Molecular Therapy
Methods & Clinical Development
Protocol

Safety of CD34$^+$ Hematopoietic Stem Cells and CD4$^+$ T Lymphocytes Transduced with LVsh5/C46 in HIV-1 Infected Patients with High-Risk Lymphoma

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Although the risk of developing lymphoma has decreased in the highly active antiretroviral therapy era, this cancer remains the major cause of mortality in HIV-infected patients. Autologous hematopoietic stem cell transplantation (ASCT) outcome does not differ for HIV-infected versus HIV-uninfected patients. We propose to develop a new treatment for HIV-associated high-risk lymphoma based on autologous transplantation of two genetically modified products: CD4$^+$ T lymphocytes and CD34$^+$ hematopoietic stem cells (HSPCs). The cells will be transduced *ex vivo* with the Cal-1 lentiviral vector encoding for both a short hairpin RNA (shRNA) against CCR5 (sh5) and the HIV-1 fusion inhibitor C46. The transduced cells will be resistant to HIV infection by two complementary mechanisms: impaired binding of the virus to the cellular CCR5 co-receptor and decreased fusion of the virus as C46 interacts with gp41 and inhibits HIV infection. This phase I/II pilot study, also entitled GENHIV, will involve two French participating centers: Saint Louis Hospital and Necker Hospital in Paris. We plan to enroll five HIV-1-infected patients presenting with high-risk lymphoma and require a treatment with ASCT. The primary objective of this study is to evaluate the safety, feasibility, and success of engraftment of Cal-1 gene-transduced CD4$^+$ T lymphocytes and CD34$^+$ HSPCs.

It is estimated that 36.7 million individuals are currently infected with HIV (https://www.who.int/hiv/data/en/). HIV/AIDS is a disease that impairs immune function primarily by decreasing CD4$^+$ T lymphocytes. Highly active antiretroviral therapy (HAART) suppresses active viral replication but is not able to eliminate the virus completely due to stable integration of HIV inside the host genome of infected cells and the establishment of a latent reservoir, which is insensitive to HAART. Nevertheless, this latent HIV reservoir is fully capable of refueling viral replication when treatment is stopped, creating a major obstacle toward a cure for HIV.

Lymphoma is the most frequent cancer in men and women infected with HIV and remains a major cause of mortality in HIV-infected patients.[1] The adjusted rate ratios of non-Hodgkin's lymphomas (NHL) for HIV-infected versus HIV-uninfected patients by calendar period

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are as follows: NHL: 34.4 (21.6–54.7) from 1996–1999, 22.6 (16.3–31.2) from 2000–2003, and 11.3 (8.3–15.3) from 2004–2007 ($p < 0.001$). The risk of NHL has fallen from a standardized odd ratio of 497 (450–546) to 93 (83–104) patients per year, but that of HL remains stable at 20 (14–28) compared to 18 (13–24) patients per year.[2] The 1-year survival rate for patients with HIV-associated NHL is 65%, and the long-term survival rate is around 50%. The advent of HAART has changed the characteristics and prognosis of HIV-associated lymphomas.

Autologous hematopoietic stem cell transplantation (ASCT) is an attractive option for salvage therapy. In a study based on around 100 relapsed or resistant HIV-positive lymphomas treated with ASCT, the percentage of complete remission ranges from 48% to 90% and overall survival ranges from 36% to 85% (median follow-up of nearly 3 years).[3] More recently, analysis of the outcome of ASCT in patients with relapsed/refractory HIV-associated lymphoma in a single center in the UK showed that, for 18 patients who received ASCT in addition to salvage therapy, the 2- and 5-year overall survival was 74%. For patients who started with salvage therapy but did not receive ASCT, the same 2- and 5 year overall survival was 15% and 10%, respectively.[4] Along the same line, a multicenter phase 2 clinical trial was carried out by the Blood and Marrow Transplant Clinical Trial Network AIDS Malignancy consortium from 2010 to 2013 in the US. At median follow-up of 24.8 months, 1- and 2-year overall survival was 87.3% and 82%, respectively.[5] Immune recovery after ASCT does not differ for HIV-infected versus HIV-uninfected patients with relapsed or refractory lymphoma. In a study of 33 patients (24 HIV infected and 9 non-HIV infected) who underwent ASCT for lymphoma treatment, $CD4^+$ cell subsets had similar recoveries.[6] This study demonstrated that ASCT in HIV-infected patients with lymphoma does not worsen the initial immune impairment and does not enhance viral replication or the peripheral HIV reservoir in the long term.

