

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

Use of Low Dose Pioglitazone to Treat Autosomal Dominant Polycystic Kidney Disease

You are invited to participate in a research study testing the use of a low dose of pioglitazone (Actos) to treat polycystic kidney disease. Pioglitazone is currently used in clinical practice to treat diabetes and this study will examine the potential use of a low dose of the same drug for the treatment of polycystic kidney disease. You were selected as a possible subject because you have been diagnosed with autosomal dominant polycystic kidney disease and you are in an early stage of the disease. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Drs. Sharon Moe and Robert Bacallao of Indiana University School of Medicine (IUSM) and Dr. Bonnie Blazer-Yost of Indiana University Purdue University Indianapolis (IUPUI).

STUDY PURPOSE

The purpose of this study is to determine whether the diabetes drug pioglitazone (Actos) is a safe and effective treatment of autosomal dominant polycystic kidney disease when treated in its early stages. Pioglitazone is approved by the FDA for the treatment of diabetes. Pre-clinical (animal) models of polycystic kidney disease have shown that low dose treatment with pioglitazone decreases the growth of the cysts and may delay progression in animals. The dosage used in the animal studies also suggest that effective pioglitazone dosing for polycystic kidney disease may be lower than that used to treat diabetes. The purpose of this study is to see if pioglitazone might slow cyst disease in humans. This drug has not previously been tested in humans with cystic kidney disease.

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If you agree to participate, you will be one of up to 45 subjects who will be participating in this research.

PROCEDURES FOR THE STUDY:

This is a placebo controlled study. This means for half of the study you will get the active drug and for the other half of the study you will get a fake pill. This study involves the following visits and tests:

Screening Visits:

This visit is to determine if you are eligible to participate in the study. This visit will be at Indiana University and you may be asked to bring previous medical records documenting your polycystic kidney disease.

During this visit you will have the following tests and procedures:

- Review and sign consent (if you agree to participate)
- A review of your medical history
- Physical exam
- Pregnancy test
- Collect a blood sample from a vein in your arm (this will be about 2 Tablespoons) if you have not had the same blood tests done in the last 3 months.
- If the above indicate eligibility, you will be scheduled to come back and undergo a magnetic resonance imaging (MRI) procedure to determine the size of your kidney and liver.

If the investigators determine that you are eligible for the study, you will be assigned by chance (like a coin toss) to the pioglitazone group or the placebo (a capsule that looks like the drug but has no active ingredients) group for the first part of the study. You and/or your doctor cannot choose the study group to which you are assigned. You will have 1 in 2 chance of being assigned to the pioglitazone group in the first year.

This is a cross-over study which means that all participants who complete the first half of the study on their assigned treatment will then cross over to the other treatment arm. You will be in the pioglitazone group for one year and the placebo group for one year. Again, you and your doctor will not know which one you are in for either year.

The study medication (pioglitazone or placebo) will be given to you by the pharmacy at Indiana University Hospital. Each time you get new medication, you will be asked to return the containers and any leftover pills to the pharmacist.

Visit 1:

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Perform a cardiac echocardiogram (heart ultrasound picture) to examine heart function
- Conduct a bioelectrical impedance analysis (BIA) to determine your body water content For this you lie flat on a table and have sticky pads (like for a heart electrocardiogram test) placed on both ankles and wrists for up to 10 minutes.
- Ask you about any medical problems or side effects you may have had in the last month
- Review your medications.
- Have 2 Tablespoons blood and urine collected.
- Pregnancy Test
- Get study drug from investigational pharmacy

Visit 2 (Month 1)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container (and any remaining drug) and get new drug from investigational pharmacy

Visit 3 (Month 3)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container (and any remaining drug) and get new drug from investigational pharmacy

Visit 4 (Month 6)

Version Date 5.31.17

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample, or bring a urine sample to the clinic
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container (and any remaining drug) and get new drug from investigational pharmacy

Visit 5 (Month 9)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container (and any remaining drug) and get new drug from investigational pharmacy

Visit 6 (Month 12)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample or bring a urine sample to the clinic
- Perform an MRI to determine kidney and liver size
- Perform a cardiac echocardiogram (ultrasound of your heart)
- Conduct a BIA test to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.

After visit 6 (Month 12) you will have what is called a “washout period”, at this time you will not take any study medication. You will have two weeks of not taking study medication before proceeding to the opposite treatment that you were on during year one of the study. All of the previous studies will be repeated. This is called Arm 2 of the study

Visit 7 (Baseline Arm 2)

During this visit you will have the following tests and procedures:

- A medical history
- A physical exam
- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (this will be about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample or bring a urine sample to clinic.
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had in the last month
- Get new drug from investigational pharmacy

Visit 8 (Arm 2 Month 1)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample or bring urine sample to the clinic
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container and get new drug from investigational pharmacy

Visit 9 (Arm 2 Month 3)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample or bring urine sample to the clinic
- Conduct an impedance analysis to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container and get new drug from investigational pharmacy

