University of Pennsylvania
Research Participant
Informed Consent Form and HIPAA Authorization

Protocol Title:	**Long-term Follow-up of Subjects Exposed to mRNA-based ZFN-modified CD4+ T cell Gene Therapy Products 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 Zinc Finger Nucleases (ZFNs). 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 ZFNs. The FDA has issued guidelines requiring long-term follow-up for all subjects who received gene therapy.

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 ZFN modified T cells used in the study in which you were previously enrolled might cause a new malignancy or other long-term side effects.

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 10 years after your last dose of ZFN modified T cells.

How long will I be in the research study?

Your active participation in this research study may be for up to 10 years. The length of time of participation will depend on two things:

1. When you finished the original research study.

2. Whether the ZFN modified T cells continue to remain in your body.

What am I being asked to do?

It is important that you notify you 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 ZFN modified 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

Below is a table that will summarize what will be done during your study visits for the first 3 years. 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 ZFN modified T cells. Someone from the research team will assist you in determining during which interval your study participation will begin.

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.

Visit	Procedures
3 months This visit is only for participants who enroll into this LTFU study less than 3 months after receiving ZFN modified T cells.	• Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.
6 months This visit is only for participants who enroll into this LTFU study less than 6 months after receiving ZFN modified T cells.	• Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are in your body.

Visit	Procedures
9 months This visit is only for participants who enroll into this LTFU study less than 9 months after receiving ZFN modified T cells.	• Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.
1 year	• Physical exam • Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Review of your relevant medical history, current medical conditions and list of medications. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.
1.5 years	• Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Review of your relevant medical history and current medical conditions. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.
2 years	• Physical exam • Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Review of your relevant medical history, current medical conditions and list of medications. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.
2.5 years	• Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Review of your relevant medical history and current medical conditions. • Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.

Visit	Procedures
3 years	• Physical exam • Routine blood tests (about 2 ½ teaspoons): to evaluate your health status. • Review of your relevant medical history, current medical conditions and list of medications.
	• Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.

If the gene-modified cells continue to be present in your body during your 3-year visit, you will continue to come in to see the study doctor to have blood drawn once every 6 months for a maximum of 7 more years, or until two successive tests show that there are no gene-modified cells detected in your blood. You will then have completed your participation in this study.

Below is a table that will summarize visits for the next 7 years.

Visit	Procedures
Biannual **visits** from years 4 to 10 if the ZFN modified T cells are present in your body. Note: You will continue to have visits every 6 months until the ZFN modified T cells are no longer detected in your blood.	• Research blood tests (about 3 tablespoons): to determine if the ZFN modified T cells are still in your body.

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. 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 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, 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.

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 4 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.

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?

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?

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.

Once placed in your EMR, these results are 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	• Results of test procedures you will undergo during this research study as described in this consent form • Current and past medications or therapies

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.

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.)

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
- National Institutes of Health, DHHS-Department of Health and Human Services
- 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.

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 for Research

In addition to the research study and the analysis of blood outlined above, researchers are also interested in using blood samples obtained from you while you are participating on this research study for additional research. These 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 for such studies without 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.

In addition, blood 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 and Sangamo BioSciences Inc. 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 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. You will not be given results of these pilot studies. You have the right to withdraw any unused blood from further use by contacting Dr. Pablo Tebas at (215) 662-6932. Any blood that has already been used for research will be retained.

Please initial next to your choice below.

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

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