Over the past 15 years, several different anti-HIV-1 gene therapy approaches have been tested in hematopoietic stem/progenitor cells (HSPCs). DiGiusto et al.[7] recently conducted a clinical trial to assess the safety and feasibility of HSPC-based lentiviral gene therapy for HIV in the context of treatment for AIDS-related lymphoma. Four patients undergoing treatment with HSPCs were also given gene-modified peripheral blood-derived ($CD34^+$) HSPCs expressing three RNA-based anti-HIV moieties (tat/rev short hairpin RNA [shRNA], TAR decoy, and chemokine receptor 5 [CCR5] ribozyme). *In vitro* assays showed that there was no difference in hematopoietic potential between gene-modified cells and non-transduced cells. Indeed, HSPCs represent an attractive cell target for gene therapy for HIV-1 because they represent the precursors of all the cells involved in HIV-1 pathogenesis (i.e., $CD4^+$ T cells, macrophages, dendritic cells, and microglia).

Our approach seeks to make targets cells, both $CD4^+$ T lymphocytes and $CD34^+$ HSPCs and their progeny, protected from HIV-1 by reducing the expression of the HIV-1 co-receptor CCR5 and blocking fusion of HIV-1 to the cell membrane through expression of the C46 peptide.

Genetic modulation of CCR5 for HIV-1 therapy has a strong theoretical basis. Hematopoietic stem cell transplantation (HSCT) from an allogeneic donor with an HIV-resistant genotype resulting from a naturally occurring 32-base pair (bp) deletion in the gene encoding CCR5 (Δ32CCR5), in conjunction with a full myeloablative conditioning regimen, resulted in apparent elimination of HIV in a leukemia-affected recipient.[8] To date (more than 8 years later), the patient remained off HAART and HIV in peripheral blood and certain tissues remained continuously undetectable.[8–10] In 2010, Sangamo Biosciences, Inc. commenced a phase I clinical trial of CCR5 zinc-finger nuclease (ZFN)-modified autologous $CD4^+$ T lymphocytes in HIV-1 infected subjects (ClinicalTrials.gov: NCT01044654). Pre-clinical *in vitro* and mouse studies have demonstrated generation of $CD4^+$ T lymphocytes that are resistant to HIV-1 infection by disruption of endogenous CCR5 through engineered ZFNs (CCR5 ZFNs) delivered by the adenoviral vector Ad5/35.[11] A first publication occurring in 2014 demonstrated the safety of CCR5-modified autologous CD4 T cell infusions. Moreover, HIV RNA became undetectable in one of four patients that could be evaluated. The blood level of HIV DNA decreased in most patients.[12]

HIV fusion inhibitors either inhibit the first step of membrane fusion (the insertion of the viral fusion peptide into the target cell membrane) or prevent the subsequent six-helix bundle formation. The membrane-anchored antiviral peptide C46 (known also as maC46) comprises 46 amino acids, 36 of them corresponding to the fusion-inhibitory peptide C36 (T-20/Enfuvirtide). Strong pre-clinical data in tissue culture and animal models show that C46 is very efficient at inhibiting HIV-1 replication and its pathogenic effects.[12–14] C46 has been tested in transduced $CD4^+$ T lymphocytes infused to HIV^+ subjects in a phase I clinical trial and was shown to be safe with ongoing detection of gene-marked cells.[15] A total number of 10 advanced HIV^+ subjects that received T lymphocytes transduced with a retroviral vector that expressed the entry-inhibiting peptide, maC46, gene-modified cells could be detected in the peripheral blood, lymph nodes, and bone marrow throughout a 1-year follow-up period, with marking levels correlating to the transduced cell dose.

