
Attachment ARRA.5
Informed Consent Document

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INTRODUCTION

You are invited to take part in a research study of an investigational drug known as LY333328 Diphosphate, hereafter called LY333328. We plan to study up to 14 volunteers. Your participation in this study is expected to last up to 3 months.

PURPOSE

LY333328 is a new drug that is under development to treat serious infections caused by bacteria that are resistant to other antibiotics. The purposes of this study are to test the safety of a single dose of LY333328 in healthy volunteers, and to find out how fast the drug is eliminated from the body. The drug will be given by vein in a solution of sugar water.

PROCEDURES

If you participate, you will receive a single dose of LY333328 dissolved in sugar water by vein using a plastic tube or catheter over at least one hour. The dose you will receive will range from 1.4 mg to 35 mg if you are an average sized person (150 lbs). On the dosing day and for at least 8 weeks afterward, you will be observed closely while you are staying at the Lilly Clinic. After this inpatient period, you will be asked to return at least weekly for at least 4 weeks to the Lilly Clinic to be seen by the Lilly Clinic personnel and for the collection of blood, urine and stool samples. The observations that we will make during the study are described below.

You will be weighed at least on three occasions: on admission, on the day you receive the study drug, and at the time of discharge from the Lilly Clinic. Your participation in the study may end if your weight changes by more than 10%. You will be served a low fiber diet throughout the study, with the exception of the dosing day when you will be asked to take nothing by mouth, except water, from midnight (on the day before) until approximately 4 hours after the LY333328 is given for a total of about 13 hours, at which time a meal will be served. The low fiber diet is one that does not contain beans, corn, fruit or raw or cooked vegetables with skins. This is necessary while you are collecting stool specimens for the measurement of LY333328 content since indigestible material from these food will interfere with the tests. After you leave the Lilly Clinic we will ask that you avoid these foods for the 2 days prior to a collection of a stool specimen if we request one.

Your blood pressure and pulse (lying and standing), temperature, and breathing rate will be taken at least once each day. On the dosing day, especially during the infusion, they may be taken 14 or more times and they may be taken at other times.

Blood will be collected from you by venipuncture (needle stick) or from an indwelling intravenous line (a small needle or plastic tube placed in the vein) during this study. The purposes of these tests are to measure drug concentrations or to check your blood counts and your liver and kidney functions. On the dosing day, up to 19 blood samples may be drawn. The maximum number of blood samples that may be drawn over a 3 month period is 44. The total amount of blood that may be withdrawn from you during this study (including safety laboratory tests) is about one and one half pints over the 3 month period of the study. The most blood you will have taken in a one day period is about one pint. Over the period of time indicated, these amounts of blood are comparable to the amounts that you might have drawn for a blood bank donation.

You will have urine collected from you during the study. On the morning you receive LY333328, a sample of urine will be collected before the study drug is infused. After you receive LY333328, all of your urine may be collected for 24 hours. Additionally, all of your urine may be collected for the first 7 days you stay at the Lilly Clinic and on occasions afterward during your stay. Other 24 hour urine collections may be done on several occasions after you leave the Lilly Clinic.

You will have stool collected from you during the study. A specimen will be needed sometime before you receive LY333328 and all stools in the 24 hours after the infusion will be collected. Additionally, your stools may be collected every day during the first 7 days after receiving the LY333328 and on other occasions while you stay at the Lilly Clinic. Specimens or 24 hour stool collections may be done on several occasions after you leave the Lilly Clinic.

You may smoke during the study, but only during supervised smoking breaks taken as a group outside the hospital building.

If you participate in this study, you will be asked not to drink alcoholic beverages for a period of 2 months after you receive the study drug. You will not be allowed to drink caffeinated beverages while you are staying at the Lilly Clinic. You will also be asked to return to the Lilly Clinic periodically after the inpatient stay to bring in urine and stool samples and to allow blood to be drawn. These visits to the Lilly Clinic are likely to occur approximately every week for 1 month and may last up to 3 months. You will be asked not to participate in any other investigational drug studies, even those that will be giving approved drugs, for a period of one year. This is because some LY333328 may still be in your body for this period of time and taking additional drugs may not be safe for you. You will be contacted by mail or phone by Lilly Clinic personnel every 3 months for up to a year after you receive the LY333328 to monitor your well being and to encourage you not to participate in other drug studies or to drink alcohol.

RISKS

You understand that there may be risks for your being in this study.

This is the first time LY333328 will be given to humans, however, LY333328 has been given to animals. In animals, one important side effect was an allergic-like reaction in dogs given a moderately high dose. This type of allergic-like reaction has been seen in some people when vancomycin, a marketed antibiotic, is given by vein. The allergic-like reaction could include red skin, rash, trouble breathing, low blood pressure, and vomiting. The severity of the reaction is probably related to the dose and the rate (over 60 minutes) the drug is given. Slower infusion and certain medications can be given which may stop some of these symptoms. If a rash were to develop or any other side effect as a result of a single dose of the study drug it might take longer to go away than it would for most other drugs. This is because LY333328 will likely stay in your body for a longer period of time.

