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

Name of Study Subject: _____

A Phase II open label study of oral Doxycycline administered as an adjunct to plasma cell directed therapy in light chain (AL) amyloidosis

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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 systemic or localized Amyloid light chain (AL) amyloidosis.

A total of about 30 people are expected to participate in this study at the Medical College of Wisconsin/Froedtert Hospital.

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

The study is funded through an American Cancer Society Institutional Research Grant through the Medical College of Wisconsin Cancer Center pilot grant program.

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 more about the addition of the antibiotic, doxycycline, to standard anti-amyloid therapy in people with AL amyloidosis. We want to find out whether doxycycline improves the response to standard anti-amyloid therapy and whether it causes any problems (side effects). Everyone in this study will receive doxycycline which is approved by the U.S. Food and Drug Administration for use in patients but not with your condition. We are testing doxycycline to see what effect it has on people with light chain (AL) amyloidosis. Results from this study might be used in a future study.

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

Screening procedures:

If you decide to join the study, you will be asked to sign this consent form. You will have the following screening tests to see if you are eligible to take part in the study:

- Medical History: A complete past and current medical history will be taken including any medications you have used or are currently using.
- Physical Exam with Vital Signs: A complete physical exam will be conducted with measurement of your blood pressure, pulse rate, respiratory rate and temperature
- Your level of activity will be assessed
- Blood Samples: Blood (approximately 4 teaspoons) for routine laboratory testing to monitor your blood counts, blood chemistry, light chains and heart function.
- Pregnancy Test: If you are a woman who is able to have a baby, a blood sample will be taken to make sure you are not pregnant.
- If your doctor determines it is necessary, urine samples will be collected over a 24 hour period of time. You will be provided collection cups for the collection of urine while you are at home. Your doctor will decide if you need to provide additional urine samples during the rest of the study.
- You will be asked to complete a questionnaire about how you are feeling. This questionnaire will take about 15 minutes to complete
- If you have localized amyloidosis and if your doctor determines it is necessary, you will have a CT scan to assess your disease. A CT Scan is a type of x-ray using computers.

The following screening procedures will be performed for patients with systemic amyloidosis. If you have localized amyloidosis, your study doctor will decide if you need to have the procedures done.

- Abdominal Imaging: Imaging of the abdomen will be performed. Your doctor will determine what type of imaging you will receive Your doctor will decide if you need additional imaging of the abdomen during the rest of the study.
- Echocardiogram (also called an “echo”): echocardiogram is a test in which ultrasound is used to examine heart function. Your doctor will decide if you need additional echocardiograms during the rest of the study.

- Bone survey: A bone survey may be done if your doctor determines it is necessary. A bone survey is a series of X-rays that evaluates the major bones of the body.
- Bone marrow aspirate and biopsy: You may have a bone marrow biopsy within 42 days before you first begin study treatment. A bone marrow biopsy is a procedure that you may have had done before. It requires the removal of a small piece of bone by a special needle, which is usually inserted into the back of the pelvis. As part of the same procedure, a bone marrow aspiration will be performed, which means that blood will be drawn out of the middle of the bone to examine cells in the bone marrow. This procedure is usually done with local anesthesia.

If the screening information shows that you meet the requirements, then you will be able to start the study. If the screening information shows that you cannot be in the research study, the study doctors will discuss other options with you and/or refer you back to your regular doctor.

Study Treatment Period:
Once it has been determined that you are able to participate in this study, you will be enrolled into the study and begin study treatment (the portion of the study where you will be taking the study drug).

You may receive a standard anti-amyloid therapy as determined by your study doctor. This anti-amyloid therapy will be selected by the study doctor from a group of drugs or treatments commonly used for patients with AL amyloidosis. The anti-amyloid therapy may consist of one or several drugs in combination. In addition, all patients in this study will receive the study drug, doxycycline. You will take 100 mg of doxycycline by mouth twice a day during the study. If you are taking an antacid containing aluminum, calcium or magnesium, or if you are taking iron-containing preparations, you must take the doxycycline at least 2 hours before or at least 2 hours after taking medications containing the ingredients listed above. Since dairy products contain calcium you should avoid dairy products 2 hours before and after taking doxycycline.