Our strategy seeks to protect lentivirally-transduced $CD4^+$ lymphocytes and $CD34^+$ HSPCs from HIV infection by two different mechanisms: (1) inhibition of the binding of the virus to the CCR5 co-receptor and (2) inhibition of the gp41-mediated fusion and entry into the infected cell. To this end, Calimmune, Inc. (now CSL Behring, LLC) developed the Cal-1 lentiviral vector. Cal-1 vector is constructed on a self-inactivating (SIN) lentiviral plasmid based on the HIV-1 backbone with modified 5′ and 3′ HIV-1 long terminal repeats. First, the HIV-1 fusion inhibitor C46 was introduced downstream of the human ubiquitin C (UbC) promoter. Next, a previously characterized shRNA against CCR5, driven by the human H1 RNA polymerase III promoter, was inserted upstream of the UbC promoter.[16] The combined construct (Cal-1) has been

effective in pre-clinical testing[16–18] and is currently in clinical testing (ClinicalTrials.gov: NCT02390297and NCT01734850). The combination of $CD4^+$ and $CD34^+$ transduced cells potentially provides the immediate benefit of large numbers of $CD4^+$ T cells that will protect against HIV-1 during the post-transplant engraftment and hematopoietic regeneration/differentiation period. Compared to other protocols targeting CCR5, the presence of C46 would efficiently block any X4 quasi-species that might be present in the patients.

Methods and Analysis

The GENHIV study is an open label phase I/II study to evaluate the safety and feasibility of Cal-1-transduced HSPCs and $CD4^+$ T lymphocytes in HIV-1 infected subjects requiring an ASCT for high-risk lymphoma. The proposed clinical trial is built upon the results of *in vitro* laboratory studies of LVsh5/C46 (hereafter referred to as Cal-1), a dual therapeutic SIN lentiviral vector that inhibits two processes required for HIV-1 infection: binding of the virus to the cellular CCR5 co-receptor and fusion of the virus with the host cell. The vector encodes for both a shRNA against the HIV-1 co-receptor CCR5 (sh5) and an HIV-1 fusion inhibitor, C46.

A total of five patients with HIV-1 infection and high-risk lymphoma requiring ASCT therapy will be screened and followed over 104 weeks in two centers (Immunopathology Department, Saint-Louis Hospital and Biotherapy Department, Necker Hospital). There is a single treatment group.

Study Objectives

This protocol is a human study of Cal-1-modified $CD4^+$ and $CD34^+$ hematopoietic cells and is designed to detect and characterize acute, sub-acute, and medium term safety considerations and toxicities of Cal-1 and the associated delivery procedures.

The primary objective is to evaluate the safety, feasibility, and success engraftment of the introduction of Cal-1 gene-transduced hematopoietic cell populations (T^{tn} and $HSPC^{tn}$) in patients with HIV-1-related high-risk lymphoma. Safety will be assessed, including successful engraftment assessed by blood count and immunophenotyping of peripheral blood subpopulation follow-up, mortality related to ASCT at day 100 post-ASCT, global survival, absence of detection of replication-competent lentivirus (RCL), detection mutagenesis related to vector integration site inducing a clonal dominance, follow-up of clinical and biological parameter following Common Terminology Criteria for Adverse Events guidelines, and absence of tropism switch toward a X4 tropism up to month 24.

Secondary objectives include:

Quantifying gene transfer efficiency and expression, including the extent of $HSPC^{tn}$ and T^{tn} survival by evaluation of Cal-1 marking and expression in peripheral blood at time points up to month 24 as well as the extent of engraftment and differentiation of $HSPC^{tn}$ over time by evaluation of Cal-1 marking and expression in peripheral blood subpopulations (monocytes and $CD4^+$ and $CD8^+$ lymphocytes) up to month 24. Vector copy number (VCN) will be assessed in peripheral blood subpopulations at the same time point. Cal-1 marking and VCN will be measured in bone marrow at 12 and 24 months of follow-up.

