1) Protocol Title

a) ABATACEPT FOR THE TREATMENT OF PRIMARY BILIARY CIRRHOSIS WITH AN INCOMPLETE BIOCHEMICAL RESPONSE TO URSODEOXYCHOLIC ACID

b) December 30, 2013

2) Author of Protocol

- ✓ **UC Davis Researcher**
- ☐ **Researcher from other institution**
- ☐ **Private Sponsor**
- ☐ **Cooperative Group**
- ☐ **Other: _____**

3) IRB Review History

n/a.

4) Objectives

1.1 Primary Objective

The primary objective of this study is to evaluate whether abatacept is effective in inducing a biochemical response in PBC patients with an incomplete response to UDCA.

1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety of abatacept in patients with PBC
- To assess effect of abatacept on liver stiffness as a measure of liver fibrosis in patients with PBC
- To determine the effects of abatacept on immunologic markers of PBC
- To assess the impact of abatacept on the quality of life in patients with PBC
- To characterize pharmacokinetics（PK）of abatacept 125mg administrated SC weekly in patients with PBC
- To assess immunogenicity of abatacept 125mg administered SC weekly in patients with PBC

5) Background

Introduction

Primary biliary cirrhosis (PBC) is a progressive autoimmune disease of biliary epithelial cells resulting in biliary cirrhosis. The prevalence of PBC in the US and Europe is estimated to be 5-40 per 100,000 persons and accounts for 3-4 % of liver transplants performed in the US. The only approved medical therapy of PBC is the hydrophilic bile acid ursodeoxycholic acid (UDCA). Multiple studies suggest that UDCA delays progression of the disease, particularly those that have a biochemical response which has defined by multiple criteria, the simplest being a decrease of the alkaline phosphatase to 1.67 times the upper limit of normal. However, 20-40% of PBC patients have an incomplete response to UDCA and remain at significant risk of disease progression leading to death or liver transplantation.

PBC is characterized by a 90% female predominance, high titers of serum anti-mitochondrial autoantibodies (AMA) directed against the pyruvate dehydrogenase complex E2 subunit and elevated plasma levels of immunoglobulin M (IgM). However, evidence from both human and murine models suggests that T-cells, particularly CD8+ T cells, are key to the destruction of bile ducts. Genetic evidence of a T-cell defect is also supported by our findings and those of others demonstrating significant associations between CTLA-4 polymorphisms and PBC. Most notable, are the results we recently published in our murine model of PBC in which both AMA and biliary inflammation are induced by immunization with the xenobiotic 2-octynoic acid (2-OA). CTLA-4 Ig treatment one day before 2-OA immunization, completely inhibited AMA production, intra-hepatic T cell infiltrates, and bile duct damage. More critically, treatment with CTLA-4 Ig initiated after the 2-OA immunization and development of disease, also resulted in reduced intra-hepatic T cell infiltrates and biliary cell damage, although AMA levels were not altered.

a) Pathology of Primary Biliary Cirrhosis

Three important observations must be taken into account for us to understand the pathogenic basis of PBC. First, appearance of AMAs before liver disease suggests that loss of tolerance to the mitochondrial autoantigen is an early event and could be independent of the development of liver disease. Second, although the autoantigen is present ubiquitously in all nucleated cells, the immune response is restricted to epithelial cells of intrahepatic bile ducts and, to a lesser degree, to cells of salivary and lacrimal glands. Finally, recurrence of PBC after liver transplantation supports the idea that the bile duct epithelial cell is a generic target and is not unique to the patient with PBC. Similar to other complex diseases, the combination of a susceptible genetic background and exposure to environmental triggers are needed to initiate and promote the disorder.

Observations that 1–6% of individuals with PBC have at least one family member manifesting disease and a 63% concordance rate in monozygotic twins (*vs* null concordance in dizygotic sets), show the substantial genetic effect on disease susceptibility, one of the strongest for any autoimmune disorder. Many candidate genes have been investigated for a role in susceptibility to PBC, disease progression, or both in case-control cross-sectional studies. Findings of a genome-wide association study undertaken in a northern American set of patients and controls indicated a significant association between PBC and polymorphisms of *HLA-DQB1*, *IL12A*, *IL12RB2*, and to a minor extent, *STAT4*, and these associations have been confirmed in an independent cohort of Italian patients and controls with a combined analysis.