Systemic amyloidosis subjects
If you have systemic amyloidosis, you will come to the clinic once a month during the study. Below is a list of the standard of care tests and procedures that will be done each month for 12 months during your participation in the study, unless otherwise specified:

- Physical exam – A physical exam will be done including taking your vital signs each month. You will be asked how you are feeling and if you are having or have had any symptoms or side effects from your last visit. You will be asked about any medications you have used or are currently using.
- As part of routine clinical care, approximately 4 teaspoons of blood will be collected to monitor your blood cell counts, blood chemistries and light chains each month. These tests would be done even if you were not participating in this

study. Additional blood tests may be performed if your doctor determines it is necessary. These tests would be done even if you were not participating in this study.
- Your level of activity will be assessed (months 3, 6, 9 and 12)
- If your doctor determines it is necessary, a 24 hour urine sample will be collected (months 3, 6, 9 and 12)
- If your doctor determines it is necessary, you will have imaging of the abdomen (month 6)
- If your doctor determines it is necessary, you will have an echocardiogram (month 6)
- Doxycycline capsules will be dispensed for you to take as scheduled at home. Following Month 1, you will bring any empty or partially empty containers with you every month.

Localized Amyloidosis Subjects

If you have localized amyloidosis, you will come to the clinic every 3 months during the study. Below is a list of the standard of care tests and procedures that will be done every 3 months for 12 months during your participation in the study, unless otherwise specified:

- Physical exam – A physical exam will be done including taking your vital signs every 3 months. You will be asked how you are feeling and if you are having or have had any symptoms or side effects from your last visit. You will be asked about any medications you have used or are currently using.
- As part of routine clinical care, approximately 4 teaspoons of blood will be collected to monitor your blood cell counts, blood chemistries every three months. Additional blood tests may be performed if your doctor determines it is necessary. These tests would be done even if you were not participating in this study.
- Your level of activity will be assessed
- If your doctor determines it is necessary, you will have a CT scan to assess your disease (month 7).
- Doxycycline capsules will be dispensed for you to take as scheduled at home. Following Month 1, you will bring any empty or partially empty containers with you every 3 months.

For all subjects, the following will be performed for research purposes:

- A part of this research study includes the collection of blood samples for research laboratory tests. Approximately 1.2 teaspoons of blood (6 mL) will be collected at the time of a routine blood collection at the start of the study and then again at your 7 month and End of Study visits.

These samples will be stored at the Medical College of Wisconsin Tissue Bank and used by Dr. D'Souza for research related to this study.

- Each visit you will be asked to complete a questionnaire about how you are feeling. This questionnaire will take about 5-10 minutes to complete.

End of Treatment (for all subjects unless otherwise specified):

You will have a final visit within 30 days after you stop the study. You will be asked to bring any empty or partially empty containers with you to this visit. The following procedures will be done:

- Physical exam including taking your vital signs
- Your level of activity will be assessed
- Approximately 4 teaspoons of blood will be collected to monitor your blood cell counts, blood chemistries. Additional blood tests may be performed if your doctor determines it is necessary.
- Approximately 1.2 teaspoons of blood will be collected for research laboratory tests
- You will be asked to complete a questionnaire about how you are feeling. This questionnaire will take about 5-10 minutes to complete.
- If you have localized amyloidosis and if your doctor determines it is necessary, you will have a CT scan to assess your disease.

If you have systemic amyloidosis the following procedures may also be performed if your doctor determines it is necessary:

- Abdominal imaging
- Echocardiogram
- A 24 hour urine sample

Long Term Follow-Up:
After your End of Treatment visit we will contact you or review your medical records once a year for 5 years to see how you are doing and if you have received any other treatments for your amyloidosis.

B2. HOW LONG WILL I BE IN THE STUDY?

You will be in the study for approximately 6 years.

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 will be asked to come back for one more visit to check your health.
⇒ You will be asked to return your research drug containers.

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.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE STUDY?

