Consent Title: Phase II Study of Atorvastatin, Micro-Dose Methotrexate and Tacrolimus Administered only to Transplant Recipients for the Prophylaxis of Acute Graft-Versus-Host Disease Following Allogeneic Hematopoietic Cell Transplantation

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MCW/FH IRB

Medical College of Wisconsin and Froedtert Hospital
CONSENT TO PARTICIPATE IN RESEARCH

Name of Study Subject: _____

Phase II study of Atorvastatin, micro-dose methotrexate and tacrolimus administered only to transplant recipients for the prophylaxis of acute graft-versus-host disease following allogeneic hematopoietic cell transplantation

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You are invited to take part in this research study. This form tells you why this research study is being done, what will happen in the research study, possible risks and benefits to you, your choices, and other important information. If there is anything that you do not understand, please ask questions. Then you can decide if you want to join this study or not.

A1. INTRODUCTION – WHY ARE WE ASKING YOU ABOUT THIS STUDY?

You are being invited to participate in this research study of the drug Atrovastatin (Lipitor®) because you are a patient undergoing a stem cell transplant (SCT) (commonly known as a bone marrow transplant) from your donor.

A total of about 55-75 people are expected to participate in this study nationally including about 30-45 at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the study is Mehdi Hamadani, MD in the Department of Medicine. A study team works with Dr. Hamadani. You can ask who these people are.

This study is being funded by a grant called; Conquer Cancer Foundation of the American Society of Clinical Oncology, which is providing the financial support to Dr. Hamadani to conduct the study. Dr. Hamadani is the sponsor of the study.

A2. DO I HAVE TO BE IN THIS STUDY?

You can decide whether to take part in this study or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this study, you do not have to stay in it. You may stop at any time.

A research study is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the study procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS RESEARCH STUDY BEING DONE?

Patients who undergo SCT from donors are at risk of suffering a common problem called acute graft-versus-host disease (GVHD). Acute GVHD is a complication where the donor cells (graft) received during transplant attacks and damages the patient's (transplant recipient) tissues. GVHD can cause skin rash, intestinal problems such as diarrhea, nausea, vomiting and decrease liver function or liver failure. These symptoms can range from mild to severe and may be life threatening and may be fatal in some cases.

The purpose of this study is to learn if prescribing atorvastatin to you starting approximately two weeks before your transplant and continuing through the first 180 days post transplant will help prevent acute graft-versus-host disease. We also want to see if atorvastatin is safe to use in transplant patients.

Atorvastatin (Lipitor®) is currently approved by the Food and Drug Administration to treat high cholesterol, but it is not approved for use in patients to prevent GVHD. This means that the use of atorvastatin in this study is considered investigational (or experimental). The use of methotrexate and tacrolimus in this study is considered part of the investigation.

B1. WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

The Director of this study or a member of the study staff will discuss with you the requirements for being in this study. A healthcare professional will evaluate your ability to be in the study.

Before you begin the study:

You will have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Baseline Tests:

- Medical history and physical examination (includes vital signs, height, weight, and current medications)
- Blood tests to check your blood counts, chemistries, liver function, and kidney function
- Blood tests to check for CMV infection, hepatitis A, hepatitis B, hepatitis C, HIV testing, syphilis, EBV infection and herpes simplex virus infection

- Blood tests to check your immune system
- Blood tests to check how many of your blood cells are from your donor
- A blood test to check for pregnancy for women of childbearing potential
- Karnofsky Performance Status to see how well you perform daily activities
- A MUGA scan or echocardiogram to test your heart function
- Bone marrow aspirate or biopsy
- A test to check your lung function

During the Study

Prior to receiving your donor's progenitor cells you will undergo your transplant conditioning therapy, which includes chemotherapy and/or radiotherapy. Transplant conditioning is a standard procedure for patients receiving a SCT and it helps prepare the body for the transplant.

This study will include patients undergoing SCT from sibling donors or unrelated donors, enrolled in two separate cohorts. If you are found to be eligible for the study after the baseline tests and procedures are complete you will start atorvastatin (40 milligrams) one tablet daily by mouth 14 days before you are scheduled to receive your donor's cells (this is also called Day 0).

There is no universally accepted standard treatment to prevent GVHD, and different transplant centers in the country use a variety of treatment to prevent this complication. In this study you will also be given two drugs called tacrolimus and methotrexate. You will take tacrolimus until your doctor feels it is safe to quit taking it but in most cases it will be at least until Day 180 post transplant. The methotrexate is given at days 1, 3, 6 and 11 post transplant. Your study doctor will help you understand the risks involved with these drugs as well.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures throughout the study.

