Title of research study: ABATACEPT FOR THE TREATMENT OF PRIMARY BILIARY CIRRHOSIS WITH AN INCOMPLETE BIOCHEMICAL RESPONSE TO URSODEOXYCHOLIC ACID

Investigator: **Christopher L. Bowlus, MD**

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you have been diagnosed with Primary Biliary Cirrhosis (PBC) and have had an incomplete response to Ursodeoxycholic Acid (UDCA).

Please read the following information very carefully. If you agree to take part in this clinical study, you will be asked to sign the attached consent form. The investigator and/or a member(s) of the clinical study staff will help answer all your questions. Do not sign the consent form until you have completely understood the study and what is involved in the study. If you take part, you are willing to participate, and you have been informed of your rights as a participant in this study.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document**.**

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at ***2000 Stockton Blvd., Suite 100, Sacramento, CA 95817; (916)703-HEPC or (916)703-4372***

You can talk to Dr. Bowlus or the study nurse about any questions or concerns you have about this study at 916-734-8696 at the UC Davis Medical Center, 2000 Stockton Boulevard, Sacramento, CA

For IRB Use

95817. You can also contact the clinical research coordinator responsible for your care. The clinical research coordinator will assist you in contacting an investigator for this study.

If you have any emergency, you may call the UC Davis Medical Center's main phone number 24 hours a day at 916-734-2011 and ask for the Liver Fellow on call.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/IRBAdmin.You may talk to a IRB staff member at (916) 703-9151, IRBAdmin@ucdmc.ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

The purpose of this study is to determine if the study drug, Abatacept, is an effective treatment for Primary Billiary Cirrhosis (PBC) patients who have tried Ursodeoxycholic Acid (UDCA) and have had an incomplete response to treatment. UDCA is the only FDA approved treatment for PBC, but it does not work for everyone. Patients who do not respond fully to UDCA treatment are at risk of their disease progressing.

In patients with PBC, the immune system attacks the bile ducts in the liver. Some of this injury is due to specific immune cells called T cells. Abatacept functions by blocking T cell activity. This may help prevent injury of the liver cells and disease progression.

We hope to learn more about the effects of Abatacept in PBC patients and whether it is beneficial in stopping disease progression in those who do not fully respond to UDCA.

How long will the research last?

We expect that you will be in this research study for up to 36 weeks. This includes 24 weeks of treatment with a follow-up visit at week 36.

How many people will be studied?

We hope to enroll about 20 people here at UC Davis.

What happens if I say yes, I want to be in this research?

The clinical study will be done only at UC Davis. The name and address of this study center and the investigator for this study center are listed on page 1 of this document. Authorized members of the study staff will do all study procedures.

An initial examination called "Screening" will help decide if you can take part in the clinical study. This will include a full physical examination including body weight, height, blood pressure, heart rate, breathing rate, and body temperature. You will also have an electrocardiogram (ECG) to check the electrical activity of your heart. This involves placing several sticky pads on your arms, legs and chest, on your bare skin. These pads are attached to a machine that will measure your heart's electrical activity. Also, your medical history and details of your illness will be recorded. In addition, you will have about 47.5ml (~1.6 ounces) of blood drawn for a few lab tests including tuberculosis , Hepatitis C Virus (HCV) antibody, Hepatitis B antigen, and HIV antibody. If you are a female of child bearing potential you will also undergo a pregnancy test. You will also be asked to fill out a questionnaire.

If you take part in the clinical study, your treatment will begin within 28 days of the first examination. The study is expected to last up to 36 weeks, during which time you will make 7 planned visits to the study center. Visits will be scheduled approximately once every 2 to 4 weeks.

You will be given enough of the study medication to last between visits. Each week, you will be asked to administer a subcutaneous injection (a shot just under the skin) of 125mg of Abatacept. The study team will teach you how to administer this shot yourself.

Blood will be collected. Some blood samples must be taken when you are in a fasting state (overnight fast, only water is allowed). Over the course of the study, a total of approximately 244 mL (about 8.25 ounces) of blood will be collected. As a comparison, 450 to 500 mL of blood is taken at a typical blood donation. On visit days, your blood will be drawn before you are given your study medication so do not take a morning dose of your study medication.

During 2 of the 7 scheduled visits, magnetic resonance elastography (MRE) will be performed. This test involves placing a small vibrating pad on your abdomen, over the area of your liver. The vibrations into your abdomen will help the study doctor to determine the stiffness of your liver.

Before entering the study, you must tell the investigator about any medications that you are taking or have taken during the last 12 months. You will also need to tell the investigator about all medications (other than study drug) that you take during the study. You may not take any new medications to treat PBC during the study or change the dose of any medications you are allowed to take.

