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

Name of Study Subject: _____

Phase I-II Study Using Tocilizumab for Treatment of Steroid Refractory Acute Graft-versus-Host Disease

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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 because you have been diagnosed with acute Graft Versus Host Disease (GVHD) that has not responded to steroid treatment.

A total of about 21 people are expected to participate in this study at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the study is William Drobyski, MD in the Department of Medicine, Division of Hematology and Oncology. A study team works with Dr. Drobyski. You can ask who these people are.

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?

In this study we want to find out whether treatment with a drug called tocilizumab can be effective in people with acute GVHD that have not responded to treatment with steroids. We want to find out whether the new drug, tocilizumab, reduces the symptoms of acute GVHD, and whether it causes any problems (side effects). Everyone in this study will receive tocilizumab which is approved by the U.S. Food and Drug Administration for use in patients but not with your condition. We are testing tocilizumab to see what effect it has on people with acute GVHD. We do not know all the ways that this drug may affect people. 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 develop a better treatment for acute GVHD in the future.

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

Before you begin the study

First we will need to find out whether you are able to be in the study. You will be asked to give information about your medical history and undergo the exams and tests listed below.

- Physical exam including an assessment of your GVHD
- Blood tests to evaluate your organ function
- Blood and urine tests to check for the presence of infectious diseases

During the study

You may receive the study drug, tocilizumab (8 mg/kg), every three weeks for 8 weeks (56 days) to determine if you have had a response. If you are responding to the study drug but your symptoms have not completely resolved, you will continue to receive the same dose every 3 weeks. If your symptoms have resolved, you will receive tocilizumab once every 3 weeks at a reduced dose of 4 mg/kg until you have been taken off all other medicines that suppress your immune system.

The following tests and exams will be done every three weeks for the first 8 weeks while receiving tocilizumab:

- Physical exam
- Assessments of your GVHD
- Blood tests to check for infectious diseases.
- Blood tests to evaluate your organ function (weekly during the first 3 weeks, then once every three weeks)
- If clinically indicated, blood cultures to check for bacteria and fungus.

After Day 56, if you are still receiving Tocilizumab, the following tests and exams will be done every 3 weeks until one year after study entry, or until discontinuation of Tocilizumab:

- Physical exam
- Assessments of your GVHD
- Blood tests to evaluate your organ function
- Blood tests to check for infectious diseases

B2. HOW LONG WILL I BE IN THE STUDY?

You will be in this research study for about 12 months. There is a small possibility that you may be on the study longer if your disease continues to respond but has not completely resolved by 12 months

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 additional visits 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 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 the 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.**

C2. RISKS OF TOCILIZUMAB

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 or cause death.

The side effects that other people have experienced so far with the tocilizumab are:

More common

- upper respiratory tract infections

- inflammation of the nasal passages (nasopharyngitis)
- headache
- high blood pressure (hypertension)
- dizziness
- bronchitis
- rash
- mouth sores
- upper abdominal pain
- inflammation of the lining of the stomach (gastritis)
- decreases in white blood cells
- decreases in platelets
- increases in liver enzymes in the blood
- increases in cholesterol (total cholesterol, LDL and triglycerides)

Serious infection
There is a risk of serious infection that could lead to death. Most patients who developed these infections were also taking drugs that suppress the immune system such as Methotrexate or corticosteroids. Serious infections leading to hospitalization or death, including tuberculosis, bacterial, invasive fungal, viral and other opportunistic infections have occurred in patients receiving tocilizumab. Viral reactivation and cases of herpes zoster exacerbation were reported in clinical trials.

Gastrointestinal (GI) Perforations
Events of GI perforation have been reported in clinical trials, primarily as complications of diverticulitis. Please contact your doctor if you have any new symptoms affecting your abdomen.

Hypersensitivity (allergic) and infusion reactions

- Sometimes mild to moderate allergic reactions may happen, such as hives, itching and skin rash. Severe or life-threatening allergic reactions, even death, although rare, may also happen. If you do have an allergic reaction, medical treatment will be given to you.

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 develop better treatments for Graft Versus Host Disease.

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

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. 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.

The billing of the study drug will be handled differently if you have Medicare. If you have Medicare, the study drug, tocilizumab, will not be billed to Medicare. The study drug will be provided to you at no charge; however, you will be responsible for all copays.

If you do not have Medicare, a prior authorization will be conducted with your insurance company to determine if the cost of the study drug, tocilizumab, will be covered by your insurance. If your insurance does not cover the cost of the study drug it will be provided at no charge; however, you will be responsible for all copays and deductibles.

If you have questions regarding study costs or if your insurance status changes, please contact Dr. Drobyski

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:

- using other medications that suppress your immune system to treat your graft versus host disease

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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D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

- If you have more questions about this study at any time, you can Dr. Drobyski 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 414-456-8844.

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:

- Hospital/Medical Records
- Physician/Clinic Records
- Lab and/or Pathology Reports
- Radiological Reports
- Biological Samples
- Data Previously Collected for Clinical Purposes

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.

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 indefinitely 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 Dr. Drobyski at 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
You can get more information about this study on the Federal government's web site for clinical trials, at http://www.ClinicalTrials.gov (trial number NCT01475162) as required by U.S. Law, or by asking the study team for a printed copy. This website will not include information that can identify you. At most, the website will include a summary of the results. You may search this website at any time.

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.

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.*