If you are taking an antacid containing aluminum, calcium or magnesium, or if you are taking iron-containing preparations, you must take doxycycline at least 2 hours before or at least 2 hours after taking medications containing the ingredients listed above. Since dairy products contain calcium you should avoid dairy products 2 hours before and after taking doxycycline.

Doxycycline can also cause increased sensitivity to sun exposure. You should use adequate sun protection with sunscreen.

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 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.**

C2. RISKS OF DOXYCYCLINE

The research drug 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. Many go away soon after you stop taking doxycycline. Drugs can affect individuals in different ways.

Doxycycline has been in use for many decades and has been fairly well tolerated. Some of the side effects seen with doxycycline are listed below:

- nausea
- stomach upset
- skin rash in sun exposed areas (sun burn)
- diarrhea

Less likely but more serious side effects include:

- allergic reaction to the drug,

- low blood counts,
- eosinophilia
- Clostridium difficile diarrhea, a form of antibiotic-induced infectious diarrhea ranging from mild diarrhea to fatal colitis.

Rare serious side effect includes:

- Drug-induced cutaneous lupus, an allergic reaction leading to skin inflammation and damage

C3. OTHER RISKS OF THIS RESEARCH STUDY
Other drugs and procedures that are part of the study also involve some risks:

Blood samples: In addition to the possibility of pain while blood samples are being drawn from your arm, there is the risk of bleeding or bruising at the needle site or risk of infection. Some people may feel dizzy or light-headed after having blood drawn.

Bone marrow aspirate and biopsy*:* Risks associated with the procedure include pain, discomfort, soreness, redness, swelling, bleeding (may be excessive), bruising, and/or drainage (such as pus) at the needle site, infection, fever, allergic reaction to the medication used to numb the skin over the biopsy site. You may be asked to sign a separate consent form for this procedure.

Bone (Skeletal) Survey: X-rays are fairly safe, but excessive use can pose some health risks. One skeletal survey in this study is equivalent to approximately 1 year of "background" radiation that you would receive from natural sources (sun, soil, food, water). The effects of radiation from repeated X-rays collect over a lifetime. Too much exposure can lead to serious illness. These include blood disorders, cataracts, skin problems, and cancer. However, healthcare providers are aware of these risks. They consider the person's total exposure before X-ray tests.

CT Scan: CT scanners use special equipment to take pictures of the inside of your body. The CT scanner is a large machine shaped like a doughnut and has a bed in the middle of the circle that you lie on. The bed can slide backwards and forwards through the hole of the doughnut. Pictures of your internal organs are taken as you move through the machine. CT scans may be used to follow your treatment. You will have some radiation exposure. Generally, the amount of radiation received during this procedure is the same as a normal person gets from exposure to natural sources of radiation in the environment in a 2- to 3-year period. The potential long-term risks from this radiation are uncertain, but have not been associated with any definite change in overall medical condition.

Echocardiogram (ECHO): This test uses ultrasound to produce images of your heart. During the echocardiogram, electrodes will be placed onto your chest to allow for an ECG to be performed. Then a transducer (a device that looks like a computer mouse) will be applied. You may feel slight pressure on your chest from the transducer. In

addition, you may be asked to breathe in a certain way or to rest on your side during the test.

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 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.

Birth control methods women who could become pregnant

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

You should continue using birth control for 1 month after stopping the study drug.

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 amyloidosis.

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. Activities / costs that are part of the study will not be billed to you or your insurance company. The study drug, doxycycline, and the processing of blood samples for research purposes will be provided at no cost to you. If your study physician feels that it is necessary to order any

additional tests, procedures or exams for your care these 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. If you have questions regarding study costs, please contact Dr. D'Souza.

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

You will not be paid for participating in the 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:

- Getting treatment or care for your amyloidosis without being in a study
- Joining a different research study
- Getting no treatment

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

If we learn any important new information about the study 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 call Dr. D'Souza 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:

- Hospital/Medical Records
- Physician/Clinic Reports
- Lab and/or Pathology Reports
- Radiological Reports
- Biological Samples
- Interviews/Questionnaires
- 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 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 Dr. D'Souza at Froedtert Hospital & Medical College of Wisconsin, 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 (NCT02207556) 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.

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.*