You should inform your general practitioner (family doctor) if you take part in this clinical study. Your general practitioner should not change your dosage of study medication, except in cases of emergency. The study investigator must be told about any medication prescribed by your general practitioner or other physicians during this study. Participation in other clinical studies within the last 30 days and during the course of this study is not allowed.

It is very important that women of childbearing age avoid pregnancy during the study. All sexually active women who take part in the study must use a reliable form of birth control. A pregnancy test will be performed at Screening and at the visits during Weeks 1, 4, 12 and 24 of the study. If you become pregnant during the study, **inform the study center immediately.**

Please see the picture below for an overview of the clinical study:

Study Design Schematic

Screening	Abatacept 125 mg SC	Off-Treatment FU

Week 0 2 4 12 24 36

Procedures	Pre-Treatment Visit	Treatment Day 1	Treatment Week 2	Treatment Week 4	Treatment Week 12	Treatment Week 24
Eligibility Assessments						
Informed Consent	X					
Inclusion/Exclusion	X					
Medical History						
Safety Assessments						
Physical Exam	X					X
Vital signs	X	X	X	X	X	X
Signs and Symptoms		X	X	X	X	X
Adverse Events		X	X	X	X	X
ECG	X					
PPD	X					
HCV antibody	X					
HBs antigen	X					
HIV antibody	X					
UPT[1]	X	X		X	X	X
Efficacy Assessments						
CMP	X	X	X	X	X	X
CBC	X	X	X	X	X	X
INR	X	X	X	X	X	X
CRP	X			X	X	X
AMA	X	X	X	X	X	X
IgG, IgM, IgA	X	X	X	X	X	X
ANA	X	X	X	X	X	X
Lipid Panel	X				X	X
MR Elastography	X					X
PBC-40	X					X
CD44+CD62L-	X				X	X
PK/IMG Samples[2]		X		X	X	X
Clinical Drug Supplies						
Abatacept 125 mg SC once weekly		X	X	X	X	X

[1] Also to be performed for any subjects discontinuing the study with documentation for reason for discontinuation.
[2] Weeks 4, 12, and 24 should be drawn pre-dosing. The precise PK sampling times relative to the actual dosing time must be accurately r
eCRF. The date and time of sample collection must be recorded so that compliance with the sampling schedule can be confirmed.

Abatacept Subcutaneous Forumulation ISR Protocol Shell
8 November 2011

For IRB Use

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to:

- Attend all study visits
- Take all study medications
- Follow instructions of the Investigator and the study staff

What happens if I do not want to be in this research?

Participation in this study is voluntary. You are free to refuse to participate or stop taking part in the study at any time without any penalty or loss of benefits to which you are otherwise entitled. Your decision to participate or not participate will in no way affect your current or future treatment. You will be given all the needed time and opportunity to ask questions about the details of this study and to decide if you want to participate.

If you choose to stop taking part in the study, for your own safety and interests, you will be asked to go through a final examination at which time blood will be drawn, you will be asked to complete the study question forms. You retain the right to refuse to participate in further data collection or follow-up examinations after stopping your participation in the study.

Instead of being in this research study, your choices may include:

1) You can go back to your usual care.
2) Find another clinical study.
3) Do nothing at all.

What happens if I say yes, but I change my mind later?

You can leave the research at any time and it will not be held against you.

If you decide to leave the research, contact the investigator so that the investigator can help you stop the study medications safely.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?

You may have unwanted effects and symptoms as a result of taking Abatacept. Abatacept has been approved by the Federal Drug Administration (FDA) for the treatment of Rheumatoid Arthritis (RA). The most common side effects in people with RA were:

Common

Headache

Cough

For IRB Use

Upper respiratory tract infection (chest cold)

Sore throat

Nausea

Nasopharyngitis (inflammation of nose)

Less Common

Dizziness

Increased blood pressure

Urinary tract infection

Herpes simplex

Runny nose

Abdominal pain

Diarrhea

Indigestion

Fatigue

Rare but Serious

Infusion and allergic reactions

Pneumonia

Cellulites (inflammation of tissue under your skin)

Urinary tract infection

Bronchitis

Diverticulitis (GI irritation)

Acute pyelonephritis (kidney infection)

COPD (chronic obstructive pulmonary disease) episodes (when COPD is existing)

Cough

Rhonchi (abnormal breath sound)

Dyspnea (shortness of breath)

Participants with a history of Chronic Obstructed Pulmonary Disease treated with abatacept had more COPD episodes, cough, rhonchi (abnormal breath sound), and dyspnea (shortness of breath) than those who did not get Abatacept.

There have also been rare cases of certain kinds of cancer in patients receiving Abatacept, but the role of Abatacept in the development of cancer is not known.

There is also an increased risk of serious infection, but is usually seen in those using immune suppressing drugs.

