# The Ohio State University Consent to Participate in Research

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| **Study Title:** | A prospective, randomized, single center pilot study comparing patient and graft survival, adverse events and tolerability of Zortress® (everolimus) versus Rapamune® (sirolimus) in combination with low dose Neoral® (cyclosporine) dosed by C2 monitoring, in deceased and living donor renal transplant recipients under a Thymoglobulin® (antithymocyte globulin) and rapid steroid induction protocol |
| **Principal Investigator:** | Amer Rajab, MD, PhD |
| **Sponsor:** | The Ohio State University |

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the 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 usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

## 1. Why is this study being done?

This study is being done to compare the effectiveness and safety of two different kidney transplant immunosuppression drugs, Zortress (the study drug) and Rapamune (which is used in the current standard immunosuppression regimen). You are being asked to participate in this study because you are receiving a kidney transplant and meet the criteria for study participation. Some procedures in addition to those required as part of standard of care will be performed in order to evaluate the effectiveness and safety of Zortress compared to Rapamune. One of these procedures is a kidney biopsy at month 12 of the study, which will be used to determine the degree (if any) of fibrosis (formation of excess connective tissue which is the earliest characteristic indicating possible future chronic rejection) of the transplanted kidney, and to evaluate whether less fibrosis is seen

in patients who take Zortress, which could result in a lower risk of chronic rejection than that observed with Rapamune.

Zortress is FDA approved, is used as standard of care at some other institutions, and may also be given as standard of care if it is believed to be the best immunosuppression regimen for a particular kidney transplant recipient. The rationale for testing Zortress vs. Rapamune is to determine which of these drugs is more effective in preventing chronic rejection of the transplanted kidney. Because these two drugs are related to each other there is no current literature addressing the replacement of Rapamune with Zortress in an immunosuppression regimen, therefore the goal of this study is to compare these two immunosuppression drugs.

## 2. How many people will take part in this study?

Approximately 85 patients will consent to participate in this study. Not all patients who wish to participate in this study will be eligible based on their medical history or current medical condition. If you are not eligible to participate in this study you will not be enrolled and you will not receive the study drug. You will be treated with standard medical care for your medical condition. Your research team will let you know if you are eligible for this study after you sign this consent form and after they review your medical history and current medical condition.

Of the 85 patients who give their consent to participation in this study a total of 60 subjects will be eligible to participate and will be enrolled in this study. Approximately 40 subjects will be given the study drug (Zortress), and approximately 20 subjects will be given the current standard drug (Rapamune).

## 3. What will happen if I take part in this study?

If you choose to participate in the study you will be followed as per the standard of care at The Ohio State University Wexner Medical Center. In addition to the normal standard of care, information from your standard physical exams and laboratory test results will be collected and analyzed on the day of your transplant and days 1 through 7, week 2, and months 1, 2, 3, 6, 12, 18, 24, and 36 after your transplant. Information regarding any adverse events (unfavorable medical occurrence which may or may not be related to the study) will also be collected at each of these time points. Additional study procedures will include a kidney biopsy at month 12 after your transplant, and some additional laboratory work (urine and blood tests) prior to your transplant and at months 6, 12, 24, and 36 after your transplant.

The only difference in medication from our current well established protocol is you will be randomly assigned to receive either Rapamune (our current standard of care), or Zortress, the study drug. All subjects will receive 5 doses of thymoglobulin and 5 doses of steroids beginning on the day of transplant through day 4 after transplant. All subjects will also receive the drug Neoral as part of their immunosuppression regimen.

## 4. How long will I be in the study?

You will be in the study for a total of three years.

## 5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

Patient participation in the trial may be withdrawn at any time by the study doctor. Examples of reasons for withdrawal include but are not limited to not coming to clinic visits or experiencing adverse effects.

