University of Pennsylvania
Research Participant
Informed Consent Form and HIPAA Authorization

Protocol Title:	**Long-term Follow-up of Subjects Exposed to Lentiviral-based C34-CXCR4-modified CD4 T-cell Gene Therapy Products (C34-CXCR4-T) in HIV Studies**
Principal Investigator:	**Pablo Tebas, MD** **Department of Medicine** **Division of Infectious Diseases (ID)** **3400 Spruce Street** **Philadelphia, PA 19104** **Tel: 215-662-6932**
Emergency Contact:	**Infectious Disease Resident on-call** **(215) 662-6059**

Why am I being asked to volunteer?

You are being invited to participate in this long-term follow-up study because you were previously enrolled in a research study where you received your own cells that had been changed (gene-modified) using C34-CXCR4 lentivirus. Your participation is voluntary which means you can choose whether or not you want to participate.

Before agreeing to participate in this research study, it is important that you read the following explanation of the proposed procedures and how long you will be in the study. This document describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes your right to withdraw from the study at any time.

Please take time to read the following information carefully. You may wish to discuss it with your family, friends, and your personal doctor (i.e., your family doctor or primary care doctor). If you have any questions, you may ask your study doctor and/or the research team for more information. Take time to decide whether or not you wish to take part. If you decide to participate, you will be asked to sign this form. If you decide to participate, you can change your mind at any time and withdraw from the study without giving a reason.

What is the purpose of this research study?

The purpose of this long-term follow-up study is to monitor the health status of individuals, such as you, who received their own cells that had been changed using lentiviral vector (also known as gene-modified cells). The FDA has issued guidelines requiring long-term follow-up for up to 15 years for all subjects who received gene therapy.

What is a lentivirus?

- A lentivirus is a type of retroviral vector. A retroviral vector is a virus that can inset genetic material (or DNA) into cells.
- Retroviral vectors enter normal cells in the body. The DNA of the vector inserts itself into the normal DNA in that cell. This process is called DNA integration.

- Most DNA integration is expected to cause no harm to the cell or to the patient. However, there is a chance that DNA integration might result in abnormal activity of other genes. In most cases, this effect will have no health consequences.

Is there a reason for study monitoring?

It is important that you know about some cancers that occurred in another gene therapy research study. The study involved a disease called X-linked Severe Combined Immunodeficiency (SCID) and showed the following:

- Years after receiving cells that were modified by a retroviral vector, some children in this small study developed a leukemia-like malignant disease (cancer).
- At least one child died from the cancer.
- A group of experts in this field studied the results from tests performed on these children's blood cells. They concluded that the leukemia-like malignancy was caused by the retroviral vector DNA. However, most of the children with X-linked SCID who have received experimental gene therapy have not been found to have a leukemia-like disease at this time. Although they appear healthy, we still do not know whether they, too, will develop a malignant growth.

We do not know if the retroviral vector used in the study in which you were previously enrolled might cause a new malignancy or other long-term side effects. However, you should be aware that the DNA contained in retroviral vectors will combine with your DNA and that, under some circumstances, this has been known to cause malignant (cancerous) growth months to years later.

The risk for developing a new cancer or any of the events listed on the next page under the section titled *"What am I being asked to do?"* is the reason we are required by the Food and Drug Administration (FDA) to follow you in this study for up to 15 years after your last dose of C34-CXCR4-T cells.

How long will I be in the research study?

Your active participation in this research study may be for up to 15 years. The length of time of participation will depend on two things:

1. When you finished the original research study.
2. Whether the C34-CXCR4-T cells continue to remain in your body.

What am I being asked to do?

It is important that you notify your study team of any new problems you may be having with your health. You will be asked to provide your current address, email, and telephone number to the study doctor and update this information throughout the research study so that the research staff will be able to contact you to give you any new information. It will be very important for you to keep follow-up visits with the study doctor. You will be informed of all clinical test results as soon as they are available and whether C34-CXCR4-T cells are still present in your body.

In addition, when you enroll onto this long-term follow-up study, a letter will be sent to you and your doctor (primary care doctor or doctor treating your HIV) to remind you, and inform them, that you have participated in a gene therapy research study and are participating in this long-term follow-up study. This letter will request you and your doctor to immediately notify the study doctor or nurse if you develop any of the following events:

1. Any type of cancer, including blood disorders such as leukemia or lymphoma.

2. Loss of feeling in any parts of your body especially your hands and feet; loss of control of any body parts (example - arms or legs); seizure; memory loss or experience a worsening of any of the symptoms or conditions listed. These types of symptoms are suggestive of a neurological disorder or central nervous system disorder.

3. Arthritis, autoimmune disease or worsening of a pre-existing arthritis or autoimmune disease (example - lupus), which you were experiencing prior to your participation in the study.

