
16.1.9.
Protocol-Specific Informed Consent Document

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Subject Information and Consent Form

Protocol-specific Informed Consent For Subject at the Lilly Clinic

Study H4Q-LC-ARRO

Effect of Single Intravenous Doses of LY333328 on the QTc Interval in Healthy Subjects

Protocol-specific Informed Consent [PSICD] Approved by Lilly: 30 March 2000
PSICD Effective Date: 10 April 2000

Subject Information and Consent Form Effect of Single Intravenous Doses of LY333328 on the QTc Interval in Healthy Subjects

Introduction

You are invited to take part voluntarily in a research study of a study drug known as LY333328 or glycopeptide. LY333328 is an antibiotic being developed to treat serious bacterial infections that are unresponsive to currently available medicines. This study is being sponsored by Eli Lilly and Company. Before agreeing to participate in this research study, it is important that you read and ask questions about anything you do not understand in this form. It describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. If you participate, you will receive a copy of this form to keep for your records.

Number of People Taking Part in the Study

If you agree to participate, you would be one of up to 16 healthy men and women participating in this study. Your participation in this study is expected to last up to 7 months. You will receive injection doses of LY333328 or sugar water (placebo) by vein on two different occasions separated by up to 7 days. You will be admitted to the research unit the night before the first dosing day. You will be required to stay on the unit for up to 4 days for each dosing period.

Purpose of the Study

The purposes of this study are to determine —

- The effect of LY333328 on ECG (heart tracing)
- The effect of various amounts of LY333328 on the heart tracing
- The safety of LY333328 at doses that are higher than have been given to healthy subjects before
- The effects, if any, of LY333328 on the normal functioning of the adrenal gland (a gland which produces cortisol, a normal chemical in your body)

It is possible that information collected during this study will be analyzed by the sponsor in the future to evaluate LY333328 for other possible uses or for other medical or scientific purposes other than those currently proposed.

Qualifications to Participate

The doctor in charge of this study or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are completely truthful with the doctor and staff about your health history. You should not participate in this study if you do not meet all qualifications.

A requirement to be in this study is --

- You must be between the ages of 18 and 65 years.

You cannot participate in this study if --

- You are allergic to LY333328, vancomycin or teicoplanin
- You have taken certain prescription or “over-the-counter” medicines within the last 7 days
- You have donated more than one cup of blood in the last 30 days
- You have a current problem with alcohol or drug dependence or abuse
- You have participated in a clinical trial with an investigational drug within the past 30 days.

Since there is no information available on the effects of LY333328 on the developing fetus or unborn child, you cannot participate in this study if you are a woman and can possibly become pregnant.

You may smoke during the study, but only during smoking breaks in the designated smoking area.

Procedures for the Study

If you participate, you have passed the blood and urine tests and the physical examination given to you by the study doctor. You also have had a chest x-ray, a heart tracing, and a test of how well your adrenal gland functions. If these tests show that you qualify for the study, you will receive injection doses of LY333328 and sugar water (placebo) by vein on two different occasions separated by up to 7 days. You will not know what medication you are taking.

Up to four days prior to your first dose of study medication, a test is done to see how well your adrenal gland is working. (The adrenal gland is a gland which produces cortisol, a normal chemical in your body.) This test is called a cosyntropin stimulation test. It is done by giving you a dose of medication intravenously (by injection through a vein) and then doing a blood test 30 minutes later to measure the cortisol level. If this test is normal, you will then be admitted to the research unit the night before the first dosing day. You will be weighed and have your vital signs (heart rate, breathing rate, and blood pressure) recorded. You will have a pregnancy test (if you are female) as well as a heart tracing performed. On the first dosing day, you will have blood and urine tests

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performed and then you will be connected to a heart monitor which will show your heart rhythm and rate. The study drug will be administered by vein over 30 to 75 minutes while you lie resting in bed. You will not be allowed to get out of bed (except to go to the bathroom) until 30 minutes after the study drug has started. Blood will be collected by venipuncture (needle stick) up to 9 times to measure the amount of LY333328 in your blood and to measure your blood counts and liver and kidney functions. Heart tracings will be performed several times throughout the day. Your vital signs will be recorded multiple times throughout the day as well. You will be required to stay on the unit for up to 96 hours for each dosing period and will continue to wear the heart monitoring equipment until you leave the unit.