Study Tests
While you are on the study the following tests will be completed:

- Physical examinations (includes vital signs, height, weight, and current medications)
- Blood tests to check your blood counts, chemistries, liver function, kidney function
- Blood tests to check your immune system
- Blood tests for CMV (virus) infection
- Blood tests to check how many of your blood cells are from your donor
- Karnofsky Performance Status to see how well you perform daily activities
- Bone marrow aspirate or biopsy (only if recommended by your physician)
- GVHD assessments

- Assessment of any side effects that you may be experiencing

You will need to keep taking atorvastatin (the study drug) until one of the following happens:

- It is 180 days after your transplant or you are done taking the standard GVHD prevention treatment described above (tacrolimus)
- You develop a moderate grade of acute GVHD, which normally occurs within the first 100 days of the transplant
- You developed severe chronic GVHD, which normally occurs beyond 100 days of the transplant and can even occur years after the transplant
- You have a bad side effect or reaction to the study drug (atorvastatin)

We will talk to you about any side effects you may have experienced during this study at your normal clinic visits or hospital stays.

Follow-up

After your transplant we will need to ask you how you are doing and if you are having any side effects, so someone from the research team will contact you. Your follow-up visits during the first two years is no more frequent than standard for most patients at our center (i.e. weekly during the first one hundred days followed by at least every 3-6 months up to the one year mark post SCT). After 1 year we will continue to follow-up yearly about your survival and disease status for five years.

We will talk to you about any side effects you may have experienced during this study at your normal clinic visits or hospital stays.

B2. HOW LONG WILL I BE IN THE STUDY?

You will be in this research study for about 5 years after your transplant.

B3. CAN I STOP BEING IN THE STUDY?

You are free to withdraw from the study at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the study doctor.

⇒ The doctor can tell you about the effects of stopping, and you and the doctor can talk about what follow-up care would help you the most.
⇒ You might be asked to come back for one more visit to check your health.

The study doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the study rules.
- The whole study is stopped.

If this happens, the study doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE STUDY?

There are risks to taking part in any research study. There is a risk that you may get a drug, drug combination or dose of a drug that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from drug itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the study for problems (side effects). **You need to tell the study doctor or a member of the study team immediately if you experience any problems, side effects, or changes in your health.** If you have problems, call Dr. Hamadani immediately at 414-805-6800. In an emergency, call 911.

C2. RISKS OF TREATMENT

The research drug itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.
Many go away soon after you stop taking the drug. Drugs can affect individuals in different ways. . Complications of some of the side effects below may lead to life-threatening events and possibly death.

Atorvastatin

More likely:

- Diarrhea
- Upset stomach
- Muscle and joint pain
- Changes in laboratory blood tests

Less likely:

- Tiredness
- Tendon problems (tendons connect your muscles to your bones)

Rare, but serious:

- Muscle problems that can lead to kidney problems, including kidney failure. You have a greater chance of this problem if you take other medicines with atorvastatin.
- Liver problems, including liver failure

Allergic Reactions

Allergic reactions can vary in degrees of severity. They may cause death in rare cases. When a severe allergic reaction develops, it usually occurs at the time the medicine is entering the body (during drug infusion). Allergic reactions may cause trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash.

Tacrolimus: This medication is used to try to prevent GVHD. The immediate side effects you may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects you may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If you experience these effects they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. You may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. In rare cases, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. It may also cause nausea (feeling sick to your stomach) and vomiting (throwing up). Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidney is already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the mediation may not be given at all.

C3. OTHER RISKS OF THIS RESEARCH STUDY

Other procedures that are part of the study also involve some risks:

The following risks are not specifically related to any one drug or the transplanted donor cells, but they are risks that are a part of the transplant procedure. The following applies to **ALL** patients.

Additional Risks and Toxicities Related to the Standard Transplant Procedure

There are certain risks related to a SCT. There are risks from the medications and/or irradiation therapy you will receive as part of the conditioning for the transplant and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. Your doctor will give you medications to lessen some of the side effects. Some of these complications can be serious and may be fatal

in some instances. The risk of death may be as high as 40% depending on individual patient related factors. You will be monitored closely during the transplant for any complications that may occur.

Your study doctor will explain the risks of transplant to you further.

Blood Draw: Although you may require a central venous catheter to donate cells, there may be an occasional need to have an intravenous catheter placed in your arm(s) or you may need to have blood withdrawn from the veins of your arm(s). Drawing blood from the arm may be associated with bleeding into the skin and may very rarely result in an infection.

Central Venous Catheter: A central venous catheter is a flexible sterile tube that can be placed into a large vein either under the collar bone or in your groin area so that blood can be withdrawn. This tube is placed under local anesthesia and will be placed just prior to receiving the cyclophosphamide/rituximab that is given during the cytoreduction process. Complications include blood clots and infection. Clotting may necessitate removal of the catheter or treatment of the clot by injecting a medicine that dissolves blood clots. If you develop an infection, you will require treatment with antibiotics. If the catheter is placed under the collarbone, other uncommon side effects may include swelling of the face and arm and/or lung collapse. If the lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs, brain and other organs can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Mouth Sores and Diarrhea: The chemotherapy causes irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea and you may need medication to help control the pain. If your mouth sores are severe you may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise.

