

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

A Phase IB, Open Label Study To Examine The Safety And PK Characteristics of the NK-1R Antagonist, Aprepitant, In HIV-Infected Subjects With undetectable viral load Receiving Atazanavir/Ritonavir Or Lopinavir/Ritonavir Containing Antiretroviral Therapy

CONSENT FORM / AUTHORIZATION (HIPAA) FOR A RESEARCH STUDY

Investigators: Pablo Tebas, MD
Wayne Wagner, RN

Phone Number: (215) 349-8092
215) 349-8092

24-hour emergency Number: (215) 662-6059 (ask for Infectious Diseases Fellow on call)

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV, the virus that causes AIDS, and you are currently taking anti-HIV treatment regimen that contains either Atazanavir/ritonavir or Darunavir/ritonavir and have a CD4 count of at least 350 cells. This study is sponsored by the National Institute of Mental Health (NIMH). The doctor in charge of this study at this site is Pablo Tebas, MD. 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.

WHY IS THIS STUDY BEING DONE?

This study is being done to evaluate the safety and tolerability of the drug aprepitant when added to a treatment regimen that contains atazanavir/ritonavir or darunavir/ritonavir. In the test tube, aprepitant has an effect on HIV and stops its replication. Aprepitant has been given to HIV-infected people who are not taking antiretroviral treatment. This is the first time aprepitant will be given as an add-on to someone already on HAART and therefore is being used in an investigational manner (not U.S. Food and Drug Administration (FDA)-approved for HIV treatment).

The FDA has approved aprepitant to prevent vomiting and nausea in patients starting chemotherapy. Aprepitant has also been studied as a possible treatment for depression. Several questionnaires involving depression and anxiety will also be administered to see if aprepitant has any effects on these parameters in people with HIV.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

All study visits will be conducted in the Clinical and Translational Research Center (CTRC) on 1 Dulles in the Hospital of the University of Pennsylvania.

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Screening Visit

You will be asked to come to the CTSC to see if you are eligible to participate in the trial. At this screening visit, you will be asked to sign this consent form that explains the study and what will be expected of you. The study nurse will ask you questions about your medical history, medications you have taken in the past and are currently taking and your current HIV medications. You will have your vital signs and weight taken and will be asked about how you are feeling. After that you will have about 3 tablespoons of blood drawn for hematology (blood counts), chemistries (tests to see how well your liver and kidneys are working), HIV viral load and CD4 cell count. If there is no documentation available, a test to confirm that you are HIV positive will also be done. In addition, you will have some blood drawn that will be used for specialized immunology and virology tests, including genotype and phenotype some of the components of the HIV virus. If you are a woman able to become pregnant, you will have a urine pregnancy test. A urinalysis will also be done.

In addition, your phone number or other contact information will be requested, so that the clinic can contact you and remind you of follow-up visits.

Entry Visit (Day 0)