You should not receive any live vaccines while on treatment in this study. The vaccines may not be as effective while you are receiving Abatacept.

In addition to these risks, this research may hurt you in ways that are unknown. There may be a minor inconvenience or may be so severe as to cause death. If you experience any unwanted effects, make a note of them and report them to the investigator at your next scheduled visit or phone call. **If you have any serious unwanted effects or if you are not sure if the unwanted effect is serious, call the investigator or the study center immediately at the telephone number listed on page 1 of this document.**

It is not known whether treatment with Abatacept may cause injury or harm to an unborn child if taken during pregnancy. For this reason, pregnant women are not allowed to take part in this study. All women of childbearing age must use a reliable form of birth control while participating in this study. If you should become pregnant during the study, **inform the investigator or the study center immediately at the address listed on page 1 of this document**. Your participation in the study will be stopped, and you may be asked to sign a separate consent form so the progress of the pregnancy can be followed until the birth of the child.

It is not known if the study medication could cause harm to a breast-feeding infant if passed through the breast milk. For this reason, breast-feeding women are not allowed to take part in this study.

It is also not known if the medication can be passed through sperm and cause injury or harm to a/during pregnancy. Therefore, it is advised that female partners of male study participants do not become pregnant during the treatment phase of this study and use effective forms of birth control.

Subcutaneous Injections:

Subcutaneous injections may be slightly painful, cause bruising or, rarely, and infection.

Blood Drawing:

Blood drawing is mildly painful and can cause bruising and, very rarely, fainting, blood clots or an infection at the site.

Electrocardiogram (ECG):

There is no pain or discomfort during an ECG; however, removing the pads may cause some irritation to your skin.

For IRB Use

Magnetic Resonance Elastography (MRE):

Magnetic resonance imaging uses a strong magnetic field, which is not harmful in itself, but implanted medical devices that contain metal may malfunction or cause problems during an MR exam. If you have any implanted devices please inform the doctors before the procedure.

HIV Testing:

Being tested for HIV may cause anxiety regardless of the test results. A positive test indicates that you have been infected with the HIV virus, but no one knows for certain when, if ever, you will become sick with AIDS or a related condition. Receiving positive results may make you very upset. If other people learn about your positive test results, you may have trouble obtaining insurance or employment. If your test is negative, there is still the possibility that you could be infected with the HIV virus and test positive at some time in the future. Also, it is always possible that the test results could be wrong.

Privacy Risks:

There may also be risks to your privacy. The Researchers will store study records and other information about you in a secure location and will grant access only to those with a need to know. However, just like with other personal information kept by your health care providers, your banks, and others, even these safeguards cannot guarantee absolute protection of the data. If private information gets into the wrong hands, it can cause harm. Although rare, there are reported cases of breaches that have resulted in discrimination in insurance or employment.

Unknown/Unexpected Risks:

In addition to the risks listed above, there are risks that are not known or do not happen often when subjects take study drugs, including severe or life-threatening allergic reactions, interactions between study drugs or interactions with another medication. You will be informed as soon as possible, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence to whether you want to stay in this study.

Will being in this study help me in any way?

You may not have any benefits from taking part in this clinical study. It is possible that treatment with Abatacept may improve your PBC.

Although you may not receive any personal benefit, taking part in this study may benefit others by providing new information about the treatment of PBC.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB

and other University of California representatives responsible for the management or oversight of this study.

The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

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.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission. Your medical records may become part of the research record. If that happens, your research records may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/compliance/pdf/notice.pdf) and in an attached document.

Can I be removed from the research without my OK?

The investigator or BMS may decide to take you out of the study without your consent. The reasons for taking you out of the study could be as follows:

- If you are unable to fulfill the requirements of the study
- If you develop another serious illness or condition
- If your physician believes that continuation of the study is not in your best interest your interests

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

This research is being funded by a grant from Bristol Myers Squibb.

There is no charge for you to participate in this study. Neither you nor your insurance carrier will be charged for your taking part in the research. All costs associated with the study will be paid by the department.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your

insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

If you agree to take part in this research study, we will compensate you $40 per study visit you attend for your time and effort. You will not be compensated for study visits you do not attend. Payments will be processed on a quarterly basis in the form of a check. You may be asked for your social security number for payment purposes. It will not be used for any other purpose without your permission.

Patients flying in from out of town will have travel (airfare and hotel) arranged by and paid for by the sponsor and be reimbursed for any study related incidentals such as meals and parking. Reimbursements will come in the form of a check and be processed quarterly. You may be asked for your social security number for payment purposes. It will not be used for any other purpose without your permission.

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

[Add the following block if a witness will observe the consent process. E.g., short form of consent documentation or illiterate subjects.]

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	Date
Printed name of person witnessing consent process	

For IRB Use