CONSENT FORM

Title of Study: Ranolazine in LQT3 (Study 2, Long Term)
Principal Investigator: Wojciech Zareba, M.D., PhD
Clinical Principal Investigator: Spencer Rosero, M.D.

This consent form describes a research study, what you may expect if you decide to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you agree to participate. You may take this consent form home to think about and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you join this study, you can change your mind and stop at any time.
- If you choose not to take part, your routine medical care will not be changed in any way.
- There are risks from participating and you should understand what these mean to you.

Introduction

You are being asked to take part in this study because you have been found to have a genetic mutation that causes Long QT Syndrome. The effect of ranolazine has been studied on one or more individuals with the same mutation that you have through our Ranolazine in LQT3 (Study 1, Short Term) research study and or/ in a prior study of intravenous ranolazine done here in the past, and the data has been analyzed for safety.

If you currently take a beta-blocker, that medication will not be changed.

This study is being conducted by Wojciech Zareba, M.D., PhD, and Spencer Rosero, M.D. of the University of Rochester's Department of Cardiology.

Purpose of Study

Research is designed to benefit society by gaining new knowledge. The purpose of the study is to determine the benefits of a medicine called ranolazine (known as Ranexa). Ranolazine is thought to be an effective way to protect the heart against arrhythmias that are common in Long QT Syndrome. Early studies have shown ranolazine to shorten the QT interval in LQT3.

Ranolazine (known as Ranexa) has been approved by the United States Food and Drug Administration (FDA) for the treatment of patients with chronic angina (pain or discomfort in the chest, jaw, shoulder, back, or arm that keeps coming back), a symptom of a heart

problem called coronary heart disease. It has not been approved for the prevention and treatment of long QT syndrome.

Ranolazine may improve the heart beat rhythm, and the level of oxygen in cells that are not receiving enough oxygen, which happens in patients with heart disease. Its use in this study is for testing purposes only.

Background

Long QT Syndrome (LQTS) is a genetic disorder characterized by prolongation of the QT wave in the electrocardiogram (ECG). People with LQTS are at risk of developing an arrhythmia that may cause dizziness, fainting, seizure or even sudden death. There are different types of LQTS. People with Long QT-3 (LQT3) are at a greater risk of developing sudden death during their first arrhythmic event than Long QT-1 (LQT1) and Long QT-2 (LQT2).

Schedule of Procedures

The University of Rochester has contracted with a company called Examination Management Services, Inc. (EMSI) to do home visits for administering ECGs and Holter monitors (and to collect a baseline blood sample from all participants and a blood specimen for pregnancy testing from female participants) for this study.

If you decide to take part in this research, a study representative will visit you to perform the following:

- An ECG and 24-hour Holter recording will be done. If you are female, a pregnancy test will be done. If you did not have a blood test for kidney function recently done, a blood sample (one teaspoon) will be drawn.
- The same (with the exception of the blood test and pregnancy test) will be done at the one-month, 5 weeks, two-month and six-month intervals.

A supply of study drug will be shipped to you from the University of Rochester at the beginning of the study and instructions about when to begin taking study drug will be provided by the study nurse after baseline laboratory results have been reviewed. On the first day, you will be given a supply of study medication or a placebo (placebo is a drug that looks like the study medication but has no active ingredients). During the six month study you will be taking both ranolazine and placebo, but you will not be told which you are on at any given time.

Description of Procedures

Electrocardiogram (ECG) & Holter Monitor

You will have an electrocardiogram (ECG) performed and recorded. An ECG is an electrical recording of your heart rate and rhythm. You will be asked to lie down and patches called electrodes connected to wires are affixed to your body. This requires cleaning the site where the electrode is attached, and if necessary, shaving or clipping of hair may occur. No electricity is sent through your body, and there is no possibility of receiving an electrical shock. You will be asked to remain still while the test is performed. The results will be recorded on graph paper.

A Holter monitor records electrical signals from the heart via a series of electrodes attached to your chest. These electrodes are connected to a small piece of equipment about the size of a cell phone that is then attached to your belt or worn with a shoulder strap, and is responsible for keeping a log of your heart's electrical activity throughout the recording period. No electricity is sent through your body, and there is no possibility of receiving an electrical shock.

