UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Letter of Amendment #3, 10/1/10

A Phase II, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, and Immunogenicity of ZOSTAVAX® (Zoster Vaccine Live) in Human Immunodeficiency Virus (HIV) -1-Infected Adults on Potent Combination ART with Conserved Immune Function

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

If you are seen at the Hospital of the University of Pennsylvania [HUP], your contacts are:

Principal Investigator: Pablo Tebas, MD (215) 615-4321
Coordinator: Joseph Quinn, RN (215) 349-8092
Study Nurse: Kathryn Maffe, RN (215) 349-8092
Aleshia Thomas, RN (215) 349-8092
Wayne Wagner, RN (215) 349-8092
Carol Di Giorgio, RN (215) 349-8092

24 Hour Emergency Number (215) 662-6059 Ask for the Immunodeficiency Program Doctor on call

Introduction:
You are being asked to take part in this research study because you are infected with human immunodeficiency virus (HIV) and you are currently taking potent combination antiretroviral (ARV) medications. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is Dr. Pablo Tebas. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Please note that:
- Your participation in this study is entirely voluntary.
- You may stop taking part in the study at any time without losing your standard health care.

Why Is This Study Being Done?

The main purpose of this study is to test a research vaccine called ZOSTAVAX®, a vaccine that helps to stimulate the immune system (part of your body that is designed to protect you against foreign materials that enter from outside your body) to help fight complications of infection with a virus called herpes zoster, the virus that causes zoster or shingles. Herpes zoster or shingles is a virus infection that causes a painful skin rash, usually in older people or people with suppressed immune systems like people with HIV infection. This study will test ZOSTAVAX® to see if it is safe and tolerable in HIV-infected people. The study will also test the ZOSTAVAX® vaccine to see if it has an effect on your immune system's ability to develop responses against the virus that causes herpes zoster or shingles.

ZOSTAVAX® has been approved by the Food and Drug Administration (FDA) as a vaccine given to people age 50 years or over to prevent them from getting herpes zoster (also known as zoster or...
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shingles) and to reduce some of the complications of zoster or shingles, such as pain after the rash has healed. The FDA has not approved ZOSTAVAX® for use in persons with HIV-infection.

ZOSTAVAX® will be given to you by injections (shots) under the skin.

What Do I Have To Do If I Am In This Study?
You will be allowed to enter into the study in two stages as noted below:

- Stage I: About 48 people with CD4+ T cell counts (the number of white blood cells called lymphocytes that help fight infection) greater than or equal to 200 cells/μL will enter the study.

At the end of Stage I, a Study Monitoring Committee (SMC) will review the study to make sure ZOSTAVAX® is safe and will evaluate some of the initial information when available about the vaccine or placebo effect on the immune system.

- Stage II: About 352 more people will enroll in Stage II. Participants with CD4+ T cell counts greater than 350 cells/μL will enter Stage II immediately. Participants with CD4+ T cell counts of 200- 349 cells/μL will wait to enter Stage II until after the review by the SMC has been completed.

If you decide to enroll in this study and sign this consent form, you will be interviewed and have a physical examination where the clinic staff will check your vital signs such as, temperature, blood pressure, and pulse, and you will have laboratory test performed as described below to be sure that you qualify.

Screening
This visit will take approximately 1 hour. During the physical examination you will be asked questions about your medical history and the medications you take or have taken in the past. You will also have approximately 4 teaspoons of blood drawn for routine safety tests, HIV viral load (the amount of HIV in your blood), and CD4+/CD8+ T cell count (the number of white blood cells that fight infection). If you are a woman able to become pregnant, you will be asked to give a urine sample or have an additional 2 teaspoons of blood drawn to see if you are pregnant. You may not enroll in the study if you are pregnant. You will be given the results of these tests when they become available.

You must also be on stable anti-HIV drugs for at least 90 days before beginning the study, and plan to continue these drugs during the study. You should also have an HIV viral load (the amount of HIV measurable in your blood) that is undetectable for at least 90 to 210 days before beginning the study. This study will not be providing anti-HIV drugs and you should continue to obtain them from your primary care doctor.