This letter will also notify your local doctor that we will contact them to provide follow-up information from your medical record and/or request assistance in collecting protocol required blood samples, if you cannot return to the University of Pennsylvania for one of your scheduled follow-up visits. We will also contact you by phone or mail to check on your health status.

Study Visits

Your first study visit under this long-term follow-up protocol will begin according to when you completed your last study visit in the gene therapy study in which you are/were previously participating. The visit interval is calculated from the time you received your first C34-CXCR4-T cells. Someone from the research team will assist you in determining during which interval your study participation will begin.

The table below lists the study visits that will occur during your participation in this long-term follow-up study, depending on when you enter this study.

Study Visits During the First 5 Years	Yearly Study Visits from Years 6 to 15
3 months	6 Years
6 months	7 Years
9 months	8 Years
1 Year	9 Years
1.5 Years	10 Years
2 Years	11 Years
2.5 Years	12 Years
3 Years	13 Years
3.5 Years	14 Years
4 Years	15 Years
4.5 Years	
5 Years	

During these study visits, the following will be done:

- Review of your medical history
- Routine blood tests (about 4 teaspoons) to evaluate your health status
- Physical examination- performed once a year
- Review of current medical conditions and list of medications you are taking for your HIV
- Research blood tests (about 2 tablespoons) to determine if the C34-CXCR4-T cells are still in your body.

If you have had routine blood tests performed as part of your regular care within 2-3 months of these study visits, these tests may not need to be repeated.

If there is no evidence of the gene-modified cells in your body during the 5-year visit**,** you will no longer be asked to come in for follow-up visits. You will be contacted annually for up to 10 more years. The research team may contact you by mail or phone. During each study contact, you will be asked to provide information about your health status, medical conditions, and a list of medications you are taking for your HIV.

If the gene-modified cells continue to be present in your body during your 5-year visit, you will continue to come in to see the study doctor and have blood drawn once a year for a maximum of 10 more years. Once there are no gene-modified cells detected in your blood, follow-up study visits will no longer be required, and you will be contacted by the study team by mail/email or phone once a year for up to 10 more years. Please let your study doctor know if you do not wish to be contacted via email as this is not a secure form of communication. If we are unable to contact you, your name and date of birth may be used to search a public federal government database to get information about your survival status.

There is a risk that portions of the vector used to manufacture the C34-CXCR4 cells you received as part of the main study could change in your T-cells and generate an active new virus that may grow and spread to other cells. This would be called a replication competent lentivirus, or "RCL". As part of this long-term follow-up study, you will continue to be monitored for RCL. If the test used to detect components of an RCL is positive, you will be notified and requested to return for additional blood tests for your safety and to determine whether or not you have developed an active RCL.

The study team may "bank" (store) some of your blood samples collected throughout your participation in this study. These samples will be kept frozen and will not identify you by name, but only by your unique study identification number. The blood samples will only be used by the study team to go back and do testing on your blood if an unexpected event occurs.

Additional Research Samples: In the event something unexpected occurs to you during your participation in the protocol, the research team may request additional samples (blood or tissue) be collected for research analysis. This is being done with the intention of evaluating the effects of the investigational product you previously received. The total amount of extra blood that will be collected from you will be 3 tablespoons of blood (not to exceed a maximum blood draw of 3 tablespoons total in an 8-week period), in addition to the protocol-specified time points.

In addition, if during your participation in this study you undergo additional blood collection as part of your routine care (such as CD4 counts and viral loads), the results of these tests may also be used for research purposes.

Pregnancy

If you do become pregnant or suspect you may be pregnant, you must tell the investigator immediately and consult an obstetrician or maternal-fetal specialist. If you become pregnant while you are on this long-term follow-up study, your study doctor will follow your pregnancy until outcome to monitor your safety.

If you are a male participant and your partner becomes pregnant, you must tell the study doctor as soon as possible. Pregnancy and outcomes monitoring for safety will be performed as is done for a female subject who becomes pregnant.

What are the possible risks or discomforts?

Below are the possible risks associated with participation in this long-term follow-up study:

Risks associated with blood draws: Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. You may also experience a decrease in hemoglobin and hematocrit (red blood cell number, called anemia) from having blood drawn frequently. Approximately 3½ tablespoons of blood will be collected at each study follow-up visit.

What if new information becomes available about the study?

During the course of this research study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the research study. We will notify you as soon as possible if such information becomes available. In order to provide this information to you, you must provide your current address and telephone number to the study doctor and must update this information so that the research staff will be able to contact you to give you any new information learned from this research study in the future.

What are the possible benefits of the study?

You are not expected to get any benefit from being in this research study. This study is for the purpose of monitoring your health status after you have received gene-modified cells.

