCEDURES																	
EKG	X																
Leukapheresis		X							X			X					
CLINICAL LABS																	
CBC/Diff	X		X			X	X	X		X	X		X		X		X
aPTT/PT	X																
Acute/Hepatic/ /Mineral	X		X			X	X	X		X	X		X		X		X
Urinalysis	X																
Pregnancy*	X	X	X			X	X	X	X	X	X	X	X		X		X
Anti-HBs, Anti-HAV, HBsAg, Anti-HCV, HCV RNA, QuantiFERON	X																
HLA Typing**			X														
RESEARCH LABS																	
HIV-1 RNA	X		X			X	X	X		X	X		X	X	X	X	X
Flow Cytometry***	X		X			X	X	X		X	X		X	X	X	X	X
Serum storage	X		X	X	X		X	X		X	X		X		X		X
Plasma storage	X		X	X	X	X	X	X		X	X		X	X	X	X	X
PBMCs storage			X			X	X	X		X	X		X		X		X
PAXgene RNA TWC (Opt.)			X	X	X	X	X										
Estimated Volume per Visit	61		126	31	31	108	116	113		113	113		113	30	113	30	113

Appendix B continued

	ATI Phase					Follow-up Phase						
Study Time Point	Week 32	Week 34	Week 36	Weeks 38-48	Repeat-End ATI	cART Start	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
ASSESSMENTS												
Consent												
Vital Signs		X					X	X	X	X	X	X
H & P		X			PRN		X	X	X	X	X	X
HIV Counseling		X										
PML Checklist												
Neurological Evaluation		X					X	X	X	X	X	X
MEDICATIONS												
Last Dose of cART												
Vedolizumab Infusion												
Restart cART	PRN	PRN	PRN		PRN	X						
PROCEDURES												
EKG												
Leukapheresis												
CLINICAL LABS												
CBC/Diff		X					X	X	X	X	X	X
aPTT/PT												
Acute/Hepatic/Mineral		X					X	X	X	X	X	X
Urinalysis												
Pregnancy*		X										
Anti-HBs, Anti-HAV, HBsAg, Anti-HCV, HCV RNA												
RESEARCH LABS												
HIV-1 RNA	X	X	X		PRN		X	X	X	X	X	X
Flow Cytometry**	X	X	X		PRN		X	X	X	X	X	X
Serum storage (Opt)			X									
Plasma storage	X	X	X		PRN		X	X	X	X	X	X
PBMCs storage		X	X				X	X	X	X	X	X
Estimated Volume Per Visit	30	113	38		10-PRN		97	97	97	97	97	97

Continue Schedule of Procedures

* for women of childbearing potential
PRN: as needed depending on when subject meets criteria to restart cART
** if not already on file
***includes $CD4^+$ T cell count

Appendix C: PML Checklist

- This checklist will be administered at specified visits as outlined in the schedule of events in the protocol and ad hoc for patient reported symptoms.
- The purpose of this checklist is to identify a definite change in the patient's neurological status from the previous evaluation.
- For all positive subjective findings that are identified, the corresponding objective test must be performed. All positive subjective findings will be recorded as an adverse event.
- Subjects with a definite change in neurological status will be referred to a neurologist for evaluation. Where possible, the proposed objective tests will be used to confirm a change that warrants referral.

Subjective PML Checklist

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Objective Checklist
	Yes	No		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				Test visual fields and ocular motility.
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				Casual observation of speech output for dysarthria or aphasia. Ask subject to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barré maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot and foot and finger tapping. Test symmetric muscle strength.
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				Ask for spontaneous writing sample. Observe finger to nose, heel to shin, and tandem gait.
5. Have you regularly been experiencing difficulty understanding others?				Test subject's ability to follow serial commands (Close your eyes; stick out your tongue, and touch your left finger to your left ear).
6. Have you had persistent problems with your memory or thinking?				Test subject's ability to recall 3 objects over 1 minute with distraction and ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

Objective PML Checklist
To be completed for subjects with positive subjective finding
Perform the objective test(s) that correspond to the subjective checklist finding

Positive Symptom(s)	Applicable Objective Test(s)	Test Result(s)		If test result is abnormal, briefly describe result
		Normal	Abnormal	
1. Difficulty with vision or reading	Test visual fields and ocular motility			
2. Difficulty with speaking	Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.			
3. Weakness in an arm or a leg	Test for pronator drift and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.			
4. Bumping into things or difficulty writing	Ask for spontaneous written sample and observe finger to nose, heel to shin, and tandem gait			
5. Difficulty understanding others	Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)			
6. Problems with memory or thinking	Recall of 3 objects over 1 minute with distraction; ability to follow commands.			
7. Problems with numbness	Test sensation side to side with pinprick.			