Blood Test

At your first visit, you will have blood drawn (1 teaspoon) for testing your kidney function.

Pregnancy Test

If you are female and are able to have children, a pregnancy test will be performed to make sure that you are not pregnant at the start of the study. This test will be done from a blood specimen (1 teaspoon).

Information about your participation in this study will be included in your electronic medical record.

Number of Subjects

We expect 30 subjects to participate in this study.

Duration of the Study

Your participation in the study will last approximately 6 months.

Risks of Participation

Risk of Ranolazine

Ranolazine has been studied in both healthy volunteers and people with heart disease. The side effects are discussed below. Common side effects have usually gone away after the drug was stopped, and no long-term side effects have been reported. There may be side effects that we don't know about at this time.

We will ask you to stop taking the drug if the side effects become severe. The most commonly reported side effects in both healthy volunteers and patients have been: dizziness, headache, nausea, fatigue, constipation, indigestion, leg or ankle swelling, chest pain, coughing, breathlessness, palpitations (awareness of a racing heart beat), abdominal pain, vomiting, and dry mouth.

The following serious side effects may be related to ranolazine and have occurred in people with heart disease: heart attack; fatal or life-threatening heart beat or rhythm (irregular, fast or slow); fainting or loss of consciousness, a spinning sensation; sweating; ringing/buzzing noise in the ear; abnormal lab tests related to the kidney, and involuntary muscle contractions. Higher doses of ranolazine have caused low blood pressure particularly when people rise from a lying or sitting position. Fainting, changes in vision, a burning or tingling feeling – in the legs, drowsiness, and confusion and disorientation have also been reported.

Ranolazine has also caused small changes in the electrical activity of the heart, as measured by the ECG. These effects, known as "QT prolongation," appeared as small changes in the ECG readings, but were not felt by the study participants taking ranolazine. Higher blood levels of ranolazine increased these effects. Other drugs that cause these effects have also caused a serious disturbance of the heart rhythm and sudden death, in rare cases. This has not happened in previous studies with ranolazine. Early studies have shown ranolazine to shorten the QT value in LQT3 patients.

If you are taking digoxin, you will be instructed to decrease the dose of digoxin in half since ranolazine increases the level of digoxin in blood. The increase of blood level of digoxin might be associated with cardiac arrhythmias.

If you are taking simvastatin, you will be instructed to limit the dose of simvastatin to 20 mg once daily as the plasma levels of simvastatin are increased when ranolazine is taken together with this drug.

If, during the study you would require treatment with moderate CYP3A inhibitors you should reduce your dosage of the drug to 500 mg twice a day (instead of 1000 mg twice a day), including:

- for your heart: verapamil, diltiazem
- for nausea and vomiting: aprepitant (Emend®)
- for bacterial infection: erythromycin
- for fungus infection: fluconazole (Diflucan®)
- grapefruit juice or grapefruit-containing products

If, during the study you would require treatment with strong CYP3A inhibitors or CYP3A inducers, your study drug would need to be stopped for the period of treatment with these drugs including:

- for fungus infection: ketoconazole (Nizoral®), itraconazole (Sporanox®, Onmel)
- for infection: clarithromycin (Biaxin®)
- for depression: nefazodone
- for HIV: nelfinavir (Viracept®), ritonavir (Norvir®), lopinavir and ritonavir (Kaletra®) indinavir (Crixivan®), saquinavir (Invirase®)
- for tuberculosis (TB): rifampin (Rifadin®), rifabutin (Mycobutin®), rifapentin (Priftin®)
- for seizures: phenobarbital, phenytoin (Phenytek®, Dilantin® Dilantin-125®), carbamazepine (Tegretol®),
- St. John's wort (Hypericum perforatum)

If, during the study you develop liver problems and/or scarring (cirrhosis) of your liver your study drug would need to be stopped. If, during the study you would require treatment with CYP2D6 substrates, such as tricyclic antidepressants and antipsychotics, the dose of study drug may need to be adjusted, as these drugs may increase your exposure to study drug.

Please inform us right away if you have any side effects or unusual health events, even if they don't disrupt your daily life, regardless of whether you think the study medication caused them or not.