What other choices do I have if I do not participate?

Your alternative is to not participate in this research study.

Will I be paid for being in this research study?

You will receive $50.00 for each study-required onsite visit to cover your travel expenses. In order to receive this payment for your participation in this study, you will be asked to provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?

The research study will cover the cost of laboratory tests performed for research purposes only.

You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

What happens if I am injured or hurt during the study?

If you have a medical emergency during your participation on this study, you should go to the nearest emergency room. You should contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the research study over? Can I leave the research study before it ends?

This research study is expected to end after all participants have completed all visits, and all information has been collected. This research study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, Study Funder, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the research study at any time. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

The investigator and staff involved with the study will keep your personal health information collected for the research study strictly confidential. Only the minimum necessary data will be provided to the people/entities named below and when possible participants will be identified with a unique study identification number.

Electronic Medical Records and Research Results

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record. If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

What information about me may be collected, used or shared with others?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

• Name, address, telephone number, email address, date of birth • Current medical history and health status information • Medical record number • Social security number	• Results of test procedures you will undergo during this research study as described in this consent form • Current and past medications or therapies • Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature

Why is my information being used?

Your information is used by the research team to contact you during the research study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- evaluate and manage research functions.

Who may use and share information about me?

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need access to your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.)
- Authorized members at the University of Pennsylvania, School of Medicine who coordinate this study and support research operations.
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB.

Who, outside of the School of Medicine, might receive my information?

<u>Regulatory and Regulatory and safety oversight organizations</u>

- The Food and Drug Administration
- The Office of Human Research Protections
- The Office of Biotechnology Activities and their committees overseeing gene therapy research
- Public Health agencies and other governmental agencies (including non-U.S.) as authorized or required by law

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific research study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this research study for a purpose other than this research study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the research study. If you withdraw your permission, you will not be able to stay in this research study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

How will my research samples be used and stored for the purposes of this study?

As outlined above, you will have blood and tissue samples collected as part of your participation in this research study. These samples will be stored at the University of Pennsylvania for research purposes. Your authorization for the use and storage of your research samples does not expire. However, you may withdraw or take away your permission to use and store these samples at any time by contacting Dr. Pablo Tebas at (215) 662-6932, but any samples that have already been used for research will be retained. After your participation in this study has ended and all research analysis on these samples is complete, these samples may be destroyed at any time without notice.

Who can I call with questions, complaints or if I'm concerned about my rights as a research participant?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research participant, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team

cannot be reached, or you want to talk to someone other than those working on the research study, you may contact the Office of Regulatory Affairs with any concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this research study.

A copy of this Informed Consent Form and HIPAA Authorization will be given to you. By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above**.**

Name of Participant	Signature of Participant	Date
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

About Using Blood and Tissue for Research

In addition to the research study and the analysis of blood outlined above, researchers are also interested in using blood, tissue, fluid, or other specimens that may be obtained from you while you are participating on this research study. Research tests may be developed during the time you are on the research study or, in some cases, years later. We ask that you give approval for these tests to be performed using these specimens. Because it is not possible for you or the researchers conducting this research study to know what will be discovered in the future and what additional tests may be appropriate at that time, we ask that you give your permission to 1) use these additional samples for future research; and 2) conduct studies on them in the future without your being contacted for permission for each test. These tests may provide additional information that will be helpful in understanding your disease or response to treatment, but it is unlikely that what we learn from these studies will have a direct benefit for you. These studies may benefit patients in the future. You will not receive the results of any testing performed on your samples.

Additional research on your samples in the future may also include genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

In addition, blood, tissue, fluid, or other specimens obtained from you may be used to establish products that could be patented or licensed. There are no plans to provide financial compensation to you should this occur.

Samples will be stored indefinitely. Researchers involved in this research study at the University of Pennsylvania will have access to the specimens. These specimens may be used to conduct pilot (new) studies regarding your disease or regarding your response to the kind of treatment you received. Samples may also be sent to other researchers for collaborative studies, including

researchers at for-profit agencies. However, prior to shipment, patient identifiers (name, initials and medical record numbers) will be removed, but these samples will still include your unique subject identification number. You will not be given results of these pilot studies or of any future testing performed on your samples. You have the right to withdraw any unused blood/tissue/fluid from further use by contacting Dr. Pablo Tebas at (215) 662-6932. Any blood/tissue/fluid that has already been used for research will be retained.

Please initial next to your choice below.

Initials	
	I AGREE to allow my blood/tissue/fluid to be kept for use in research to learn about, prevent or treat HIV or other diseases.
	I DO NOT AGREE to allow my blood/tissue/fluid to be kept for use in research to learn about, prevent or treat HIV or other diseases.

Name of Participant	Signature of Participant	Date
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date