Several environmental factors—mainly infectious and chemical—are also thought to contribute to the onset of PBC, largely through molecular mimicry or modification of autoantigens. Geographic clustering of cases near toxic waste sites in New York City and space-time clustering in northeast England provide epidemiological evidence for a role of chemicals, infectious agents, or both. Additional data that lend support to a role for infections in disease development include the significantly higher prevalence than usual of recurrent urinary-tract infections in patients with PBC and experimental findings of sequence similarity between the E2 enzyme of the pyruvate dehydrogenase complex recognized by autoantibodies and bacterial proteins. Several bacterial strains—including the non-pathogenic gram-negative bacterium *Novosphingobium aromaticivorans*—have the highest known homology to the immunodominant autoepitope of the E2 enzyme. Several other infectious agents have been proposed, including *Escherichia coli*, *Helicobacter* spp, organisms of the genus *Mycoplasma*, and a human β retrovirus, although support for the retrovirus has not been substantiated.

Other environmental factors proposed to trigger disease onset are foreign chemicals (ie, xenobiotics) that can either alter or form a complex with a defined self or non-self protein, causing a change in the protein's molecular structure that induces an immune response. Lipoic acid is attached to only a few proteins, yet it is a vital component of the E2 epitope. The structure of the E2 enzyme exposes lipoic acid at the exterior of the protein complex, making this compound accessible to chemical modification. The role of xenobiotics in PBC is supported by serum reactivity against specific organic compounds with structures similar to lipoic acid; furthermore, two of these compounds (6-bromohexanoate and 2-octynoic acid) can induce AMAs and liver lesions similar to those of PBC in guinea pigs and mouse models.

AMAs in serum are highly sensitive and specific for PBC: they are detected in nearly 95% of patients, with specificity close to 100% when tested with recombinant antigens. Indirect immunofluorescence remains the test used for screening, but it can be associated with a substantial number of false-positive results. Follow-up data from AMA-positive individuals without signs of liver disease suggest that autoantibodies arise several years before onset of PBC and have a high predictive value. Epitopes recognized by AMAs

include lipoylated domains (via the Asx-Lys-Ala motif) within subunits of the 2-oxoacid dehydrogenase family of enzymes of the mitochondrial respiratory chain, in particular, E2 subunit and E3 binding-protein components of the pyruvate dehydrogenase complex and E2 components of the 2-oxoglutarate dehydrogenase and branched-chain 2-oxo acid dehydrogenase complexes.

b) Role of T cells in Primary Biliary Cirrhosis

In addition to AMAs, autoreactive CD8+ and CD4+ T cells to the E2 component of the pyruvate dehydrogenase complex have been identified both in peripheral blood and within the liver of patients with PBC, and the immunodominant epitope of these T cells maps in close proximity to the epitope recognized by AMAs in serum. Autoreactive CD4+ cell clones specific for the E2 enzyme have been isolated in intrahepatic and peripheral lymphocytes, not only in AMA-positive individuals but also in patients without antibodies, thus corroborating the notion that PBC either positive or negative for AMAs is one nosological entity.

CD4+ $CD25^{high}$ regulatory T cells act to prevent autoreactivity, as shown in several autoimmune diseases, including autoimmune hepatitis. Patients with PBC are characterized by substantially lower frequencies of CD4+ $CD25^{high}$ regulatory T cells as proportions of total T-cell receptor-αβ+/CD4+ cells, and this factor could be important in the breakdown of tolerance.

c) Summary of Results of Investigational Program

Pharmacology of Abatacept

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge- CH2-CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

Abatacept is the first drug in a new class of agents termed “selective costimulation modulators.” Abatacept binds specifically to the CD80 and CD86 molecules, proteins prominently displayed on the surface of antigen-presenting cells (APCs). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific; antigens are presented by APCs, with the signal transmitted to the T cell through the T cell’s antigen receptor. The second, or costimulatory, signal is not antigen-specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell.

A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both CD80 (B7-1) and CD86 (B7-2) on the APC. A

costimulatory signal is required not only for the full activation of naive T cells, but also may be required for the survival of memory and autoimmune effector cells. At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface, which engages the CD80 and CD86 molecules on the APC surface interfering with CD28's ability to bind to its ligands on the APC; CD80 and CD86 preferentially bind to CTLA4 with a much higher avidity than with CD28. Although the precise mechanisms are as yet unclear, CTLA4 expression is associated with a decrease in T cell activation.

After the T cell activity has been dampened, the CTLA4 recycles into the T cell's cytoplasm. The CTLA4 section of abatacept binds specifically to CD80 and CD86 (B7-1 and B7-2, respectively) and down-modulates the CD28-mediated costimulation of T cells. Thus, abatacept uses a segment of a molecule that is part of the normal immune homeostatic mechanism to suppress T cell activity involved in the immunopathogenesis of autoimmune diseases. The FC region of abatacept was engineered with several point mutations designed to inactivate it. Because of these changes, abatacept does not mediate pathways such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity.

