

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Tibotec Therapeutics Clinical Affairs, A Division of Centocor Ortho Biotech Services, LLC.
TMC114HIV4023, Amendment 2, 18 FEB 2009

A multicenter, open-label, randomized study to assess the metabolics, efficacy, and safety of once-daily darunavir versus atazanavir in HIV-infected treatment-naïve adult patients

CONSENT FORM TO PARTICIPATE IN THE METABOLIC SUBSTUDY

Your contacts at the Hospital of the University of Pennsylvania, Philadelphia for this study are:

Principal Investigator:	Pablo Tebas, MD	(215) 349-8092
Coordinator:	Joseph Quinn, RN	(215) 349-8092
Study Nurse:	Larisa Zifchak, RN	(215) 349-8092
E-clamp Nurse:	Carissa Fuller, RN	

Infectious Disease Clinical Trials Unit, 502 Johnson Pavilion, Philadelphia, PA 19104
24 Hour Emergency Number (215) 662-6059 Ask for the Immunodeficiency Program Doctor on call

INVITATION TO PARTICIPATE:

In addition to the main study, you have been asked to participate in a substudy that will evaluate data obtained from two additional metabolic tests. Specifically, these are the euglycemic hyperinsulinemic clamp and brachial artery reactivity tests, which are explained further in the consent form. However, before you agree to take part in this substudy, please read this consent form carefully and ask as many questions as you need in order to be sure you understand the study procedures, including possible risks and benefits.

This consent form contains important information to help you decide whether or not it is in your best interest to take part in this substudy. Your participation in the substudy is voluntary. If you have questions that are not properly explained or answered in this consent form, a member of the research staff will be available to give you more information.

INTRODUCTION:

PREZISTA™ is a protease inhibitor with the generic name of darunavir. Its function is to help prevent the spread of human immunodeficiency virus (HIV) in the body. PREZISTA is marketed in the U.S. to treat human immunodeficiency virus (HIV) infection in adults.

PURPOSE OF THE SUBSTUDY:

This substudy involves research. The main purpose of this substudy is to look at the effect of PREZISTA/ritonavir 800/100 mg once daily versus REYATAZ (atazanavir)/ritonavir once daily on insulin sensitivity (a sign for diabetes risk over time) at 12 and 48 weeks of study treatment using the euglycemic hyperinsulinemic clamp method. Also, to assess the effect of PREZISTA/ritonavir 800/100 mg once daily versus REYATAZ/ritonavir once daily on endothelial function (an indirect sign of cardiovascular risk) at 12 and 48 weeks of study treatment using ultrasound to determine brachial artery reactivity.

DESCRIPTION OF THE SUB-STUDY

Up to 20 subjects will participate in this substudy; about 2-5 people are expected to participate at the University of Pennsylvania. Patients who take part in this substudy will also participate in the main study at the same time for up to 48 weeks of treatment.

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

TMC114HIV4023: Metabolic Substudy

CONSENT FORM

PROCEDURES:

Euglycemic hyperinsulinemic clamp

Euglycemic hyperinsulinemic clamp is a procedure used to measure insulin sensitivity. Your pancreas secretes insulin, a hormone responsible for your cells' ability to uptake, store, and use glucose for energy. Without insulin, glucose (the energy your body converts from food) cannot get inside your cells where it is used for energy or stored for energy use later on. Normal levels of insulin are healthy and necessary. To be healthy, your body needs to produce the right amount of insulin and respond to the insulin appropriately. The euglycemic clamp is used to assess the effects of the different study drugs on insulin sensitivity. The procedure takes at least 3 hours and an additional hour for recovery. Hence, the minimum time you will spend in the CTRC is about 4 hours.

This is a research procedure in which a person receives insulin (a natural hormone) through an intravenous (IV) catheter (small flexible plastic tube used to take fluids out or put fluids in the body). Insulin increases the removal of sugar from the blood, and the amount of sugar (also given by vein) required to keep a person's blood sugar normal, is a measure of how effective insulin is in that person. One catheter will be placed in your hand and your hand will be warmed to 45-50 degrees Celsius (113-122 degrees Fahrenheit) in a heated box to increase blood flow in the hand. This catheter will be used for removing all blood samples during the study (the total amount of blood removed is about ½ cup). The other catheter will be placed in your opposite arm and will be used for giving you insulin and glucose.

You will receive a constant infusion of insulin, which will raise your blood level of insulin to about the level it would normally reach after a large meal. Your blood sugar will then be checked at 5-minute intervals through the IV line, i.e. you will not need a finger stick or blood draw, and you will receive a glucose (sugar) solution by vein at a rate adjusted to keep your blood sugar normal. The insulin will be continued for 3 and one half hours.

After completing the euglycemic clamp, the insulin infusion will be turned off, and you will be given lunch. During the next hour the sugar solution will gradually be tapered and stopped. When the IV sugar solution is stopped and your blood sugar is normal, the IV catheters will be removed and you will be allowed to leave.