There were several other effects on animals when high doses of LY333328 were given to them daily for periods of 2 to 4 weeks. These doses were higher than what you will be asked to take in this study, and you will be asked to take only one dose. These effects included decreased amounts of all blood cells, increases in liver enzymes, increases in the size of some organs including the liver and spleen, and other changes, some of them in certain cells of the liver, spleen, lymph nodes and kidney. There were cell changes in the liver suggesting moderate damage when the study drug was given every day for 2 or more weeks at much higher doses than we intend to use in this study. These changes, and the increase in liver enzymes in blood which were seen in both the dog and rat studies, appeared to be reversible, though slowly. If you should develop one of these problems after taking the LY333328 you may be asked to return to the Lilly Clinic and stay until the problem resolves.

The most important finding from the animal studies was the fact that once the LY333328 was in the body it did not leave the tissues very quickly. In rats, measurable levels remained in the body after 45 days, primarily in the lymph nodes, liver, spleen, lung and kidney and most other tissues to a smaller degree. The study drug appears to be cleared from the body over a longer time than most other drugs.

In humans it is not known if any of these problems will occur or if problems that the animals did not have or could not have (like a skin rash) might happen. Because the study drug leaves the body slowly, any problem that occurs may last a long time.

Needle punctures for blood draws are usually well-tolerated by most people. However, they may cause bleeding, bruising, discomfort, infections and/or pain at the needle site and dizziness.

You should not participate in this study if you have any allergy to any antibiotics or if you have ever received vancomycin.

In addition to these effects, LY333328 or the procedures in this study, may have other unknown risks. In case you have any bad effects, make sure that you immediately tell the nurses or Dr. Holly Thomasson or Dr. Mark Goldberg at the Lilly Clinic at (317) 276-4757.

VOLUNTARY PARTICIPATION

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may quit the study at any time without a penalty of 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. Holly Thomasson or Dr. Mark Goldberg will talk to you about the process for stopping and the medical consequences of your making this choice. Dr. Thomasson or Dr. Goldberg 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.

TREATMENT AND COMPENSATION FOR INJURY

If you follow the directions of the doctor in charge of this study and you are physically injured due to any substance or procedure given during your participation in this study, Eli Lilly and Company will provide treatment for the injury, or pay for those medical costs that are not covered by your medical insurance. Eli Lilly and Company does not agree to pay any additional money for injury. For further information about compensation or treatment available if injury occurs, contact Dr. Thomasson or Dr. Goldberg at (317) 276-4757.

BENEFITS

You will be paid for taking part in this study according to a payment schedule to be provided to you. Since you do not have any of the conditions for which this drug is being developed, you will not medically benefit from being a part of this study. However, information obtained from the study will be of benefit to Eli Lilly and Company and may benefit patients in the future.

QUESTIONS

If you have any questions about this study or your rights, please contact Dr. Thomasson or Dr. Goldberg at (317) 276-4757. 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.

CONFIDENTIALITY

If you agree to participate in this study, the information obtained will be shared with Eli Lilly and Company, the United States Food and Drug Administration, and similar agencies in other countries, all of whom may look at your medical records. Medical records that contain your identity will be treated as confidential by Eli Lilly and Company and will be shared only with these agencies or as required by law.

This informed consent has been read to me and all my questions have been answered to my satisfaction. I voluntarily agree to be part of this research study. I am between the ages of 21 and 55 years of age inclusive and as far as I know, am healthy.

I understand that I may freely stop being a part of this study at any time.

I have received a copy of this informed consent form to keep for myself. I understand that a copy of this form will also be retained by Eli Lilly and Company.

Volunteer's Signature: _____

Volunteer's Name: _____
(printed)

Witness (Investigator): _____

Witness (Other): _____

Date: _____ Time: _____

ESTIMATE OF PAYMENT SCHEDULE

You will be paid \$60.00 for each day you spend in the Lilly Clinic during this study. You will be paid \$100.00 for each week you spend in the study after the initial stay at the Lilly Clinic. In addition if you satisfactorily complete your part in this study, you will receive an additional payment (Satisfactory Completion Payment) calculated at the rate of \$25.00 for each day of inpatient participation.

(total inpatient time = 9 weeks, outpatient time = 4 weeks)

Payment Schedule for 63 days	@ \$60/day =	\$3780.00
4 weeks as an outpatient	@ 100/week =	\$400.00
Satisfactory Completion Payment	@ \$25 x 63 days =	\$1,575.00
TOTAL		\$5,755.00