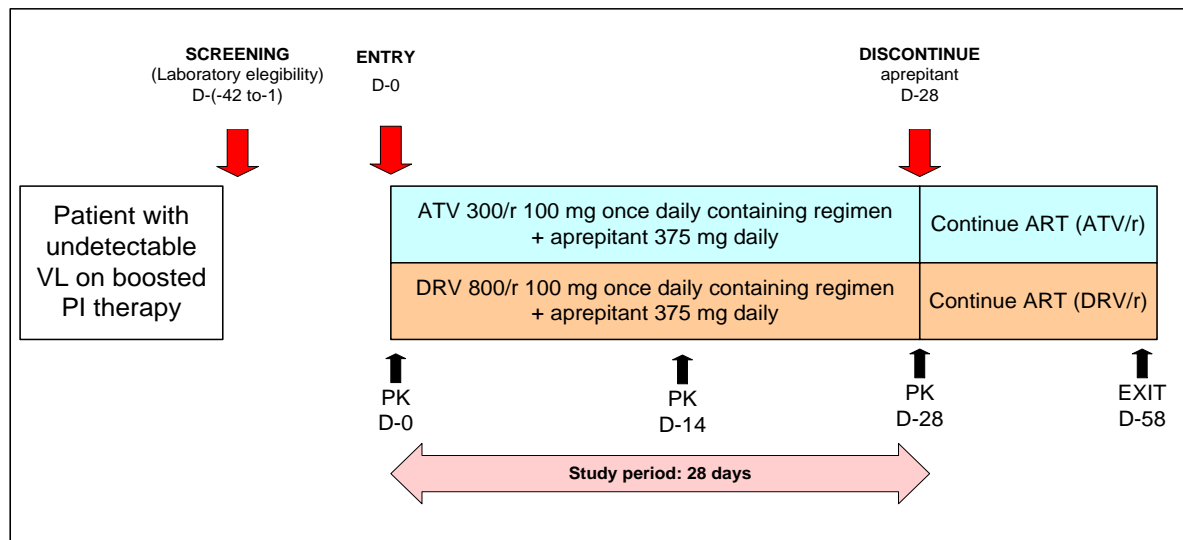
You will come to the Entry visit having fasted (nothing to eat or drink 8 hours before your visit with the exception of water). You will have a brief physical exam and will be asked about any medicine changes since your last visit as well as any symptoms you may have. You will have about 7 tablespoonfuls of blood drawn for routine safety labs (hematology, chemistries with liver functions tests, fasting lipid panel), CD4 and HIV viral load test will be performed. If you are a woman able to become pregnant, you will have a urine pregnancy test. You will also be asked to complete three questionnaires about depression, anxiety and your sleep patterns.

You will also have a full day Pharmacokinetic study or "PK" study done at this visit. PK studies measure the amount of study drug that is in your blood. For this procedure, a small thin tube for drawing blood samples will be placed into a vein in your arm and left in place during your stay in the clinic. You will have a pre-dose blood sample (approximately 1 teaspoon) drawn and then will take your first dose of study medication in the clinic. A small sample of blood (one teaspoon at each time point) will be taken to test for the level of drug in your blood at 30 minutes, 1 hour, 2 hours, 4 hours and 8 hours after taking the medication. The total amount of blood drawn for the PK portion of your visit will be about 2 tablespoons.

You will be given study drug in a blister pack. You will bring your study drug, including empty blister packs, with you to all study visits.

This is an open label (you will know what treatment you are taking) study. You will continue taking your current HIV treatment on this study and will **ADD** aprepitant (375 mg) for 28 days. When the 28 days of treatment with aprepitant are over, you will continue taking the same HIV medications. Below is a schematic of the study design which the study staff will review with you.

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**Study Visits**

After your Entry visit, you will come to the CTRC for study visits on days 7, 14, 28 and 58. You will be called a couple of days before each visit to remind you of your appointment, to come to the clinic in a fasting state for your study visit, and to bring your study drug with you. The research staff will check your study drug and count any remaining pills. Most importantly, you will be reminded NOT to take your study medicine in the morning of all of your study visits, as a blood sample will be drawn in the clinic to measure the level of the study drug.

Day 7

At these visits, you might have a brief physical exam performed, your vital signs will be taken and you will be asked about your health and if you have any side effects from the study drug. You will also be asked about any other medicines you may be taking. Routine safety labs (chemistries and hematology), HIV viral load, and CD4 count will be checked at all visits and will require about 2 tablespoons of blood. These visits should last less than an hour.

Days 14 and 28

In addition to the procedures and laboratory evaluations done at Day 7, specialized immunology and virology testing, as well as a fasting lipid panel, a urine pregnancy test and PK analyses will be done at these visits.

The PK (Pharmacokinetic tests) will be performed exactly as they were at the entry visit. A small thin tube for drawing blood samples will be placed into a vein in your arm and left in place during your stay in the clinic. You will have a pre-dose blood sample drawn (approximately 1 teaspoon) and then will take your first dose of study medication in the clinic. A small sample of blood (1 teaspoon at each time point) will be taken to test for the

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level of drug in your blood at 30 minutes, 1 hour, 2 hours, 4 hours and 8 hours after taking the medication.

These extra tests will require about 3 tablespoons of blood, so 5 tablespoons will be drawn at these visits.

On Day 28, you will be asked to complete the same questionnaires regarding anxiety, depression and sleep patterns that you completed at the enrollment visit.