You will be required to come back the following week for repeat blood tests and heart tracings. The second dose of study drug will be administered by vein approximately 8 days after the first dose. Again it will be given over 30 to 75 minutes and you will be required to lie in bed until 30 minutes after the drug has started. You will be connected to the heart monitoring equipment again during the administration of the study drug. All the blood tests and heart tracings will be repeated as before. The test to check your adrenal function will be repeated two days after your second dose of study drug.

You will be required to return to the unit over the next 2½ months to have repeat blood and urine tests and have your heart tracings repeated. You will not be allowed to participate in another study for at least 3 months after you complete this study. You must not drink alcohol until you have completely finished this study.

The maximum number of blood samples that may be drawn from you is 52. The total amount of blood which may be drawn from you during the study is less than 1½ cups. This is considered a safe amount of blood to donate over the time interval involved.

At the conclusion of the study, a physical examination will be performed.

Your blood or urine sample will be tested for certain types of drugs (known as controlled substances in the United States) that may affect behavior and that may be regulated by law. If your test results show that you have taken these types of drugs, you will be notified of the test results and may be discontinued from the study based on the investigator's decision. The results of this test will be kept confidential and disclosed only as required by law.

Risks of Taking Part in the Study

There may be risks to you if you participate in this study. LY333328 has been taken by about 150 people. Possible side effects identified in animal studies include allergic-type reactions (such as rash, redness, flushing, shortness of breath, and low blood pressure), nausea, vomiting, diarrhea, lowered ability to fight infection, and abnormalities in red blood cell count, white blood cell count, liver tests, kidney tests, and some blood clotting tests.

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In animal studies, these side effects completely or partially reversed following discontinuation of the drug. Animals receiving LY333328 at 200 times the rate planned for people have experienced possible convulsions.

Preliminary examination of test-tube data suggests but does not confirm the possibility that LY333328 could cause changes in heart rhythm (arrhythmia). The meaning of these test-tube findings is not known, but it suggests the study drug could cause an irregularity in your heart rhythm. There has been no evidence of life-threatening arrhythmias in animals or in subjects given to LY333328 to date.

Of 19 people given single doses of LY333328, one had low blood pressure and fast heart rate, another had a rash and itching, and one person experienced dizziness. Several people had temporary changes in liver tests. LY333328 may interfere with some blood clotting tests, but no bleeding problems have been noted. In two previous studies 27 of 39 people were given multiple doses of LY333328. Thirteen of these people had mild to moderate irritation at the site of injection. One woman out of 10 had vaginal irritation. Some people also experienced mild abnormalities in liver tests but no symptoms.

In a blinded study (investigator and patient do not know which study medication the patient is receiving) where patients were given multiple doses of either LY333328 or other antibiotics (vancomycin/cephalexin) for skin infections, one patient experienced acute hepatitis that went away within a month. Another patient in this study had extra heartbeats while receiving study drug.

Because LY333328 is similar to the antibiotics vancomycin and teicoplanin, people who are known to be allergic to either of these two antibiotics should not receive LY333328. Antibiotics can cause diarrhea in some people, so this could also occur with LY333328. LY333328 may stay in the body for a longer period of time than most drugs. Therefore, side effects may take longer to go away.

For most people, the cosyntropin stimulation test does not cause any problems. Sometimes people have an allergic reaction to the medicine and sometimes some redness and/or mild swelling at the place where the medicine was injected. These reactions are very rare.

For most people, needle punctures for blood draws do not cause any serious problems. However, they may cause bleeding, bruising, discomfort, infections and/or pain at the needle site or dizziness.