## 6. What risks, side effects or discomforts can I expect from being in the study?

Zortress can cause serious side effects, including:

- Increased risk of getting certain cancers. People who take Zortress have a higher chance of getting lymphoma and other cancers, especially skin cancer.
- Increased risk of serious infections. Zortress weakens the body's immune system and affects your ability to fight infections. Serious infections can happen with Zortress that may lead to death. People taking Zortress have a higher chance of getting infections caused by viruses, bacteria, and fungi (yeast). Certain viruses can live in your body and cause active infections when your immune system is weak. Viral infections that can happen with Zortress include BK virus-associated nephropathy. BK virus can affect how your kidney works and cause your transplanted kidney to fail. Call your doctor if you have symptoms of infection including fever or chills.
- Blood clotting problems, including blood clot(s) in the blood vessels of your transplanted kidney. If this happens, it usually occurs within the first 30 days after your kidney transplant. Tell your doctor right away if you:
    - have pain in your groin, lower back, side or stomach (abdomen)
    - make less urine or you do not pass any urine
    - have blood in your urine or dark colored urine (tea-colored)
    - have fever, nausea, or vomiting
- Serious problems with your transplanted kidney (nephrotoxicity). Zortress may cause kidney problems when taken along with a standard dose of Neoral instead of a lower dose. Your doctor will do regular blood tests to check your levels of both Zortress and Neoral and will also do tests to monitor your kidney function.
- Swelling under your skin especially around your mouth, eyes and in your throat (angioedema). Your chance of having swelling under your skin is higher if you take Zortress along with certain other medicines. Tell your doctor right away or go to the nearest emergency room if you have any of these symptoms of angioedema:
    - sudden swelling of your face, mouth, throat, tongue or hands
    - hives or welts
    - itchy or painful swollen skin
    - trouble breathing
- Delayed wound healing. Zortress can cause your incision to heal slowly or not heal well. Call your doctor right away if you have any of the following symptoms:

- your incision is red, warm or painful
- blood, fluid, or pus in your incision
- your incision opens up
- swelling of your incision

- Lung or breathing problems. Tell your doctor right away if you have new or worsening cough, shortness of breath, difficulty breathing or wheezing. In some patients lung or breathing problems have been severe, and can even lead to death. Your doctor may need to stop Zortress or lower your dose.
- Increased cholesterol and triglycerides (fat in your blood). If your cholesterol and triglyceride levels are high your doctor may want to lower them with diet, exercise and certain medicines. Your doctor will do blood tests to monitor your cholesterol and triglycerides.
- Protein in your urine (proteinuria).
- Diabetes. Tell your doctor if you have frequent urination, increased thirst or hunger.
- Male infertility (low or no sperm count).
- The most common side effects of Zortress in people who have had a kidney transplant include:
    - nausea
    - swelling of the lower legs, ankles and feet
    - high blood pressure
    - constipation
    - low red blood cell count (anemia)
    - urinary tract infection
    - increased fat in the blood (cholesterol and triglycerides)
- These are not all of the possible side effects of Zortress. Tell your doctor about any side effect that bothers you or that does not go away.
- There is a possibility that taking Zortress can cause liver problems
- Zortress may interact with other medicines. Make sure that your doctor is aware of all prescription and over-the-counter drugs that you are taking, including vitamins, herbs, and nutritional supplements

Rapamune can also cause serious side effects, including:

- An increased risk of developing infections or certain cancers, especially lymphoma and skin cancers. Tell your doctor if you have skin cancer or it runs in your family.
- Allergic reactions. You should not take Rapamune if you know you are allergic to sirolimus or any of the other ingredients in Rapamune. Symptoms of an allergic reaction include swelling of your face, eyes, or mouth; trouble breathing or wheezing; throat tightness; chest pain or tightness; feeling dizzy or faint; and rash or peeling of your skin.
- Problems with your liver. Tell your doctor if you have existing liver problems.
- Rapamune may interact with other medicines. Make sure that your doctor is aware of all prescription and over-the-counter drugs that you are taking, including vitamins, herbs, and nutritional supplements.
- Rapamune may cause swelling in your hands, feet, and in various tissues of your body. Call your doctor if you have trouble breathing.