Assessing the impact on thymopoiesis for each subject, as measured by changes in quantification of signal joint (sj) T cell receptor excision circles (TRECs) in peripheral blood relative to the pre-infusion baseline over time.

Measuring the effects of transplantation on the expression of disease-specific biological parameters and clinical events, including the PBMC-associated DNA and, for subjects stopping HAART at month 6 post-ASCT, the plasma HIV-1 RNA detection of HIV-1 viral DNA, $CD4^+$ T cell count, and $CD4^+/CD8^+$ T cell ratio after HAART disruption and potentially HAART reintroduction time.

Study Design

For safety reasons, there will be an interval of 3 months between the treatment of patients 1 and 2, 1 month between the treatment of patients 2 and 3, and 1 month after the treatment of patient 3. The treatment will continue without safety intervals. The patients will be enrolled following the treatment scheme (Figure 1).

Autologous $CD34^+$ hematopoietic stem cells will be isolated from mobilized peripheral blood stem cells (mPBSCs). Autologous $CD4^+$ cells will be isolated from peripheral blood. The first apheresis procedure is for the collection of $CD4^+$ T lymphocytes. It will be performed after the second cycle of chemotherapy. It is anticipated that apheresis will yield at least a total dose of 1×10^8 $CD4^+$ T lymphocytes.

Combined antiretroviral therapy will be transiently replaced by darunavir/ritonavir monotherapy 8 days before apheresis to avoid any possible drug interaction between reverse transcriptase inhibitors/integrase inhibitors and the transduction procedure. Combined HAART will be started again immediately after the apheresis procedure.

A first check point will take place just before the harvest for $CD34^+$ to confirm the following criteria: the good response of the lymphoma to chemotherapy and a good HIV suppression (with HAART), defined by a plasma HIV-1-RNA level below 3 $\log_{10}$ copies/mL.

Harvest of $CD34^+$ cells will be performed after a cycle of chemotherapy (usually the third one) followed by granulocyte colony-stimulating factor (G-CSF) treatment. The recommended dose of G-CSF for the mobilization of peripheral blood progenitor cells is 5 μg/kg subcutaneously. It is recommended to start G-CSF at day +6 after the beginning of the cycle of chemotherapy and to continue G-CSF until the last apheresis. Harvest will start at the end of aplasia (leucocytes $> 1 \times 10^9$/L and $CD34^+ > 10$/μL). The aim of apheresis is to collect at least 10×10^6 $CD34^+$ cell/kg of body weight. If the $CD34^+$ cell number is <10/μL or if the total number of $CD34^+$ cells harvested during the first cytapheresis is $< 5 \times 10^6$ cells/kg of body