Visit 10 (Arm 2 Month 6)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample or bring urine sample to the clinic.
- Conduct an impedance analysis to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container and get new drug from investigational pharmacy

Visit 11 (Arm 2 Month 9)

During this visit you will have the following tests and procedures:

- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (about 2 Tablespoons)
- Pregnancy Test
- Conduct a BIA to determine your body water content
- Ask you about any medical problems or side effects you may have had since your last visit.
- Return study drug pill container and get new drug from investigational pharmacy

Visit 12 (Arm 2, Month 12 – last study visit)

During this time you will have the following tests and procedures;

- A review of your medical history
- A physical exam
- Collect your vital signs (including blood pressure, heart rate, height, weight and temperature)
- Collect a blood sample from a vein in your arm (this will be about 2 Tablespoons)
- Pregnancy Test
- Collect a urine sample

- Conduct a BIA to determine your body water content
- Perform an MRI
- Perform a cardiac echocardiogram
- Ask you about any medical problems or side effects you may have had in the last month

RISKS OF TAKING PART IN THE STUDY:

While on the study, the risks, side effects and/or discomforts are:

BLOOD DRAW:

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

ECHOCARDIOGRAM:

This test uses sound waves to look at your heart. The person doing the test will press on your chest with a machine to obtain the pictures. The pressure may be uncomfortable.

BIOELECTRIAL IMPEDANCE ANALYSIS:

This is a test to measure your body water content to determine if the drug is causing you to retain fluid. It is performed by putting sticky pads on each of your wrists and ankles and taking a measurement.

There is no sensation or pain associated with this procedure. Patients with amputated limbs cannot participate in this test. The test takes less than 10 minutes

MRI:

There is no radiation associated with MRI, but people who have metal devices like pacemakers cannot have an MRI and will not be able to participate in the study. Some people with claustrophobia (fear of being closed in small spaces) may feel too closed in and may not tolerate MRI scanning. If you feel too confined in the MRI scanner you can inform the technologist and the MRI scan will be stopped. The MRI machine makes loud knocking sounds when it is scanning. Because of this you will be asked to wear earplugs while getting your MRI scan. The earplugs minimize discomfort from noise and keep the MRI noise within the safety range.

PIOGLITAZONE:

Pioglitazone may cause or worsen some types of heart failure and is not indicated for patients with certain types of heart disease. Subjects will be monitored for signs and symptoms of heart failure after initiation and if heart failure occurs the drug will be discontinued.

Common side effects of Pioglitazone are as follows:

- Fluid retention including swelling of the ankles (edema)
- Increased weight
- Headache
- Gastrointestinal: Diarrhea, Flatulence, Indigestion, Malabsorption syndrome (when the body cannot fully absorb nutrients from the intestines), Nausea and Vomiting
- Respiratory symptoms such as sore throat, sinus infection and upper respiratory infection.

- Hypoglycemia or low blood sugar. The symptoms include dizziness, sweating and decreased ability to concentrate.

Less common but serious side effects include:

- Congestive heart failure or inability to breath due to fluid in the lungs

- Elevation in liver enzymes (0.3%)
- Malignant tumor of urinary bladder (0.16% to 0.44%)
- Pneumonia
- Diabetic macular edema (swelling and fluid retention in the eyes)
- Fracture: Your risk of fracture may be lower than in other studies because of your younger age, lower dose, and shorter time on the drug, but the precise risk is currently unknown.

As with all drugs, it is possible that pioglitazone may cause allergic reactions, although this has not been seen so far. Tell your doctor immediately if you have symptoms of an allergic reaction which include:

- itching
- rash
- swelling in the mouth, tongue, face, or throat.

UNKNOWN RISKS:

During the study, tell your study doctor if you get any side effect, whether it is listed here or not. If you are worried, contact your study doctor immediately. Pioglitazone is used to lower blood sugar in patients who have diabetes. It is unknown if it will lower blood sugar levels in individuals who do not have diabetes.

BREAST FEEDING:

Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Women who wish to breast feed will be excluded from the study.

PREGNANCY:

The effect of pioglitazone on a fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these risks, women of child bearing age may take part in this study if they agree to use birth control and take a urine pregnancy test each month while participating in this study. Urine pregnancy tests will be given to women at each visit for them to take home and use for months in between each visit. If a woman becomes pregnant during the study, she will be removed from the study.

If you learn you are pregnant between study visits, you must notify the study staff immediately.

If you are a female and sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below and take a monthly UPT:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

If you are a male and sexually active and able to father a child, you must agree to use one of the birth control methods listed below:

- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Hormonal methods used by your partner, such as birth control pills, patches, injections, vaginal ring, or implants
- Intrauterine device (IUD) used by your partner
- Abstinence (no sex)

You must use birth control for the entire study and for at least one month after your last dose of study drug.

PROTECTION AGAINST RISKS

Blood will be drawn by experienced technicians.

Heart echo will be done by experienced technician.

Earplugs minimize discomfort from noise and keep the MRI noise within the safety range.

