

Official Title: The Effects of Single Dose Rifampin on Pharmacokinetics of Fluvastatin in Uninduced and Hepatically Induced Healthy Volunteers

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**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY**

**Study Title
THE EFFECTS OF SINGLE DOSE RIFAMPIN ON THE PHARMACOKINETICS OF
FLUVASTATIN IN HEALTHY VOLUNTEERS**

This is a medical research study. Your study doctors, Leslie Benet, Ph.D., Professor of Bioengineering & Therapeutic Sciences, Lynda Frassetto, M.D., Professor of Medicine, and/or study coordinators Yue Xiang, Doctor of Pharmacy Candidate and Ivan Kozachenko, Doctor of Pharmacy Candidate will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctors.

You are being asked to take part in this study because you are a nonsmoking person with no active medical problems, taking no medications between the ages of 18-65 years old. If you are determined to be eligible for participation in this study, you may be asked to consider to participate in another similar clinical study (study number: 18-27007). Participation in both studies is not a requirement.

Why is this study being done?

The purpose of this study is to look into the interaction between Fluvastatin (Lescol®) and rifampin when the two drugs are taken together. Fluvastatin is a cholesterol-lowering medication used in combination with diet and exercise to treat high cholesterol and related conditions, and to prevent heart disease. Rifampin is an antibiotic used to treat tuberculosis and a variety of other infections caused by certain germs called bacteria. Both drugs affect a protein found in your liver cells called organic anion transporting polypeptides (OATPs). This protein regulates drugs getting into and out of your body. We want to find out what effect taking the two drugs together has on the level of fluvastatin in the blood of patients.

Who pays for this study?

Private research funds of the primary investigator, Dr. Benet, will help pay for the conduct of this study. This disclosure is made so that you can decide if this relationship will affect your willingness to participate in this study.

How many people will take part in this study?

About 10-12 healthy people will take part in this study.

What will happen if I take part in this research study?

Study location: All study procedures will take place in the Clinical Research Center (CRC) at UCSF (400 Parnassus Ave).

Before you begin the main part of the study...

You will need to have the following “screening” medical history, physical exam and tests to find out if you can be in the main part of the study.

- **Medical History:** You will have a medical history taken, similar to those done for regular medical care.
- **Physical exam:** You will have a physical examination, similar to those done for regular medical care.
- **Urine sample:** You will be asked to give a urine sample for laboratory tests.
- **Blood drawing (venipuncture):** You will be asked to give a blood sample for laboratory tests. Approximately 2 tablepoons (30ml) blood will be drawn by inserting a needle into a vein in your arm for these tests.
- **Pregnancy testing:** Because the drugs in this study can affect a fetus, pregnant women may not participate in this study. If you are a female and have had your first menstrual period, a urine test will be done at the screening visit to make sure you are not pregnant. If you know that you are pregnant or trying to become pregnant, you should tell the investigators now. You will need to use a reliable form of birth control throughout study enrollment 1) abstinence, i.e. not participate in sexual intercourse or 2) condom AND spermicidal agent 3) copper intrauterine device (IUD). Because hormonal contraceptives may interfere with the results of the study, the oral, ‘patch’, and ‘IUD’ ‘ring’ forms of hormonal contraceptives may not be used.

During the main part of the study...

If the screening history, exams and tests show that you can continue to be in the study, and you choose to take part, then you will return to the Clinical Research Center (CRC) at UCSF for two study periods. Each study period is approximately 13-14 hours in length. The two periods will be separated by at least one day.

During both study periods, you will have the same tests and procedures done. The only difference between periods is the medication(s) you receive.

Period 1 and Period 2 Tests and Procedures

Study period 1

- You will avoid grapefruit, oranges, alcoholic beverages, caffeinated beverages, grapefruit juice, and orange juice from 7am the day before study period 1 and until completion of study period 2.
- You will fast (no food or beverages except water) from midnight the night prior to study period 1 until 3 (three) hours after medication administration. You are allowed and encouraged to drink water during this time.
- You will arrive at the Clinical Research Center (CRC) at UCSF by 7:30 am.
- One or two intravenous catheters (small tubes inserted in your vein for withdrawing or introducing fluids) will be placed in an arm vein for collection of blood and rifampin dosing. If you are receiving the rifampin infusion, you will have 2 IVs placed.
- You will then receive one of the following treatment regimens:

- a) Fluvastatin by mouth
- b) Rifampin infused through the vein (IV) for 30 minutes, then fluvastatin by mouth

- The exact order you receive the above treatments may not be in the order listed above, and the order will be determined by chance. After completing the study you will have received both treatment regimens listed (a and b).
- The separate catheter for rifampin infusion will be removed at the end of the infusion (about 30 minutes). The other catheter will be removed after the final blood sample (after about 12 hours).
- Blood samples (~2 teaspoons each) will be collected from the intravenous catheter before you are given each of the study medications and at 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours after receiving fluvastatin. If the intravenous catheter falls out or fails during the study day, you may choose to have another intravenous catheter placed in an arm vein OR have the remaining blood samples drawn by inserting a needle into a vein in your arm.
- Throughout the study visit you will have your blood pressure, heart rate and respiratory rate measured.
- You will also be asked to report any side effects that you notice from the treatments and/or procedures.
- After the 12 hour blood draw, you will be discharged from the CRC to home.