Entry
If you qualify to participate in this study, you will return to the clinic for an entry visit. The entry visit will occur at least 24 hours after the screening visit. This visit will take approximately 1 hour.
At entry, you will be asked about the lowest CD4+ count you have ever had. You will also have a physical examination and will be asked to give a urine sample or have about 2 teaspoons of blood drawn to see if you are pregnant. You may not enroll in the study if you are pregnant. You will be given the results of the pregnancy test when it becomes available. Once you complete your entry tests, you will be randomized, or assigned by chance, to either the active vaccine group, or the placebo group. You may not choose which group you are in. Your chances of being assigned to the vaccine group instead of the placebo group are three to one. A placebo looks like the zoster vaccine, but it does not have any active drug in it. This part of the study is called double blind because you may not choose which group you are in, and neither you nor your doctor nor the clinic staff will know if you are assigned to the active vaccine group or the placebo group.

You may receive your first vaccination at this visit or up to 3 days later. The day you receive your first vaccination is day 0.

Day 0
On day 0 of the study, you will have a physical examination and may have up to 3 teaspoons of blood drawn for HIV viral load, CD4+ T cell count, and immune function tests. You will be given the results of these tests when they become available. This visit will take approximately 1 hour.

NOTE: If this is not the same day as your entry visit and you are a woman able to become pregnant, you will be asked to give a urine sample or have an additional 2 teaspoons of blood drawn to see if you are pregnant. You may not receive vaccination if you are pregnant.

- You will then receive the first of 2 vaccine shots. At this visit, you will be given a vaccination report card for you to record any injection site (local skin) reactions, rashes, or fever for the next 5 days and also record your body temperature everyday until your week 6 visit. If you develop rashes after each of your vaccinations, you may have a sample taken from your rash (by swabs) to see if it was caused by the vaccine. You will also be seen by your doctor every 3 days until your rash disappears.

Visits during the study
After you enter the study and have received your first shot, you will come to the clinic 2, 6, 8, and 12 weeks after for various tests. At week 6, you will receive your second vaccine shot. For most visits you will be at the clinic for about one hour.

In addition, you will be called at home or at a number of your choosing 2 to 3 days after each vaccination to ask how you are doing. If you prefer not to be contacted by telephone, you may come to the clinic for this follow-up visit. The telephone call (or clinic visit) will take about 5-10 minutes. The study staff may ask you to come to the clinic if you are having injection site reactions or other symptoms related to the vaccination, such as fevers, that are more than just mild in nature.

At all visits
- You will have a brief physical exam which will include an examination of the vaccination sites. You will also be asked how you are feeling.
You will be given the results of all tests performed during the visits as soon as they are available.

The report card given to you on your previous visit will be collected and reviewed by the study staff at this visit. If you develop rashes since your last clinic visit, you may have a sample taken from your rash to see if it was caused by the vaccine.

At week 2 you will receive all of the tests listed above in the section for all visits plus:
You will have about 2 teaspoons of blood drawn for HIV viral load and CD4+/CD8+ counts test. If your second vaccination is postponed due to an increase in your HIV viral load or a decrease in your CD4+ T cell count, you may be asked to have additional laboratory testing done to evaluate your CD4+ T cell count or HIV viral load before your second vaccine shot is given. Your second vaccination may be postponed for up to 14 days if needed.

At week 6 you will receive all of the tests listed above in the section for all visits plus:
- You will have about 2 teaspoons of blood drawn for immune function tests (to see if your body reacted to the vaccine).
- If you are a woman able to become pregnant, you will be asked to give a urine sample or have an additional 2 teaspoons of blood drawn to see if you are pregnant. You may not receive the second vaccination if you are pregnant.
- You will receive your second and final vaccine shot and you will be given another report card for you to record any injection site reactions, rashes, or fever for the next 5 days and also to record your body temperature everyday till your week 12 visit.

At week 12 you will receive all of the tests listed above in the section for all visits plus:
- You will have about 2 teaspoons of blood drawn for immune function tests.

Week 24
At 24 weeks following your first vaccination shot, you will be called at home or at a number of your choosing to see how you are doing. If you prefer not to be contacted by telephone, you may come to the clinic for this follow-up visit. The telephone call (or clinic visit) will take about 5 to 10 minutes.