Brachial artery reactivity by ultrasound

An ultrasound is a test using high frequency sound waves that evaluates the flow of blood through the veins in the body. Sound waves are transmitted from the ultrasound device into your body. As the sound waves bounce off structures in body, images are produced and recorded. The brachial artery is the main artery of the upper arm and the ultrasound will be used to assess the effects of the different study drugs on the blood flow of the artery.

Screening:

The screening visit will be conducted up to 4 weeks before you begin participation in this substudy. This visit will be completed to determine your eligibility for enrollment into this substudy. The informed consent will be reviewed and signed during this visit. This is to occur before any study specific procedures occur.

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

TMC114HIV4023: Metabolic Substudy

CONSENT FORM

Baseline (Day 1), Week 12 and Week 48 Visits:

These visits will occur at the same time as the Baseline, Week 12 and Week 48 visits from the main Study. The following substudy procedures will be performed at these visits:

- Euglycemic hyperinsulinemic clamp
- Brachial artery reactivity by ultrasound

POSSIBLE RISKS/SIDE EFFECTS

You may feel discomfort during this some of these tests and some may also have risks, such as:

- Possible side effects from drawing blood include: faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- There is a very small chance of having a low blood sugar reaction (called hypoglycemia) while getting the insulin and glucose drips, but the glucose is being given specifically to prevent this and your blood sugar is being tested frequently to help adjust the glucose to keep it normal. A low blood sugar reaction can have many symptoms, most commonly feelings like shakiness, sweating, clammy skin, weakness, hunger, nausea, confusion, fast heart beat, or mood change; you could feel any combination of these types of symptoms. Treatment for a low blood sugar reaction would involve giving you more sugar directly into your vein, at which point your symptoms would stop.
- Possible side effects from the blood draw: while a catheter is in your vein it is typically painless, but it can result in some swelling, discomfort, or (rarely) infection at that site. Also rarely, a little blood clot can form at the end of the catheter so that blood cannot be drawn out through it. If this were to happen, the catheter would need to be removed and a new one placed at a different location. You may also experience a burning or stinging sensation as a result of the glucose infusion.
- There is a possibility of other risks not mentioned here which are unforeseeable

Risks associated with the use of the study medications are described in the informed consent form that you already signed for the main study.

OTHER POSSIBLE RISKS:

The study drug treatment and study procedures may involve risks that are currently unknown or unpredictable. Significant new findings developed during the course of this research, which may affect your willingness to continue participation, will be provided to you. Your study doctor and research staff will ask you about any side effects you have experienced at every visit. If you have any problems, you should let the doctor know immediately.

POSSIBLE BENEFITS

There will be no additional direct benefit for you if you decide to take part in the substudy.

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

TMC114HIV4023: Metabolic Substudy

CONSENT FORM

ALTERNATIVE PROCEDURES FOR TREATMENTS:

You do not have to participate in this substudy. If you choose not to participate in this sub-study you can still be in the main study.

VOLUNTARY PARTICIPATION/WITHDRAWAL FROM THIS STUDY:

Your participation in this substudy is completely voluntary. You may decide not to participate or you may withdraw from the study at any time without penalty and without affecting your medical care or eligibility for future medical care at this site. No new data will be added to the database after you withdraw your consent.

If additional information becomes available during the trial that might change your decision to be in the trial, you or your legally authorized representative will be informed in a timely manner.

The study doctor or sponsor also has the right to withdraw you from the research at any time without regard to your consent if they feel that it is in your best interest. In this situation, you will be asked to complete any laboratory tests and examinations your doctor thinks necessary. You will also be asked questions about your experience with the drug.

With your permission, your study doctor, will inform your primary care doctor about your participation in this trial.

COMPENSATION:

You will be compensated \$300 (as a check) for each of the substudy evaluations you attend. Thus, if you attend all substudy evaluations (3), the maximum compensation you will receive from your participation in the substudy is \$900.

Tibotec Therapeutics Clinical Affairs, a division of Centocor Ortho Biotech Services, LLC is paying your study doctor and/or your study doctor's institution, University of Pennsylvania to conduct this study. The amount of this payment is sufficient to cover the doctor's and/or institution's expenses to perform the study but provides minimal personal financial benefit to your study doctor and/or his/her institution.

COMPENSATION FOR INJURY:

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 direct result of taking the study drug or the study procedures in this research study, please contact the investigator listed on page one of this form.

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

TMC114HIV4023: Metabolic Substudy

CONSENT 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 sponsor, Tibotec Therapeutics Clinical Affairs, a division of Centocor Ortho Biotech Services, LLC. 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.

Tibotec Therapeutics Clinical Affairs, a division of Centocor Ortho Biotech Services, LLC will pay for any immediate care and/or treatment beyond what is covered by your health insurance. This agreement to provide free medical treatment does not include treatment for any injury/illness, which is not the result of the research.

STATEMENT OF PRIVACY:

We will do our best to make sure that the personal information in your medical record 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. Please refer to the separate "HIPAA Privacy Authorization" document (from the main study) that explains more specifically how your personal information will be protected.

CONTACT INFORMATION :

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

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

TMC114HIV4023: Metabolic Substudy

CONSENT FORM

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 signed 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 in BLOCK LETTERS) 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.