Capillary Leak Syndrome: This may occur as a result of chemotherapy and radiation therapy. The blood vessels may become ‘leaky’ and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: Although your major organs function well, it is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that cannot always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage can be life threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. It is rare, but your kidneys could be affected, causing anemia or high blood pressure. There is also a 1-3 % risk you may develop a second cancer including leukemia as a result of the chemotherapy and/or radiation ,. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant but can occur sometimes within five years after transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating this fluid. Furosemide is a drug that is often given to help eliminate this excess fluid. This drug may cause hearing loss and loss of body chemicals such as potassium and sodium.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant

The drug in this study might affect a baby, before or after the baby is born. We do not know if the drug causes harm to a baby, so we do not want anyone who might be pregnant to enter the study. You should not become pregnant or nurse a baby while in this study. You must tell the study doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the study.

Risks of fathering a child

You should not father a baby while taking part in this study because it is unknown if the drug in this study could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the study doctor right away if you think your partner is pregnant.

Birth control methods for all subjects

Check with the study doctor about the birth control methods needed for this study and how long to use them. Some methods might not be good enough for this study. If you are having sex that could lead to pregnancy, you should use birth control while you are in this study.

This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms ("double barrier")
- Limiting sexual activity to a male partner who has had a vasectomy

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

We don't know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us learn how to better prevent acute GVHD.

D1. ARE THERE ANY COSTS TO BEING IN THE STUDY?

Some of / most of the medical care that you will receive in this study is considered routine care for your condition and would be recommended whether you join the study or not. Costs for routine care will be billed to you or your insurance carrier. Activities / costs that are part of the study will not be billed to you or your insurance company. These are the study drug (Lipitor®). Some insurers will not pay for drugs, tests or hospitalization that are part of research studies, so check with your insurer before you join this study. If you have questions regarding study costs, please contact Dr. Hamadani.

D2. WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

There is no payment for being in this study.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this study. You are free to say yes or no. If you do not join this study, your doctor can discuss other healthcare choices with you.
Your other choices may include:

- Routine care for this condition or symptoms
- Joining a different research study

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE STUDY?

If we learn any important new information about the drug that might change your mind about being in the study, we will tell you about it right away. You can then decide if you want to stay in the study.

D5. WHAT HAPPENS IF I AM HARMED BECAUSE I TOOK PART IN THE STUDY?

No funds have been set aside to pay any costs if you become ill or are harmed because of this study. If you think that you have become ill or were harmed because of this study, let the study doctors know right away by calling 414-805-6800. By signing this form, you do not give up your right to seek payment for harm you receive while participating in this study.

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By signing this form, you do not give up your right to seek payment for harm you receive while participating in this study.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

- If you have more questions about this study at any time, you can call Dr. Hamadani at 414-805-6800.
- If you have questions about your rights as a study participant, want to report any problems or complaints, obtain information about the study, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this study?

To do this research study, we need your permission to collect and use some of your health information, or you cannot be in the study. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the study.

The health information to be collected and used for this study is:
All or portions of your medical chart:

- ⇨ Hospital/Medical Records
- ⇨ Physician/Clinical Records
- ⇨ Lab and/or Pathology Reports
- ⇨ Radiology Reports
- ⇨ Biological Samples

E2. Who will see the health information collected for this study?
The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the study team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

The study team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this study. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this study, we plan to share information with those doctors, researchers or government representatives working with us on this study at the institutions or companies listed here:

U.S. Food and Drug Administration, Rockville, MD
Any Independent ethics committee, which approved this study
Other Regulatory Agencies and/or Their Designated Representatives
Those required by law

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different study without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed, the information might be used or released for other purposes without asking you. Results of the study may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?
One risk of taking part in a research study is that more people will handle your personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the study doctor about whether this could apply to you.

E4. How long will you keep the health information for this study?
If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this study.

E5. Can I cancel my permission to share this health information?
If you change your mind later and do not want us to collect or share your health information, you need to send a letter to:

Mehdi Hamadani, MD
Froedtert & Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee, WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the study. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE STUDY

A description of this clinical trial will be available on http://www.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.

You can look up this study by referring to the ClinicalTrials.gov number (NCT01665677) or by asking the study team for a printed copy.

CONSENT TO PARTICIPATE IN THE STUDY

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The study's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the study team use and share the health information and other information gathered for this study.
- I voluntarily agree to participate in this research study. I agree to follow the study procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

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Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Legally Authorized Representative (if applicable) *please print*	**Signature of Legally Authorized Representative**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the study team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. In all research study protocols the Principal Investigator is responsible and accountable for the study.*