On Day 28, you can be expected to be in the CTRC for at least 8 hours; meals will be provided to you on a regular schedule to coincide with the blood draws for the PK sampling.

Final Study Visit (Day 58)

Finally, you will return to clinic on day 58 about 8 weeks after entering the trial. You will be asked about your health and have about 7 tablespoons of blood drawn for routine safety labs, HIV viral load, CD4, special immunology and virology samples. You will be asked to complete the same questionnaires regarding anxiety, depression and sleep patterns that you completed at the enrollment and Day 14 visits. This visit may last an hour.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

12 people will take part in this study; 6 people in the Darunavir/ritonavir Arm and 6 people in the Atazanavir/ritonavir Arm. The University of Pennsylvania is the only center participating in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will take the study drug aprepitant for 28 days and then come in for a follow-up visit on or about day 58, which is about 8 weeks after starting the study.

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:

- the study is cancelled by the U.S. Food and Drug Administration (FDA), National Institute of Mental Health (NIMH), the Safety Monitoring Committee for 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 are not able to attend the study visits as required by the study.

The study doctor may also need to take you off the study drug without your permission if:

- continuing the study drug may be harmful to you
- you need a treatment that you may not take while on the study
- you are not able to take the study drug as required by the study.
- you become pregnant.

If you must stop taking the study drug before the study is over, you will be asked to come in for a final visit.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug 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 are taken with the study drugs. 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.

If you have any injuries or medical problems during this research study, you should inform your treating physician that you are in a research study.

Risks of Study Drugs supplied by the study:

Aprepitant Side Effects

The main use of aprepitant has been for the prevention of nausea and vomiting with chemotherapy. Clinical adverse experiences in conjunction with chemotherapy (incidence greater than 10%) are: alopecia (hair loss), anorexia (weight loss), asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea. Clinical adverse experiences (incidence greater than 5%) are: constipation, hypotension (low blood pressure), nausea, pruritus (itchy skin), pyrexia (fever).

In a study conducted at PENN using the dose that is planned for this study, participants experienced adverse events that were mild to moderate in severity and included diarrhea, fatigue, and grogginess. The events reported in the placebo group were similar. In this study, participants were given study drug for 14 days. In the current study, Aprepitant will be given for 28 days; this is the first time Aprepitant will be given for this length of time to HIV+ people and side effects are therefore unknown.

Risks of Drugs Received by Prescription, but are required for the study:

These risks are for the drugs used as part of your standard of care treatment. The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug 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 are taken with the study drugs. 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.

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If you have any injuries or medical problems during this research study, you should inform your treating physician that you are in a research study.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

Autoimmune disorders such as Graves' disease (a disease in which the thyroid produces excessive thyroid hormones), polymyositis (a disease caused by inflammation leading to weakness of the muscles), and Guillain-Barre syndrome (a disease that occurs when the body's immune system attacks part of the nervous system, leading to nerve inflammation that causes muscle weakness), have also been reported to occur in the setting of immune reconstitution, however, the time to onset is variable and can occur many months after starting treatment. Call your study doctor right away if you notice any signs or symptoms of an infection after starting study medication.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Protease Inhibitors (class of drugs which includes ATZ, DRV and RTV)

The use of protease inhibitors may be associated with the following:

- Increases in the amount of triglycerides (fat in blood) and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Risks of Atazanavir (ATV, REYATAZ®):

- Increased bilirubin, which may be associated with yellowing of the eyes
- Upset stomach, vomiting, and diarrhea
- Abdominal pain
- Increases in liver function tests
- Headache
- Rash (redness and itching)
- Numbness, pain, or tingling in the arms and legs

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- Trouble sleeping
- Flu-like syndrome
- Increased cough
- Fever
- A change in the way your heart beats (heart rhythm change). Symptoms you may experience if this occurs include dizziness or lightheadedness.