- Rapamune may cause your wounds to heal slowly or not heal well resulting in redness, drainage, or opening of the wound.
- Rapamune may increase the levels of cholesterol and triglycerides (lipids or fat) in your blood. Your doctor will do blood tests to check your lipids during treatment with Rapamune. Your doctor may recommend treatment if your lipid levels become too high. Your lipid levels may remain high even if you follow your prescribed treatment plan.
- Decreased kidney function has been observed in patients taking Rapamune with Neoral. Your doctor will regularly check your kidney function.
- Rapamune may increase protein in your urine. Your doctor may monitor you for abnormal protein in your urine.
- Rapamune may increase your risk for viral infections. Certain viruses can live in your body and cause active infections when your immune system is weak. One of these viruses, BK virus, can affect how your kidney works and cause your transplanted kidney to fail. A certain virus can cause a rare serious brain infection called Progressive Multifocal Leukoencephalopathy causing death or severe disability.
- Rapamune may cause potentially life-threatening lung or breathing problems. Symptoms may include coughing, shortness of breath, or difficulty breathing.
- You may develop a blood clotting problem resulting in unexplained bleeding or bruising when Rapamune is taken with Neoral.
- Common side effects associated with Rapamune include high blood pressure, pain (including stomach and joint pain), diarrhea, headache, fever, urinary tract infection, low red blood cell count (anemia), nausea, and low platelet count (cells that help blood to clot). If you experience any side effects, contact your doctor.

Women who are pregnant or nursing a child may not participate in this study. You must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant during the study. If you are capable of childbearing then before entering the study you and the study doctor must agree on the methods of birth control you will use during the entire study. You must use two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent. Reliable contraception should be maintained throughout the study and for 12 weeks after study drug discontinuation. If you suspect that you have become pregnant during the study, you must notify the study doctor immediately. Pregnant women will be withdrawn from the study because the drugs administered as part of this study may involve unknown risks to the fetus.

Drawing blood from your arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

A kidney biopsy can cause pain when the needle is inserted through the skin. A numbing medication will be injected under the skin near the kidney area. An ultrasound or CAT

scan will be used to guide the needle to the surface of your transplanted kidney. In a small number of cases, there can be bleeding at the site of the biopsy or in the transplanted kidney or infection at the site of the biopsy, and you may experience pain and soreness after the biopsy. Rarely (in less than 2% of cases), this has required blood transfusion or an operation to stop the bleeding.

As we currently do for Rapamune, Zortress dosing will be decreased or discontinued when the transplant physician deems appropriate due to deleterious side effects or the presence of infection or malignancy where a reduction in overall immunosuppression is desired.

There may be risks or side effects which are unknown at this time.

## 7. What benefits can I expect from being in the study?

You will have increased monitoring of your health by the study center personnel. You are not expected to receive any other direct medical benefits from your participation in the study. You could potentially benefit from the additional information obtained about your kidney transplant function obtained from the biopsy findings. This study may help develop new testing requirements for monitoring of persons who have received a kidney transplant.

## 8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. If you decide not to enter this study your transplant physician will discuss with you which immunosuppression regimen is best for you.

## 9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices; and
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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 the website at any time.

You will also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

## 10. What are the costs of taking part in this study?

Novartis Pharmaceuticals Corporation is providing funding to The Ohio State University which will cover the cost of all procedures required solely for the study, but will not cover the cost of any standard of care procedures.

Participating in this research study may lead to additional costs to you. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

## 11. Will I be paid for taking part in this study?

You will be paid $250.00 after the kidney transplant biopsy at Month 12 for your time and to help cover any additional expenses associated with the procedure, such as lodging, meals, and parking.

By law, payments to subjects are considered taxable income.

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

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

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

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

## 14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. Amer Rajab at 614-293-6322.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Dr. Amer Rajab at 614-293-6322.

## Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

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|---|---|
| **Printed name of subject** | **Signature of subject** |
| | **AM/PM** |
| | **Date and time** |
| **Printed name of person authorized to consent for subject (when applicable)** | **Signature of person authorized to consent for subject (when applicable)** |
| | **AM/PM** |
| **Relationship to the subject** | **Date and time** |

## Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

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| **Printed name of person obtaining consent** | **Signature of person obtaining consent** |
| | **AM/PM** |
| | **Date and time** |

**Witness(es) -** *May be left blank if not required by the IRB*

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|---|---|
| **Printed name of witness** | **Signature of witness** |
| | **AM/PM** |
| | **Date and time** |
| **Printed name of witness** | **Signature of witness** |
| | **AM/PM** |
| | **Date and time** |