

Merck & Co., Inc. 033-01, 21-Jun-2007

A Multicenter, Double-Blind, Randomized, Active-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 Versus KALETRA™ in HIV-Infected Patients Switched from a Stable KALETRA™-Based Regimen

## CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Your contacts for this study are:

|                         |                      |                |
|-------------------------|----------------------|----------------|
| Principal Investigator: | Ian Frank, MD        | (215) 662-7419 |
| Investigators:          | Pablo Tebas, MD      | (215) 615-4321 |
| Coordinators:           | Joseph Quinn, RN     | (215) 349-8092 |
|                         | Randee Silverman, RN | (215) 349-8092 |

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

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**INTRODUCTION**

You are being invited to take part in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. This consent form has information to help you decide if you want to participate. The research team will also talk to you about the study. You may also decide to discuss it with your family, friends or family doctor. You may find some of the medical language difficult to understand. Take your time, read this form carefully, and ask the study doctor or staff any questions you may have. There may be reasons why you are not allowed to take part in this study. The study doctor or staff will discuss these with you. If you decide to participate, you will be asked to sign this form.

The study doctor will be paid by the Sponsor, Merck & Co., Inc., for conducting this study.

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to:

- Test the safety of the research study drug, MK-0518.
- Test how well MK-0518 works against HIV-1 compared to KALETRA™.
- Test the effect MK-0518 has on levels of cholesterol and blood lipids, compared to KALETRA.

This is a research study to test MK-0518, a new drug that has been approved by the United States Food and Drug Administration (FDA) to help control HIV infection. MK-0518 is approved for use with other anti-HIV medicines in patients who are already taking or have taken anti-HIV medicines and the medicines are not controlling their HIV infection. MK-0518 is also known by the trade name, ISNETRESS™, or generic name, raltegravir.

KALETRA (lopinavir/ritonavir) is available by prescription for use in combination with other anti-HIV medicines to treat people with HIV infection.

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MK-0518 is an integrase inhibitor and Kaletra is a protease inhibitor. HIV is a virus that uses the body's CD4 (immune fighting) cells to make copies of itself. There are several steps in the replication process; anti-HIV medications are designed to interrupt this process and are named according to where they work in the virus' life cycle. Protease inhibitors stop a specific enzyme from cutting proteins into the smaller pieces that are needed for new viruses. As a result the new viruses that are made are incomplete and cannot infect new CD4 cells. Integrase inhibitors prevent HIV-DNA from combining with the CD4 cell's DNA and thus, new viruses are unable to be made.

#### HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 340 people will be in the study; about 5-10 people will be in the study at PENN. You will be in the study about 50 weeks (approximately one year).

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

If you take part in the study, you will need to do the following:

- Visit the study doctor about 9 times.
- Fast (nothing to eat or drink except water) for 12 hours before some of your study visits.
- If you are a woman who can have a baby, you must agree to use acceptable methods of birth control during the entire study. If you are a heterosexual male, you and your sexual partner must agree to use acceptable methods of birth control during the entire study. Acceptable methods of birth control include intrauterine device (IUD), diaphragm with spermicide, condoms, or not having sex. **Oral birth control pills, hormone patches or hormone injections, are not an acceptable method of birth control during the study.**
  - If you become pregnant during the study, you must immediately stop taking all study medication and call one of the investigators on page 1 of this form to tell them about your pregnancy. Your condition will be followed until the end of the pregnancy. If you deliver a baby, the health of the infant must be reported to the Sponsor.
- Take study drugs as instructed. You will need to take 3 tablets of study drugs twice a day plus your background anti-HIV medications.
- Complete a diary about when you take the study drugs.

You will be assigned by chance to get either MK-0518 or to continue receiving KALETRA. You have a 1 in 2 chance of getting MK-0518 and a 1 in 2 chance of continuing to receive KALETRA. Neither you nor the study doctor will know which of these you are receiving. In case of an emergency, the study doctor can get this information.

#### WHAT WILL HAPPEN DURING THE STUDY VISITS?

When you come in for your study visits, the study doctor or staff may do any or all of the following:

- Review your medical history.
- Review medications you are taking.
- Review adverse events.
- Perform a physical exam.
- Measure your height and weight.
- Measure your hips, waist, arm, thigh, neck and chest.
- Check your vital signs (including blood pressure, heart rate, temperature, breathing rate).

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- Collect blood and urine samples.
- Perform a pregnancy test for women who are able to have children.
- Have you complete surveys about your treatment, symptoms, and health-care visits.
- Give you study drug, diary cards and instructions.

Some of these tests will be used to measure if the drug is working while other tests will be used to monitor your health.

#### WHAT EFFECTS COULD THE TESTS HAVE ON ME?

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

- Fasting for 12 hours before your visit could cause dizziness, headaches, stomach discomfort or fainting.
- Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection. About 323 mL (22 tablespoonfuls) of blood will be collected during the entire study.

#### ABOUT THE STUDY DRUG(S)

KALETRA is made by Abbott Laboratories and not by the Sponsor. The matching placebo for KALETRA is made by the Sponsor, according to laws about clinical testing, to look like KALETRA. Neither the matching placebo nor this study is sponsored by, approved by, or affiliated with Abbott Laboratories.