Darunavir (DRV)

The following side effects are associated with the use of darunavir given together with ritonavir (RTV):

- People taking darunavir together with ritonavir may develop severe liver problems, which may be life-threatening. People who have increased (abnormal) liver function tests before starting darunavir and people with liver diseases such as hepatitis B or C have an increased risk of worsening liver disease. If you are developing liver problems, you may have one or more of the following: yellowing of the skin or whites of your eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale colored stools, itchy skin.
- Rash, which could blister, and may be severe or life-threatening. Contact your health care provider immediately if you develop a rash.
- Diarrhea
- Nausea
- Stomach discomfort
- Vomiting
- Headache
- Abnormal increases in cholesterol
- Abnormal liver function blood tests
- Abnormal pancreatic blood tests
- Bone death that may lead to bone collapse

Note: Before starting darunavir, you should inform your healthcare provider if you are allergic to sulfa medicines.

Ritonavir (RTV)

The following side effects have been associated with the use of ritonavir:

- Feeling weak and tired
- Stomach and bowel problems including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools
- Loss of appetite
- Headache
- Dizziness
- Abnormal increases in triglycerides and cholesterol in blood
- Numbness and tingling in the arms, legs and around the mouth
- Rash
- Abnormal liver function blood tests which may be due to possible liver problems. Liver problems including cases of death have occurred in people taking ritonavir.
- Fever

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- A change in the sense of taste
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal heart rhythm and electrocardiogram (EKG) changes. If you develop abnormal heart rhythm you may experience lightheadedness, fainting spells, or an abnormal heart beat.
- Allergic reactions that can be serious that may include symptoms like hives, trouble breathing and mild to severe skin rashes or reactions.

Risks of Blood Draw and -IV line:

The process of drawing blood in some cases may cause bleeding, bruising, pain, blood clots, lightheadedness, and some minor swelling around the area of the needle sticks. Occasionally an infection or bleeding may develop where the needle was placed in the vein. The iv line may need to be replaced during the PK visit due to repeated blood draws. In rare instance, fainting may occur.

In addition, the multiple blood draws and visits to the research center may be time consuming and inconvenient.

ARE THERE RISKS RELATED TO PREGNANCY?

In studies with rats, no effect on fertility or embryonic development was noted. However, there have been no studies conducted in humans and therefore, if you are pregnant you will not be able to participate in this study. If you become pregnant while on study, you will be asked to stop taking the study medication.

All subjects are requested not to participate in a conception process while on study, ie. no egg or sperm donations and for all subjects able to become pregnant, use of at least one of the forms of contraception listed below while receiving the protocol-specified medication and for 30 days after stopping the medication.

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- IUD

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, your HIV viral load may go down while you are receiving aprepitant, but it will very likely return to where it started (the baseline level) once the drug is stopped. Aprepitant may also have no effect on the HIV in your blood. You may receive no benefit from being in this study, but the information learned from this study may help others who have HIV and lead to a new way to treat HIV infection.

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WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of continuing with your current treatment regimen or participating in another study with experimental drugs, if you qualify.

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?

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

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

Your personal information may be given out if required by law. If you test positive for HIV or if a CD4 or viral load is done at a study visit, by law we have to report the result to the City of Philadelphia Health Department/PA Department of Health. We would report your name, gender, racial/ethnic background, and the month and year you were born. This is to keep track of how many people in the U.S. have HIV infection. It is also to make sure that states get enough money from the federal government to support the medical care of people living with HIV. The Health Department does not share the names of HIV infected people with anyone else. It removes all personal identifiers, such as your name, before giving information on the number of HIV infections to the federal government.

By signing this Consent/Authorization Form 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 processing of this study.

What personal health information is collected and used in this study, and also might be shared?

Personal health and contact (phone number, address) information collected as part of this study is recorded in your clinical trial chart. This record is separate from your medical chart. Data collected for the study is reported to the study team on a case report form, which includes the information listed below, but not your name or other identifying information. Results of laboratory tests or study procedures will be copied and sent to your primary care physician by name, at your request only.

Personal health information that is collected and will be disclosed to the agencies listed on the following page as part of this research study is:

- Email addresses, medical record number (MRN) and social security number

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- Demographics (Race, Gender)
- Study medication compliance and toxicities
- Signs and symptoms you experience while on the study
- Current and past medical diagnoses; allergies
- Current and past medications and therapies
- Information from a physical exam: weight, blood pressure, heart rate, temperature
- Data from laboratory tests (blood chemistry and hematology tests), CD4 count, viral load, tropism assays; immunology studies; virology studies, genotyping/phenotyping studies
- Data from pharmacokinetic studies (drug levels in your blood)

Why is your personal health information being used?