Study Period 2

The second period of the study will preferentially begin 48 hours after study period one. This will follow the same procedures as above. The only difference is you will receive the other treatment medication(s).

Study Chart

The chart below shows what will happen to you during the entire study. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Day	What you do
At least a week before starting the study	<ul style="list-style-type: none"> ● Get screening visit completed.
Day before study period 1	<ul style="list-style-type: none"> ● All day: Avoid grapefruit, oranges, alcoholic beverages, caffeinated beverages, grapefruit juice, and orange juice. ● Night before: Fast (no food or drink other than water) after midnight.
Period 1	<ul style="list-style-type: none"> ● Check-in to CRC at 400 Parnassus Ave by 7:30 am. Leave the hospital after the 12 hour blood draw is completed.
Day before study period 2	<ul style="list-style-type: none"> ● All day: Avoid grapefruit, oranges, alcoholic beverages, caffeinated beverages, grapefruit juice, and orange juice. ● Night before: Fast (no food or drink other than water) after midnight.

Period 2	<ul style="list-style-type: none">● Check-in to CRC at 400 Parnassus Ave by 7:30 am. Leave the hospital after the 12 hour blood draw is completed
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What amount of blood will I have collected in the study?

The total amount of blood drawn during the entire study is about 1/2 pint (approximately 250 ml), which is less than the amount taken during a blood donation. You will not be able to donate blood for 8 weeks after the study.

How long will I be in the study?

The required time for each option is estimated as follows: One 2-3 hour screening visit, and two 13-14 hours stays in the CRC (separated by 1 day). The maximum total time required is approximately 31 hours over a several week period.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while in the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your study doctors may give you medicines to help lessen side effects. Most side effects go away soon after you stop taking fluvastatin and/or rifampin. **In extremely rare cases,** side effects can be serious, long lasting, or may never go away. You should talk to your study doctor about any side effects you experience while taking part in the study.

Fluvastatin:

Fluvastatin is generally well-tolerated. Adverse events are usually mild, go away after the drug is stopped, and require no treatment. Risks and side effects related to fluvastatin include those which are:

Less likely (1-10% chance)

- Muscle pain and/or joint pain
- General weakness
- Headache
- Insomnia
- Gastrointestinal: Dyspepsia, abdominal pain, diarrhea, nausea

Rare but serious (< 1% chance)

- Fluvastatin has been associated with altering certain laboratory blood tests including elevation of blood liver enzyme levels and increases in creatine phosphokinase (a muscle breakdown test).
- Very rare cases of rhabdomyolysis (breakdown of muscle fibers) with kidney failure have been reported with fluvastatin. This usually occurs when taking this medication every day for months.

Rifampin:

Rifampin is generally well tolerated. Adverse events are usually mild, go away after the drug is stopped, and require no treatment. Since only a small number of doses of rifampin will be given, we anticipate side effects to be much less frequent than reported when rifampin is given for months or years. Risks and side effects related to rifampin include those which are:

Likely

- IV Rifampin produces a harmless reddish coloration of the urine, sweat, tears and sputum and may stain contact lenses.

Less Likely (1-10% chance)

- Nausea, vomiting, heartburn, abdominal pain, passing gas, cramps, diarrhea, elevation of blood liver enzyme levels.
- Rash or itching

Rare but serious (<1% chance)

- Headache, drowsiness, dizziness, difficulty with concentration, fatigue

- Decreases in blood cell counts, including decreases in red cells, white cells and platelets
- Changes in menstrual cycles
- Allergic reactions, including rash, itching, swelling, skin breakdown, and transient worsening of kidney function.

Risk and side effects of other procedures include...

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.
- **Intravenous catheter placement and infusion risks:** Placing the intravenous catheter may cause temporary discomfort from the needle stick, bruising, and infection. The risk of rifampin infusion through the vein include pain at the infusion site, irritation of the vein and inflammation. The infusion will be stopped if any discomfort occurs.
- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Appropriate birth control is one of the following: 1) abstinence (i.e. not participate in sexual intercourse) or 2) condom AND spermicidal agent. Because hormonal contraceptives may interfere with the results of the study, the oral, 'patch', and 'ring' forms of hormonal birth controls may not be used.
- **Inconvenience and boredom:** There is inconvenience and boredom from the time spent in the research unit and from eating the same diet on the study days. To decrease boredom, you may bring books, magazines, a radio with headphones, and/or a computer to the research unit.
- **Unknown risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.
- For more information about risks and side effects, ask your study doctor.

Things to follow while in the study...