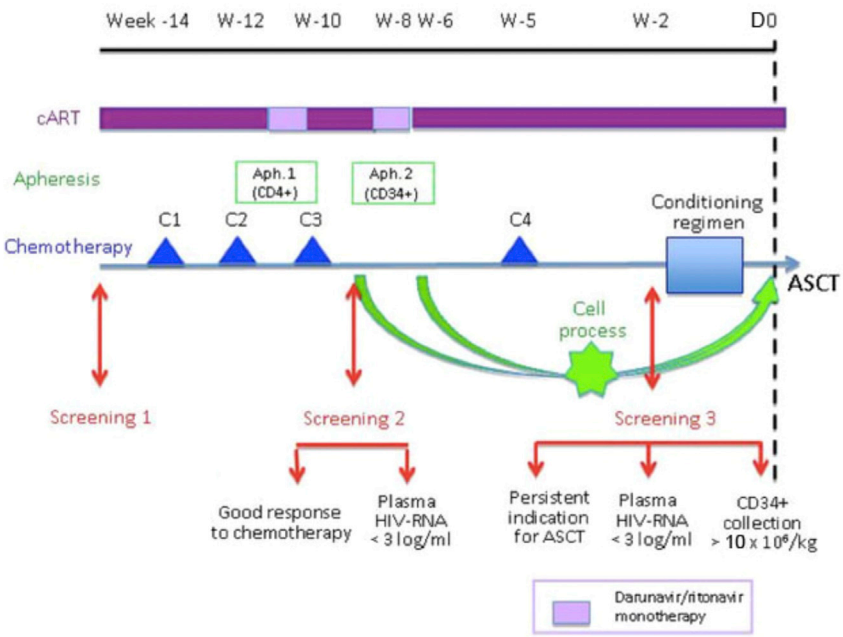

Figure 1. Treatment Overview

weight, plerixafor treatment (0.24 mg/kg of body weight) could be started. Combined antiretroviral therapy will be transiently replaced by darunavir/ritonavir monotherapy 8 days before apheresis to avoid any possible drug interaction between reverse transcriptase inhibitors/integrase inhibitors and the transduction procedure.

A backup harvest of PBMCs ($\geq 2 \times 10^6$/kg body weight unselected $CD34^+$) will be retained, frozen, and stored un-manipulated in liquid nitrogen vapors. The backup will be used in case no hematopoietic recovery is observed after 6 weeks following the gene therapy treatment. $CD34^+$ or $CD4^+$ isolation of PBMCs procured by apheresis is carried out by immuno-magnetic sorting using the CliniMACS system (Miltenyi Biotec, Bergisch Gladbach, Germany). Prestimulation of cells will be as follows:

$CD34^+$: the following cytokines will be used: stem cell factor (SCF), 100 ng/mL; Fms-related tyrosine kinase 3 ligand (Flt-3L), 100 ng/mL; thrombopoïétine (TPO), 100 ng/mL; and interleukin 3 (IL-3), 20 ng/mL. Cells are incubated for 18–24 h at 37.5°C, with 5% CO_2 in cell culture bags. Bags for $CD34^+$ cells are coated with 0.25 mg/mL RetroNectin (Takara).

$CD4^+$: cells will be pre-activated with Miltenyi Transact (CD3/CD28) reagent, IL-2 (200 UI/mL) for 36–48 h at 37.5°C, with 5% CO_2 in cell culture bags.

After the pre-stimulation step, cells will be pelleted, resuspended in fresh medium, and then transduced with Cal-1 lentiviral vector supernatant at:

A cell concentration of 3×10^6 cells/mL at a vector concentration of 2×10^8 immunoglobulin (Ig)/mL for $CD34^+$ in bags (precoated with 0.25 mg/mL clinical grade RetroNectin) with 4 μg/mL protamine sulfate (Choay).

A cell concentration of 1×10^6 cells/mL and a vector concentration of 1×10^7 Ig/mL for $CD4^+$ with 4 μg/mL protamine sulfate (Choay).

Ritonavir will be added at 1 μg/mL to the cell culture medium. Following the cell transduction, the cells will be washed, and a portion of cells will be removed for release testing, with the remainder cryopreserved as described below.

Following transduction and washing, the cells will be suspended in a cryopreservative medium. The frozen product will be stored in the vapor phase of liquid nitrogen. Release testing will include:

$CD34^+$: cell count and viability, microbiology, endotoxin and mycoplasma testing, quantification of VCN by qPCR, C46 expression by flow cytometry, and RCL testing by qPCR.

$CD4^+$: cell count and viability, microbiology, endotoxin and mycoplasma testing, quantification of VCN, by qPCR, C46 expression by flow cytometry, CCR5 expression by qPCR, and RCL testing by qPCR.

At least one additional cycle of chemotherapy will be performed between harvest and ASCT. A second check will take place just before the ASCT procedure to confirm that the subject can be kept in the trial. The following three criteria should be confirmed: (1) a persistent oncological indication for ASCT according to the benefit/risk evaluation by the investigator; (2) a sustained good HIV suppression (with HAART), defined by a plasma HIV-1-RNA level below 3 $\log_{10}$ copies/mL; and (3) a sufficient collection of $CD34^+$ ($\geq 2 \times 10^6$/kg of body weight).