In addition to the risks named above, LY333328 or the study procedures may have other unknown risks.

There may be unknown risks of possible harmful interaction with other medication you may be taking.

If any important new information is found during this study that may affect your wanting to continue to be part of this study, you will be told about it right away.

Reporting Health Experiences

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the nurses or Dr. Turik at 317-276-4757. You may call at any time, day or night, to tell us about your health experiences.

Voluntary Participation in the Study

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop your participation in the study at any time, without a penalty or loss of benefits to which you were entitled before taking part in the study.

If you decide to stop being part of this study, Dr. Turik or one of the doctor staff members will talk to you about your making this choice.

Dr. Turik or Eli Lilly and Company (the sponsor of this study) may stop this study, or your being a part of it, at any time for any reason without your consent. If this happens, it might be the result of a bad reaction that you have to LY333328 or new information that your physician or the sponsor learns about the LY333328 safety.

Treatment and Compensation for Injury

If you follow the directions of the doctors in charge of this study and you are physically injured due to any substance or procedure given under the plan for this study, Eli Lilly and Company will pay the medical expenses for the treatment of that injury.

Possible Benefits of Taking Part in the Study

Study drug and study procedures will be provided at no cost to you. You may receive information about your health from any physical examinations and laboratory tests to be done in this study.

Since you do not have any of the conditions for which LY333328 is being developed, you will not medically benefit from being a part of this study.

You will be paid for your participation in this study according to a separate payment schedule given to you (Attachment 2). If the results of your adrenal function test are not normal, you will be discontinued from the study and paid for the amount of time you have participated. If Dr. Turik decides that you are experiencing a medical problem that requires you to stop participating in the study before it is finished, you will be paid the full daily rate and completion bonus for the entire study. In order to receive this full payment, you may be required to complete the schedule of visits to the Lilly Clinic or undergo additional medical evaluation. If you are discontinued from the study because of failure to comply with study procedures, or if you choose to stop for personal reasons, you will be paid only the daily rate for the days that you completed. All payments may be made at the end of the study by check and by mail.

Information obtained from this study will benefit the sponsor of the study, Eli Lilly and Company, and may benefit subjects in the future.

Investigator Payment

Your study doctor is an employee of Eli Lilly and Company, and is being paid for his work in this study.

Contacts for Questions or Problems

If you have any questions about this study please contact Dr. Turik at 317-276-4757.

If you have any questions about your rights as a participant in a research study, please feel free to contact the Indiana University Hospital subject representative at (317) 274-8265.

Confidentiality

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law.

Data obtained from this study that does not identify you individually will be given to the sponsor and/or its representatives and may be published or given to regulatory authorities in the United States or other countries in which regulatory approval of LY333328 may be sought.

Your original medical records may be reviewed by the sponsor and/or its representatives, the Ethical Review Board for this study, and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. Your medical information may be held and processed on a computer.

By signing this consent form, you authorize the record review, information storage and data transfer described above.

Signatures

To be entered into the study, you must sign and date the signature page (see Attachment 1).

Subject Information and Consent Form
Attachment 1
Signature Page

Signature Page

To become a part of this study, you must sign and date this page, and record the time of your signature. By signing this page, you are confirming the following:

The doctor in charge of this study or a member of the doctor's staff has discussed with you the requirements for participation in this study.

You have read all of the information in this Subject Information and Consent Form, and you have had time to think about the information discussed with you.

All of your questions have been answered to your satisfaction.

You voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.

You may freely choose to stop being a part of this study at any time.

You have received a copy of this Subject Information and Consent Form to keep for yourself.

Subject's Consent:

In consideration of all the above, I give my consent to participate in this research study

Subject Name (Print or Type)

Subject Initials

Signature of Subject

Date/Time

Name of Individual Conducting Informed
Consent Discussion (Print or Type)

Signature of Individual Conducting Informed
Consent Discussion

Date/Time