Risk of Electrocardiogram (ECG) and Holter Monitor

There is minimal risk from ECG monitoring and Holter monitoring. The sticky patches (electrodes) placed on your skin detect only the electrical signals from your heart. No electricity is sent through your body, and there is no possibility of receiving an electric shock. There may be skin irritation (redness and itchiness) from the electrode gel or adhesive.

Pregnancy

There may be risks to the mother (or to an embryo, fetus or nursing infant) that are currently unknown or unanticipated. If you are a woman capable of having children, you must use a medically approved method of birth control, i.e., oral contraceptives; barrier method (condom AND diaphragm combined with spermicide); implants; injections; IUD or abstinence. A diaphragm or condom alone is not considered adequate contraception.

Risks associated with the Home Visits

The researchers are required to report information reported by you, your partner, or your child, regarding potential child abuse or neglect. The researcher will also report if there is a reasonable suspicion, based on information provided by you, your partner, or your child, that you may present a danger of harm to others or that you may harm yourself unless protective measures are taken.

Potential Loss of Confidentiality: The risk associated with this study also includes loss of privacy and confidentiality because we will collect data from your medical record. Protected health data will be kept as confidential as it can be but complete confidentiality cannot be assured.

Compensation for Injury:

If you are directly injured by the drug that is being studied, or by clinical procedures solely required to participate in the study, you may need to pay for treatment of your injuries, but you will be reimbursed for the reasonable and necessary medical expenses for such treatment. You will not be required to pay for emergency medical treatment provided at Strong Memorial Hospital or Highland Hospital. The University may seek payment for treating study-related injuries from your health insurer or the study sponsor.

Benefits of Participation

You might not benefit from being in this research study. The potential benefit to you from being in this study might be identifying an effective treatment for your Long QT syndrome

New Study Findings

If we discover anything that might make you change your mind about continuing in the study, we will let you know.

Sponsor Support

The University of Rochester is receiving payment from Gilead Sciences, Inc. for conducting this research study.

Costs

There will be no cost to you to participate in this study.

Payments

You will be paid $200/month ($1200 maximum) for participating in this study.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes

The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will use coded identifiers on records we create. Password-protected electronic records are accessible only to authorized study personnel. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to the study
- Results of medical tests done as part of this study

Who may use and give out information about you?

- The study doctor and the study staff
- URMC and Affiliates

Your information may be given to:

- The Department of Health and Human Services;
- The University of Rochester;
- The U.S. Food and Drug Administration (FDA) may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about you private.
- The study sponsor, Gilead Science, Inc. and its study monitors
- Examination Management Services, Inc. (EMSI) will be given your name and contact information in order to schedule home visits according to our study contract
- Other LQTS researchers collaborating with the University of Rochester

Your name will not be provided unless required.

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

How long will this be permission be valid?
This permission will last indefinitely. Records will be maintained for a minimum of seven years and for as long as University of Rochester researchers deem the records to be important to keep.

May I cancel my permission to use and disclose information?
You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

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

Contact Persons

For more information concerning this research or if you believe that you have suffered a research related injury, emotional or physical discomfort, please contact:

Spencer Rosero, M.D.
School of Medicine and Dentistry
601 Elmwood Ave, Box 679
Rochester, New York 14642
(585) 275-4775

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420315, Rochester, NY 14642-8315, Telephone (585) 276-0005 or (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

Voluntary Participation

Taking part in this study is voluntary. You are free not to take part or to withdraw at any time, for whatever reason. No matter what decision you make, there will be no penalty or loss of benefit to which you are entitled. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

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SIGNATURE/DATES

After reading and discussing the information in this consent form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to you;
- Other options you may have instead of being in the study;
- How your personal information will be protected;
- What to do if you have problems or questions about this study.

Subject Consent

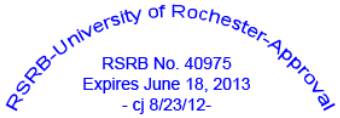
I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

_____
Subject Name (Printed by Subject)

_____ _____
Signature of Subject Date

Person Obtaining Consent

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.



_____
Name and Title (Print)

_____ _____
Signature of Person Obtaining Consent Date