The subject will be able to continue the study only if these three criteria have been confirmed.

Patients will receive a myeloablative conditioning regimen adapted to those recommended in the international hematological guidelines as "BEAM" (bicnu, etoposide, cytarabine, melphalan), "R-BEAM" (bicnu, etoposide, cytarabine, melphalan, rituximab), "Thiotepa-Busulfan" (thiotepa, busulfan, cyclophophamide), or "Thiotepa-Busulfan" (thiotepa, busulfan, cyclophophamide, rituximab).

Lymphoma will be treated according to standard international guidelines, with a conditioning regimen associating bicnu, etoposide, cytarabine, and melphalan ("BEAM" regimen) with or without

rituximab. According to specific hematological indications, an alternate regimen with thiotepa and busulfan may also be indicated. Anti-retroviral therapy (ART) will be continued until at least 6 months post-ASCT.

All subjects are to receive transduced $CD34^+$ on day 0 and transduced $CD4^+$ lymphocytes on day 15 via intravenous (i.v.) infusion to accelerate T compartment reconstitution, with vital signs being monitored concurrently.

Dosage will be as follows:

3×10^6/kg body weight of genetically modified cryopreserved $CD34^+$ cells with a transduction efficiency of ≥ 0.6 and <5 copies of the transgene per cell in an approximate volume of 50 mL.

1×10^8 total genetically modified cryopreserved preserved $CD4^+$ with a transduction efficiency of ≥ 0.6 and <5 copies of the transgene per cell in an approximate volume of 100 mL.

A potential risk could be low transduction efficiency, with reduced protection against the endogenous wild-type virus. The benefit for the patient will then be the benefits of autologous HSCT for pre-existing lymphoma.

The following assessments will be performed at months 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 and will include physical examination, clinical laboratory testing of the blood count, biochemistry, HIV-1 RNA in plasma/HIV-1 DNA in PBMCs, immunophenotyping and thymopoiesis studies (at months 1, 2, 3, 4, 6, 12, 18, and 24), Cal-1 marking/expression analysis—PBMCs and subsets (at months 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24), Cal-1 expression analysis—$CD34^+$ (bone marrow) (at months 12 and 24), and Cal-1 integration site analysis (at months 3, 6, 12, and 24).

RCL testing will consist of a co-culture between the $CD4^+$ or $CD34^+$ transduced cells to be tested and C8166-45 to amplify any RCLs present, thus increasing the assay's sensitivity. The assay also will consist of a quantification of specific sequences of qPCR intended to detect the vector-modified woodchuck hepatitis virus post-transcriptional regulatory element (WPRE) sequence.

ART interruption will be discussed more than 6 months post-ASCT in patients with $CD4^+ \geq 250/mm^3$ and detection of transduced cells in blood samples. If accepted by the advisory board and the patient, the subject will remain off ART unless confirmed plasma HIV RNA values reach the level of 3 $\log_{10}$ copies/mL (confirmed in two consecutive blood samples). In case of HAART interruption at month +6, additional evaluations will be planned at months +7, 9, 11, and 12.

All enrolled subjects will be followed for a maximum period of 24 months post-infusion.

At week 104 post-infusion, all enrolled subjects will complete this study and automatically transfer into long-term follow up. The patients will be reviewed annually off study for an additional 10 years. Long-term follow up will be the subject of a new protocol and will last for 13 years.

Inclusion Criteria

Potential subjects must satisfy all of the inclusion criteria to be enrolled in the study.

Prior to any study-related procedures, signed informed consent must be obtained, indicating that they understand the purpose, risks, and procedures required for the study and that they are willing to participate in the study.

Individuals must be aged 18 to 60 years of age (inclusive) at the time of consent.

HIV-1 infection must be documented at or before the time of lymphoma diagnosis.

Treatment with antiretroviral agents (excluding non-nucleoside reverse transcriptase inhibitors) must be introduced or optimized at the time of screening,

Biopsy-proven lymphoma meeting one of the following criteria must be present.