Personal contact information, such as phone number and address, will be used only by clinical trial staff to get in touch with you while you are participating in this study. Your health information and results of tests and procedures are being collected as part of the research study and for the advancement of medicine and clinical care. The Principal Investigator will use the results to monitor your safety and ability to tolerate the study medications.

Which of our personnel may use or disclose your personal health information?

The following individuals and organizations may use or disclose your personal health information for this research project:

- The Principal Investigator and other University staff associated with this study;
- The University of Pennsylvania Institutional Review Boards (the Committees charged with overseeing research on human subjects) and the University of Pennsylvania Office of Regulatory Affairs
- Authorized members of the University of Pennsylvania and the University of Pennsylvania Health System and School of Medicine work force who may need to access your information in the performance of their duties, for example, to provide treatment, to ensure the integrity of the research, accounting or billing matters, etc.

Who, outside of the University of Pennsylvania Health System and the School of Medicine, might receive your personal health information?

As part of the study the Principal Investigator, study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures to the following:

- Pharmaceutical Sponsors: Drug companies (Merck Pharmaceuticals) who supply treatment for the study will have access to safety information.
- Government Agencies: Data from this study will be made available to the Food and Drug Administration and the National Institute of Mental Health, for them to evaluate the safety and efficacy of the treatments being used in this study.

Study staff will inform you if there are any changes to this list above during your active participation in the trial. Once information is disclosed to others outside the University of

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Pennsylvania Health System or School of Medicine the information may no longer be covered by federal privacy protection regulations.

In all disclosures outside the University of Pennsylvania Health System or School of Medicine, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier, unless disclosure of the direct identifier is required by law. Personal health information will be disclosed by a unique code number. Only study staff can break the code and identify you to your code.

How long will the University of Pennsylvania Health System and the School of Medicine be able to use or disclose your personal health information?

Your authorization for use of your personal information for this specific study does not expire. This information may be stored in a database (research repository). However, the University of Pennsylvania Health System and the School of Medicine may not re-use or re-disclose your personal health information collected for this study for another purpose other than the research described in this consent form unless you have given written permission to the Principal Investigator to do so. However, the University of Pennsylvania Institutional Review Board may grant permission to the Principal Investigator or others to use your information for another purpose after ensuring that appropriate safeguards are in place. The Institutional Review Board is a committee whose job is to protect the safety and privacy of research subjects. Results of all tests and procedures done solely for this research study and not as part of your regular care will not be included in your medical record unless you want them to be sent to your primary care provider. You will need to complete a medical records release of information to allow us to provide study data to your doctor.

Will you be able to access your records?

You will be able to request access to your medical record when the study is completed. During your participation in the study, you will not be able to access your medical records. Your information will be available should an emergency arise that would require your treating physician to know the information to best treat you. You will have access to your medical record and study information that is part of that record when the study is over. The Investigator is not required to release to you research information that is not part of your medical record.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your personal information for research, but you must do so in writing to the Principal Investigator at 502 Johnson Pavilion. Even if you withdraw your permission, the Principal Investigator for the research study may still use your personal information that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission to use your personal health information that means you will also be withdrawn from the research study.

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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 ARE THE COSTS TO ME?

The study drug, exams, and blood tests will be provided for free.

WILL I RECEIVE ANY PAYMENT?

You will receive \$25 for the Screen visit , Day 7 and Day 58 visits. At the entry, Day 14 and Day 28 visits [PK visits] you will receive \$150. Thus, if you attend all study visits [\$75] and have the three PK analyses performed [\$450], the maximum compensation you can receive for the study is \$525. In order to be compensated for your participation in this study, you must 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.

WHAT HAPPENS IF I AM INJURED?

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.

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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. You will be treated 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 would like the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Pablo Tebas, MD (215-349-8092)
- 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

SIGNATURE PAGE FOR STUDY

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date