MK-0518 is an HIV-integrase inhibitor being developed by Merck & Co., Inc., for the treatment of HIV infection. This drug may be effective in the treatment of HIV infection when given in combination with other anti-HIV drugs.

#### WHAT ARE THE RISKS OF THE STUDY MEDICATIONS?

##### MK-0518 (raltegravir):

##### **Treatment experienced patients**

The safety profile of raltegravir (also known as MK-0518 or ISENTRESS™) in treatment-experienced patients is based on the combined safety data from three patient studies. In these studies, raltegravir was given at 400 mg twice a day, in combination with other HIV drugs to 507 patients, in comparison to 282 patients taking the comparator placebo ( a drug that looks the same as raltegravir but has no active ingredient) in combination with other HIV drugs. In these studies, the longest that anyone took raltegravir was about 2 ½ years.

For patients in the raltegravir + other HIV drugs and in the placebo + other drug groups, the most commonly reported side effects (>10% in either raltegravir or placebo group), of all intensities and regardless of causality were:

- Diarrhea
- Headache
- Nausea
- Fever (pyrexia)

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In this combined analysis, the rates of discontinuations of therapy due to side effect were similar in patients receiving raltegravir + other HIV drugs, and in patients receiving placebo + other HIV drugs.

For patients in the raltegravir + other HIV drugs and in the placebo + other HIV drugs groups, common side effects occurring in greater than or equal to 2% of patients and considered by investigators to be of moderate (discomfort enough to cause interference with usual activity) or severe (not able to work or do usual activity) intensity, and related to any drug in the combination regimen (raltegravir or placebo alone or in combination with other HIV drugs) are:

- Diarrhea
- Nausea
- headache

Less common side effects occurring in at least 1% but less than 2% of patients and considered by investigators to be of moderate or severe intensity, and related to any drug in the combination regimen are:

- Abdominal pain
- Vomiting
- Weakness (asthenia)
- Fatigue
- Dizziness
- Acquired lipodystrophy

The following serious drug-related reactions were reported in the treatment -experienced studies:

- Hypersensitivity or drug sensitivity (was seen in 2 patients, the patients stopped taking raltegravir, and restarted with no further side effects)
- Low amounts of red blood cells (anemia)
- Low amount of white blood cells (neutropenia)
- Heart attack (myocardial infarction)
- Irritation of the stomach lining (gastritis)
- Liver problem (hepatitis)
- Herpes simplex
- Problem with the kidney (toxic nephropathy and renal tubular necrosis)
- Decrease in kidney function (renal failure)
- Continuous decrease in renal function (chronic renal failure)

Moderate (grade 3) or severe (grade 4) laboratory abnormalities observed in greater than 2% of patients treated with raltegravir + other HIV drugs or in patients treated with placebo + other HIV drugs included:

- Increased liver related enzymes and tests which may be a sign of liver problems: AST, ALT and bilirubin
- Increase in an enzyme that helps digest fats: pancreatic amylase
- Decrease in amount of white blood cells: absolute neutrophil count
- Increase in an enzyme released by muscle cells: creatine kinase
- Elevations in creatine kinase were observed in patients treated with raltegravir. Myopathy (disease causing muscles not to work properly) and rhabdomyolysis (disease causing a breakdown of muscle tissue) have been reported, however, the relationship of raltegravir to these events is not known. Possible symptoms related to these abnormal blood tests are unexplained muscle pain, tenderness or weakness.

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Cancers have been seen both in patients who took raltegravir with other HIV drugs and in patients receiving placebo plus other HIV drugs. Some were cancers that the patient had before. Several cancers were seen in the first three months of treatment. The specific cancers were cancers expected in patients with very sick immune systems. Most patients had other risk factors for cancer. It is unknown if the cancers were related to raltegravir use.

A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when combination antiretroviral treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to control the HIV infection and strengthen the immune system.

**Treatment-naïve patients**

In treatment naïve patients, raltegravir when administered with tenofovir and lamivudine, as compared with efavirenz plus tenofovir and lamivudine has a generally similar safety profile to that in treatment-experienced patients.

**KALETRA (lopinavir/ritonavir):**

The following serious side effects have been reported by some patients being treated with KALETRA:

- Inflamed pancreas
- Increased blood lipids/fats (such as cholesterol and triglycerides)
- Immune reconstitution syndrome (an increased response of the immune system to a low-grade or symptom-free infection)

Other serious side effects have been seen in patients taking protease inhibitors (such as KALETRA):

- Diabetes / Increased blood sugar
- Increased bleeding
- Increased body fat / Changes in body fat distribution
- Decreased liver function / Liver toxicity

The following side effects of KALETRA have been commonly reported:

- |                                     |                       |
|-------------------------------------|-----------------------|
| • Diarrhea                          | • Nausea              |
| • Abdominal Pain                    | • Feeling Weak        |
| • Headache                          | • Vomiting            |
| • Dyspepsia (upset stomach)         | • Intestinal gas      |
| • Rash                              | • Vein distended      |
| • Decrease in appetite              | • Weight Loss         |
| • Muscle pain                       | • Depression          |
| • Insomnia                          | • Decreased sex drive |
| • Tingling skin                     | • Bronchitis          |
| • Decrease in testicle size (males) | • Chills              |
| • Fever                             | • High blood pressure |

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Abnormal blood tests considered by the study doctor to be a side effect of KALETRA in combination with other anti-HIV drugs include:

- Increased liver function tests which may be a sign of liver problems
- Increased levels of amylase
- Increased levels of uric acid
- Decreased levels of phosphorus
- Increased levels of blood fats such as total cholesterol and triglycerides
- Increased levels of blood sugar
- Decreased white blood cells (neutrophils) associated with immune response

Other less common side effects have been reported for both MK-0518 and KALETRA. The study doctor or staff can discuss these with you.

There may be other side effects or risks that are not known at this time. Your doctor will explain to you the side effects known about the other anti-HIV drugs you may receive with the study drug.

It is not known whether the study drug(s) may affect an unborn baby.

It is recommended that any patients who meets the criteria for virologic failure (two consecutive viral load measurements greater than 50 copies/mL taken at least 1 week apart) should discontinue participation in the study. If you develop virologic failure your study doctor will talk to you about the best medicines for you to take.

If you enroll in this study, there is a risk that the study medicines will not work as well as the medicines that you were taking before the study. There is also a risk that if you stop taking the study medicines, and start taking your old medicines again, your old medicines would no longer work for you.

**WHAT IF NEW INFORMATION BECOMES AVAILABLE ABOUT THE STUDY?**

You will be told in a timely manner about significant new information that might affect your decision to stay in the study.

**WHAT HAPPENS IF I AM INJURED?**

In the event of any physical injury resulting from the research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the University of Pennsylvania.

If you are injured directly from the study drug, the Sponsor will pay for the reasonable costs of medical treatment, to the extent they are not covered by your medical or hospital insurance or governmental or other programs providing coverage. No other form of compensation is available from the Sponsor.

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You or your third party payer, if any, may be billed for medical expenses associated with this study only if they are deemed medically necessary and if such expenses would have incurred independent of the study.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

If the drug works, you may have some benefit. If the drug does not work, you will not benefit. Information learned from the study may help other people in the future.

**WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?**

Your options include:

- Enrolling in another HIV research study if you are eligible.
- Taking other anti-HIV medications.

The study doctor can discuss these options with you.

**WHEN IS THE STUDY OVER? CAN I LEAVE THE STUDY BEFORE IT ENDS?**

This study is expected to end after all participants have completed all visits, and all information has been collected. This 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, 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 study at anytime. Withdrawal will not interfere with your future care.

**HOW WILL MY PRIVACY BE PROTECTED?**

If you agree to be in this study, health data that identifies you will be kept confidential. Unless required by law, only those listed below will have direct access to your medical records to check the study information:

- the study doctor and staff;
- the sponsor;
- those working for the sponsor;
- independent ethics committees;
- inspectors from government regulatory agencies.

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A more detailed explanation of how health data about you will be used and shared is included in a separate form. If you decide not to sign this separate form, you will not be able to participate in the study.

**WHAT ARE THE COSTS TO ME?**

You will not have to pay for the study-related clinic visits, examinations, study drugs (MK-0518 or Kaletra) or laboratory tests. You will need to continue your other HIV medications and will be responsible for the associated costs.

**WILL I RECEIVE ANY PAYMENT?**

You will be paid \$25 per study visit for a total up to \$225 (9 visits) if you complete the study.

**WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?**

If you wish further information regarding your rights as a research subject, you may contact the Director of Regulatory Affairs at the University of Pennsylvania by telephoning (215) 898-2614. If you ever have questions pertaining to your participation in this research study or about research-related injuries, you may contact the investigators or study nurse listed on the first page of this form.

**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 want the results of the study, let the study staff know.

**By signing below, you agree that:**

- You have read this consent form.
- You have had the chance to ask questions and they have been answered.
- You are aware that taking part in this study is voluntary.
- You may choose not to be in the study or to leave the study at any time by telling the study doctor. You will not be penalized or lose any benefits to which you are otherwise entitled.
- You may have to leave the study without your consent if you need other treatment, do not follow the study plan, have a study-related injury, or for any other reason.
- If you leave the study for any reason, the study doctor may ask you to have some end-of-study tests.
- 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.

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You will receive a signed copy of this consent form.

|                                    |                    |                               |
|------------------------------------|--------------------|-------------------------------|
| _____<br>Printed Name of Volunteer | _____<br>Signature | _____<br>Date<br>(MM/DD/YYYY) |
|------------------------------------|--------------------|-------------------------------|

|   |                    |                               |
|---|--------------------|-------------------------------|
| _____<br>Printed Name of Person Conducting<br>Review Of Consent | _____<br>Signature | _____<br>Date<br>(MM/DD/YYYY) |
|---|--------------------|-------------------------------|