- Avoid consuming alcoholic beverages, caffeinated beverages, orange juice, grapefruit juice, grapefruit, and oranges from 7am the day before a study day until completion of that study day.
- Maintain adequate birth control throughout study participation without the use of hormonal contraceptives.

Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study. However, this study will help doctors learn more about fluvastatin and rifampin, and it is hoped that this information will help future patients treated with these medications.

What other choices do I have if I do not take part in this study?

Participation in this study is entirely voluntary and subjects can choose not to participate. Subjects have the right to withdraw at any time.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all healthcare providers treat information in medical records with confidentiality. 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.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- UCSF's Institutional Review Board and Clinical Research Center.

What are the costs of taking part in this study?

You will not be charged for any of the study activities or study medications.

Will I be paid for taking part in this study?

In return for your time, effort, and travel expenses, you will be paid a total of \$350 for taking part in this study. If you complete only the study period 1, you will receive \$75. If you complete both study periods 1 and 2, you will receive another \$75 for study period 2 and an additional \$150 bonus. A check will be mailed to you about 4-6 weeks after your participation in the study has ended. You will receive \$25 each study day for meals. You will also receive parking vouchers to allow you to park in the UCSF parking garage.

You will have to provide your name, address, and social security number in order to receive payment by check. As payments for research participation in excess of \$600 per calendar year are reportable to the IRS, you will have to pay taxes on payments if you receive more than \$600 in the year by participating in other research studies.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Lynda Frassetto, M.D., Yue Xiang, or Ivan Kozachenko if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call Lynda Frassetto, M.D. at **415-476-6143**, Yue Xiang at **206-617-3735** or Ivan Kozachenko at **858-842-8529**.

- **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board at 415-476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctors Lynda Frassetto, M.D. at **415-476-6143**, Yue Xiang at **206-617-3735** or Ivan Kozachenko at **858-842-8529**.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of Institutional Review Board at 415-476-1814.

ClinicalTrials.gov is a website that provides information about clinical trials. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

OPTIONAL GENETIC TESTING AND STORAGE OF BLOOD FOR FUTURE RESEARCH

Why is blood being stored?

By storing a sample of your blood, the researchers will be able to perform future genetic research on your blood that may help them understand the results of this study. The results of these genetic tests will not be put into your medical health record.

What will be done if I agree to have my blood stored?

If you agree to let researchers collect and store your blood for future research, the following will happen:

- Two teaspoons of blood will be obtained at the same time as your routine blood draw at the screening visit. The blood sample will be frozen and stored at the study doctor’s laboratory (Dr. Leslie Benet, 533 Parnassus Ave, Room U-66, San Francisco, CA 94143). Your specimen will be kept for up to 3 years from completion of the study.
- The blood sample will be kept for research purposes only. The blood may be used only by investigators in this study for future genetic research purposes. You or your doctor will not be told the results of any genetic testing or any future research.

What risks are involved with donating specimens for research?

Confidentiality: Donating specimens may involve a loss of privacy, but information about you will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Your name will not be used in any published reports from research performed using your specimen. The researchers involved in this study will have access to information about you but they will not release any identifying information about you to researchers using your specimen. The UCSF Institutional Review Board and other University of California personnel also may see information about you to check on the stored blood specimens. Once your health information is disclosed to the research team it is not protected under the Health Information Portability and Accountability Act (HIPAA). The investigators of this study will continue to protect your personally identifiable health information as described in this consent form. The University of California complies with the requirements of HIPAA and its privacy regulations, and with all other applicable laws that protect the confidentiality of your health information.

Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record.

How do I have my blood specimen removed from storage at a later time?

If you decide later that you do not want your specimens and information to be used for future research, you can notify the investigator in writing at (Dr. Leslie Benet, School of Pharmacy, Department of Bioengineering and Therapeutic Sciences, 533 Parnassus Ave, San Francisco, CA 94143), and we will destroy any remaining identifiable specimens and information if they are no longer needed for your care. However, if any research has already been done using portions of your specimens, the data will be kept and analyzed as part of those research studies.

What are the benefits of donating specimens for research?

There will be no direct benefit to you from allowing your specimens to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease.

What financial issues should I consider before donating?

You will not be charged for donating and storing your specimen. You will not be paid for donating your specimen. If any new products, tests or discoveries that result from this research have potential commercial value, you will not share in any financial benefits.

What other choices do I have if I do not donate blood for storage?

Deciding to donate blood for storage is your choice. You may choose either to take part or not to take part in this part of study. No matter what decision you make, there will be no penalty to you and you will still be able to take part in the main study.

Consent for Storage of Blood

Please read the sentence below and think about your choice. After reading, put your initials in the "Yes" or "No" box.

No matter what you decide to do, it will not affect your care.

- 1. My blood may be taken and stored for genetic testing and for future research use.

<i>YES</i>	<i>NO</i>
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- 2. Someone may contact me in the future to ask me to take part in more research.

<i>YES</i>	<i>NO</i>
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CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date Participant's Signature for Consent

Date Person Obtaining Consent