Other Study Required Evaluation for participants that enter in Stage II
You may also be one of 80 study participants who will be asked to have an additional 2 tablespoons of blood drawn at visit Day 0, weeks 6 and 12, or at your final visit, if you decide to quit the study early.

The blood samples collected will be stored with usual protectors of identity, such as assigning codes to the samples rather than names, storage in secure locations, and allowing only study staff to have access to your information. These samples will be used for immunological testing that is required for this study. These tests will look at your body's defense against illness and its reaction to the vaccine. You will not be told the results of these extra tests because they will be done in the future.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements and you signed this consent form, we will still use some of your information. As part of the screening visit, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis), and laboratory (e.g., CD4+ T cell count, viral load) information is being collected from you so that
ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study. A code number that will not identify you and that is not linked to any other ACTG data will be used to enter this information into the database.

Other
If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protectors of identity) indefinitely and used for future ACTG-approved HIV-related research.

Storage of leftover blood is not a requirement to participate in the study and you may withdraw your approval for the storage of your leftover blood, at anytime. Please indicate below whether you approve the use of your leftover blood.

_________ YES ___________ NO

What Happens If I Decide To Quit The Study Early?
If you decide to no longer be a part of the study you will be asked to have the following tests:
- A brief physical exam which will include an exam of the vaccination sites. You will also be asked how you are feeling.
- About 3 tablespoons of blood will be drawn for immune responses test.
- Any report card that was given to you at a previous visit will be collected.

How Many People Will Take Part in This Study?
About 400 (48 in stage I and 352 in stage II) people will take part in this study. About 25-30 people are expected to participate at the University of Pennsylvania.

How Long Will I Be in This Study?
You will be in this study for about 24 weeks.

Why Would the Doctor Take Me Off This Study Early?
The study doctor may need to take you off the study early without your permission if:
- You are not able to attend three study visits as required
- The study is cancelled by the U.S. Food and Drug Administration, National Institutes of Health, the Office for Human Research Protections, the ACTG, the drug company supporting this study, or the University of Pennsylvania's Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- You chose to stop your participation in the study
- A Study Monitoring Committee (SMC) recommends that the study be stopped early (An SMC is an outside group of experts who monitor the study)
- Your primary care doctor feels the study is not in your best interest
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The study doctor may also need to take you off the study treatment without your permission if:

- continuing the study treatment may be harmful to you
- You have a bad reaction to the vaccine and need treatment
- Your CD4+ T cell count drops lower than 160 cells/μL
- Your HIV RNA level increases over 5,000 copies/mL
- You stop taking your anti-HIV medications and your HIV viral load level remains above 5,000 copies/mL
- you need a treatment that you may not take while on the study
- you are not able to receive the study treatment as required by the study
- you become pregnant or start breast-feeding

If you must stop taking the study treatment before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

What Are The Risks Of The Study?

The vaccine used in this study may have side effects, some of which are listed below. Please note that the list does not include all the side effects seen with this vaccine. The list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study vaccine side effects please ask the medical staff at your site.

There is a risk of serious and/or life threatening side effects when non-study medications or supplements are taken with the study vaccines. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risk of Drawing Blood

- Discomfort
- Dizziness/feeling lightheaded
- Bleeding or bruising at the spot where the needle enters your body
- Small risk of fainting or infection
- Blood clot

Risk of Injections

- Arm discomfort
- Bleeding or bruising at the spot where the needle enters your body
- Small risk of fainting or infection
- Stinging, pain, soreness, redness, itching, swelling, burning, warmth at injection site

Risks of ZOSTAVAX® (Investigational Vaccine)

Some reported risks include:

- Injection site reactions such as: local redness, swelling, pain and tenderness, itching, bruising, and warmth.
- Headache
- Fever
- Allergic reaction, which may be life-threatening
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- Rash, which may resemble chickenpox.
- Swollen glands near the injection site (that may last a few days to a few weeks).
- Joint pain
- Muscle pain

NOTE: If you develop a rash at any point after any of your vaccinations during the study, you must tell the study doctor immediately and come to the clinic to have a sample of your rash taken.

Risk of Specimen Collection Procedure (for lesions/rashes)
Having a sample taken from your rash, if you develop one, may cause discomfort and rarely, bruising.