Patients will be monitored for signs and symptoms of fluid retention and heart failure after initiation and if heart failure occurs the drug will be discontinued. If edema or swelling of the legs is observed, you will be asked to follow a low salt diet, and possibly take a water pill. If you become short of breath on the study, you will be asked to get an additional heart echo study. This will require 1 to 2 additional visits.

If you have abnormal blood tests of your liver, you will be asked to come back for another visit and repeat the blood tests. If the tests remain elevated to greater than two times the upper limit of normal, you will be removed from the study. This will require an additional visit.

If you are found to have a blood sugar level below the normal limits on your study visits and or have low blood sugar symptoms (eg. dizziness, nauseated, or confused) , you will be given a glucometer to test your blood by a finger stick (using a lance, or small needle) at various time points and when you feel dizzy, nauseated or confused. You will be asked to keep a log of these symptoms and check the blood sugar for one month. If the blood sugars are found to be repeatedly low then you will be dropped from the study. This may require an additional visit.

While you are receiving pioglitazone or placebo, you will be questioned at each visit about possible side effects and you will be monitored by the blood tests we are obtaining.

Records will be stored in a locked cabinet in a locked office and subjects will be identified by a study number and not a name.

BENEFITS OF TAKING PART IN THE STUDY:

You may not receive any benefit from participation in the study. However, you will have laboratory tests, MRIs and cardiac echocardiograms that you may give to your own physician to help him/her with your care at the end of the study, and the blood tests will be given to you throughout the study.

ALTERNATIVES TO TAKING PART IN THE STUDY:

Instead of being in the study, you can continue to be treated by your doctor and not participate.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published and databases in which results may be stored.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigators and their research associates, the Indiana University Institutional Review Board or its designees, the study sponsor, the FDA, the Indiana Clinical Research Center (ICRC), and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) who may need to access your medical and/or research records.

A description of this clinical trial will be available on 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.

GENETIC INFORMATION

This research follows the Genetic Information Nondiscrimination Act (GINA), a federal law which generally makes it illegal for health insurance companies, group health plans, and most employers to request the genetic

information we get from this research and discriminate against you based on your genetic information.

COSTS

The study drug will be provided to you free of charge. Taking part in this study may lead to added costs to you or your insurance company. You or your insurance company will be responsible for testing done for medical problems that may arise during the course of the study but were not directly related to the study. You will not be responsible for these study-specific costs: laboratory testing, MRIs or cardiac echocardiograms.

PAYMENT

You will receive a \$10 payment in cash at each visit in the study to pay for parking and gas to get to the visits. If you travel more than 100 miles, round trip, you will receive an additional \$40 to equal \$50 total per visit.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

FINANCIAL INTEREST DISCLOSURE

While funding is being provided for the investigators and their staff to conduct the study, there is no financial gain anticipated. The Institutional Review Board (an ethics committee which helps protect people involved in research) has reviewed the possibility of financial benefit. The Board believes that the possible financial benefit is not likely to affect your safety and/or the scientific integrity of the study. If you would like more information, please ask the researchers or study staff.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact the researcher, Dr. Sharon Moe, at 317-278-2868. If you cannot reach the researcher during regular business hours (i.e. 8:00AM- 5:00PM), please call the IU Human Subjects Office at (317) 278-3458 [for Indianapolis] or (812) 856-4242 [for Bloomington] or (800) 696-2949. After business hours, please call (317) 274-5000 and ask for the nephrology physician on-call.

If you are unable to reach the investigator at the above number, in an emergency you may contact the Indiana University Hospital Pharmacy at (317) 944-0362 (or at Methodist Hospital, (317) 963-5697).

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at (317) 278-3458 or (800) 696-2949.

VOLUNTARY NATURE OF STUDY

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with your doctor. If you decide to leave the study before it is done, please contact Dr. Moe so we can arrange for basic safety testing.

Your participation may be terminated by the investigator without regard to your consent in the following circumstances: an abnormality in liver function as determined by the blood analyses, edema or abnormal findings in the cardiac echocardiogram, if you have fluid retention that is not treatable, persistent liver test elevation, repeated low blood sugars, or miss a study visit despite reasonable efforts to reschedule to accommodate your schedule.

You will be told about new information that may affect your health, welfare, or willingness to stay in the

study.

If you leave the study due to side effects from the treatment, you may still chose to participate in the study and undergo the same tests. You may also choose not to continue to undergo these tests.

USE OF SPECIMENS

Some of your blood samples will be kept by Dr. Sharon Moe for both genetic and non-genetic laboratory assays in the future to examine the factors that influence the cause or treatment of heart and kidney disease. These samples may be used so far in the future, that it may even be after your death.

I agree to allow my blood to be stored and possibly used in the future to look at factors that cause or treat heart and kidney disease. I understand that these samples may be used at any time and may not be available for destruction if I decide to withdraw from the study.

Yes No Initials _____ Date _____

SUBJECT’S CONSENT

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

I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Subject’s Printed Name: _____

Subject’s Signature: _____ **Date:** _____
(must be dated by the subject)

Printed Name of Person Obtaining Consent: _____

Signature of Person Obtaining Consent: _____ **Date:** _____