1. Intermediate- or high-grade B cell NHL, meeting one of the following criteria:
   a. in first complete remission with high-risk features
   b. in partial remission
   c. relapsed after initial complete remission
   d. failed induction therapy but responds to salvage therapy (i.e., chemosensitive disease)
2. HL, meeting one of the following criteria:
   a. in first or greater relapse after initial complete remission
   b. in partial remission
   c. failed induction therapy but responds to salvage therapy (i.e., chemosensitive disease)
3. High-risk lymphoma requiring a treatment with combined chemotherapy and ASCT

Exclusion Criteria

Potential subjects will not be eligible if they meet any of the following criteria.

Left ventricular ejection fraction < 50% at screening 1

Abnormal biochemistry at screening 1: alanine and/or aspartate aminotransferase (ALT/AST) > 10 × ULN, total bilirubin > 2.5 × ULN, and creatinine clearance < 60 mL/min

Severe coagulopathy

Prothrombin time > 2 × ULN

Evidence of co-infection with hepatitis B virus ($HBsAg^+$), hepatitis C virus, West Nile virus, or HTLV-1 as detected at screening 1

Stay in West Nile virus endemic area less than 6 weeks prior to $CD34^+$ collection

Evidence of non-treated opportunistic infection during the pre-infusion period

Evidence of non-treated CNS involvement of lymphoma at screening 1

Isolated CNS relapse of the lymphoma without other evidence of active disease at screening 1

Known hypersensitivity to G-CSF, filgrastim (Neupogen), or plerixafor (Mozobil)

Evidence of uncontrolled HIV-1 viremia at screening 2 and/or 3 (plasma HIV-1 RNA $\geq$ 1,000 copies/mL confirmed in two successive blood samples)

Evidence of chemoresistant lymphoma at screening 2

Any contra-indication to ASCT at any time during the pre-infusion period

Participation in any study involving any investigational drug or medical device within 30 days prior to screening 1

Receipt of a vaccine for HIV-1 or any gene transfer product at any time

Will not accept transfusions of blood products

Pregnant or breast-feeding woman at any time

Woman of child-bearing potential not under adequate contraceptive protection at any time

Inability to understand and provide informed consent

Psychological or psychiatric disability thought to be clinically significant in the opinion of the investigator

Participation in a prior gene therapy study, which may confound analysis and interpretation

Ethics

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said code. The free and informed consent, in writing, of the subject will be obtained by the investigator, or by a doctor representing the investigator, before the subject is included in the research. The consent form must be signed before any study-related procedure is performed and may be signed up to 2 months prior to the screening 1 study visit.

The clinical study was approved by the local ethics committee on May 12, 2016 and by the French Competent Authority (ANSM) on August 28, 2017 (Eudract No. 2015-004453-41).

During the study, a data and safety monitoring board (DSMB) will review the accumulated safety data on a regular basis. The DSMB will include HIV and gene therapy experts and representatives from the association TRT5 (Groupe Interassociatif Traitements & Recherche Thérapeutique), which represents 10 major associations fighting AIDS, including Actions Traitements, Act Up-Paris, Act Up-Sud Ouest, AIDES, Arcat, Dessine-Moi Un Mouton, Envie, Nova Dona, Sida Info Service, and SOLENSI.

AUTHOR CONTRIBUTIONS

All authors were part of the conceptualization and the methodology of the study. M.D. and F.T. wrote the original draft. All authors reviewed and edited the initial draft. M.D., F.T., E.O., and M.C. were responsible for the acquisition of the financial support.

CONFLICTS OF INTEREST

G.S. and O.W. were employed by Calimmune, Inc. and are presently employed by CSL Behring, LLC. M.D., F.T., C.C., I.H., L.D., A.O., F.L., C.T.-D., C.M., J.-R.F., N.F., L.L., A.M., E.M., V.J., A.S.-C., P.F., H.M.-T., M.C.-B., A.T., J.L., N.P., A.C.B., F.B.-S., E.O., and M.C. declare no competing interests.

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