In other clinical trials with ZOSTAVAX®, the vaccine virus has not been reported to spread to other people. However, a person who receives ZOSTAVAX® may rarely spread the vaccine virus to a person who is susceptible. For this reason, you should tell your study doctor or study nurse if you expect to be in close contact (including household contact) with newborn infants, someone who may be pregnant and has not had chickenpox or been vaccinated against chickenpox, or someone who has problems with their immune system. It is important to find out if these close contacts have immunity to VZV (varicella zoster) either through vaccination or having had the chicken pox. Should these close contacts not have immunity, then you may want to consider not participating in the study.

There are other less common side effects which your study doctor can identify for you.

There may be other side effects or risks that are not presently known about ZOSTAVAX.

Are There Risks Related To Pregnancy?
The vaccine in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant for the duration of the study. Because of the risk involved, you and your partner must use at least two methods of birth control that you discuss with the study staff. You must continue to use at least two methods during the 24-week duration of the study and also for an additional three months after the scheduled study duration. You may choose two of the birth control methods listed below:
- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intra-uterine device
- Hormone-based contraception
- Contraceptive sponge
- Vasectomy

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. If you become pregnant while on the study you will be asked if you wish to continue in the study and
come for study visits. You will not receive any further vaccine shots that are scheduled. You will be asked to sign a pregnancy consent form.

Are There Benefits to Taking Part in This Study?
ZOSTAVAX® was shown to be 51% effective in preventing herpes zoster in those with a normal immune response, but may not be beneficial to those with HIV. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

What Other Choices Do I Have Besides This Study?
Instead of being in this study you have the choice of:
- treatment that is available to help reduce the severity of shingles if you develop the disease. Examples of this treatment are: acyclovir, valacyclovir, and famciclovir. However, there are no licensed vaccines to prevent shingles in patients with weakened immune systems
- treatment with experimental drugs, if you qualify
- no treatment

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

What About Confidentiality?
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the U.S. Food and Drug Administration, University of Pennsylvania IRB, National Institutes of Health, Office for Human Research Protections, the ACTG, study staff, study monitors, drug company supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

What Are the Costs To Me?
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Taking part in this study may lead to added costs to you and your insurance company. In the unlikely event that something happens to you and the University of Pennsylvania does not consider it to be a result of the study vaccine/procedures, but the insurance does consider it related to the study and neither entity wants to pay, then you might be responsible for the costs.

Any vaccine (ZOSTAVAX®/Placebo) that you may receive will be supplied by the study. During this study you will continue your ART therapy, however the drugs will not be provided by the study. You must pay for them through some other manner, such as your insurance or local AIDS Drug Assistance Program (ADAP).

Will I Receive Any Payment?
You will be compensated $25 for each clinic visit you attend with the exception of the screening visit for which you will be compensated $5 for your time and inconvenience. In addition, you will be compensated $5 for each of the three telephone follow up contacts at your next scheduled clinic visit. Thus, if you attend all study visits (6) and participate in the 3 telephone contacts, the maximum compensation you will receive from the study is $170. If you are requested to come into the clinic for additional visits or to have your blood re-checked, you will also be compensated for that visit. There is no other additional compensation (parking coupons, meal vouchers or token) for your participation in the study.

What Happens If I Am Injured?
If you have a medical emergency during the study you should go to the nearest emergency room. You may 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.

In the event that you are hurt or injured as a result of participation in this research study, please contact the investigator listed on page one of this form.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise offered from the University of Pennsylvania or the National Institutes of Health. If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

What Are My Rights As a Research Subject?
Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your healthcare provider will treat you the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.
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What Do I Do If I Have Questions Or Problems?

For questions about this study or a research-related injury, contact:
• Pablo Tebas, MD (215-615-4321)
• Clinical Trials Unit (215 349-8092)

For questions about your rights as a research subject, contact:
• Director of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614

CONSENT

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 the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine’s Notice of Privacy Practices that contains more information about the privacy of your health information.

Name of Subject (Please Print)  Signature of Subject  Date

Name of Person Obtaining Consent (Please Print)  Signature  Date

For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

Authorized subject representative [print]  Authorized subject representative Signature  Date

Provide a brief description of above person authority to serve as the subject’s authorized representative.

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