Study Rationale

This is an open label, single center, active treatment study of the effects of abatacept on PBC patients with an incomplete response to UDCA. These patients have been demonstrated to have increased morbidity and mortality with standard-of-care treatment. An abundance of human and pre-clinical data suggests that T cell activation is central to the immune-mediated destruction of biliary epithelial cells and that abatacept may be effective in halting this process.

6) Inclusion and Exclusion Criteria

Inclusion Criteria

1. **Signed Written Informed Consent**
   a) Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.
2. **Target Population**
   a) Confirmed PBC diagnosis based upon at least 2 of 3 criteria
      i) AMA titer > 1:40
      ii) Alkaline phosphatase > 1.5 times the upper limit of normal for at least 6 months
      iii) Liver biopsy findings consistent with PBC

b) Incomplete response to UDCA defined by an alkaline phosphatase > 1.67 times the upper limit of normal after 6 months of UDCA at a minimum dose of 13 mg/kg/d.

c) Taking a stable dose of UDCA for at least 3 months prior to Day 0.

d) Willing and able to comply with all study requirements.

e) AST and ALT $\leq$ 5 X the upper limit of normal

3. Age and Reproductive Status

a) Men and women, 18 to 80 years of age.

b) **Reproductive Status: Definition of Women of Child-Bearing Potential (WOCBP).** WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below).

1) Post-menopause is defined as:

- Women who have had amenorrhea for ≥ 12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL.
- Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.
- Women who are taking hormone replacement therapy (HRT).

The following women are WOCBP:

- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
- Women who are practicing abstinence.
- Women who have a partner who is sterile (eg, due to vasectomy).
- WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 10 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.
- WOCBP must have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 0 to 48 hours before the first dose of study drug.
- Women must not be breast-feeding.
- Sexually active fertile men must use effective birth control if their partners are WOCBP.

Exclusion Criteria

2) **Target Disease Exceptions**
   a) Presence of other concomitant liver diseases including viral hepatitis, PSC, alcoholic liver disease, Wilson's disease, hemochromatosis, or Gilbert's syndrome.
   b) Prior liver transplantation
   c) Decompensated liver disease defined by the presence or history of any of the following
      i) MELD score > 15
      ii) Hepatic encephalopathy
      iii) Ascites
      iv) Hepatorenal syndrome or serum creatinine > 2 mg/dL
      v) Total Bilirubin > 3.0 mg/dL
      vi) INR > 1.8 unless on anticoagulation such as Coumadin.
   d) Use of immunosuppressants within 6 months of Day 0, including azathioprine, prednisone, prednisolone, budesonide, cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil.
   e) Use of biologic agents including anti-cell and anti-cytokine therapies within 12 months of Day 0.
   f) History of tuberculosis or positive PPD skin test.
   g) Positive hepatitis B surface antigen
   h) Presence of hepatitis C RNA
   i) QT or QTc interval > 500 milliseconds

3) Medical History and Concurrent Diseases
   a) Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.
   b) Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, whether or not related to RA and which, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.
   c) Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ. Existing non-melanoma skin cell cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug.
   d) Subjects who currently abuse drugs or alcohol.
   e) Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including subjects

with evidence of human immunodeficiency virus (HIV) detected during screening.

f) Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months before the informed consent document was signed.

g) Subjects who have received any live vaccines within 3 months of the anticipated first dose of study medication.

h) Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (eg, chronic pyelonephritis, osteomyelitis, or bronchiectasis).

i) Subjects at risk for tuberculosis (TB). Specifically excluded from this study will be subjects with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (≥ 4 weeks).

4) Physical and Laboratory Test Findings

a) Subjects with any of the following laboratory values

i) Hemoglobin < 8.5 g/dL

ii) WBC < 3000/mm^3 (< 3 x 109/L)

iii) Platelets < 75,000/mm^3 (< 3 x 109/L)

iv) Serum creatinine > 2 times the ULN

v) Serum ALT or AST > 5 times the ULN

b) Any other laboratory test results that, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.

5) Allergies and Adverse Drug Reactions

c) Any prior adverse reaction to abatacept.

6) Prohibited Treatments and/or Therapies

d) Subjects who have at any time received treatment with any investigational drug within 28 days (or less than 5 terminal half-lives of elimination) of the Day 1 dose.

e) Any concomitant biologic DMARD, such as anakinra.

7) Other Exclusion Criteria

f) Prisoners or subjects who are involuntarily incarcerated.

g) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

7) Number of Subjects

a) Study- Wide/Local:

Up to 20 subjects with PBC will be enrolled in this trial.

8) Recruitment Methods

a) Local:

Patients will be recruited by direct person to person contact within the GI/Hepatology clinic when the potential patients come in for routine care.

If, during their normal visit, it is noted they may qualify for a clinical trial, they will be approached by the investigator.

The principal investigator is also heavily involved in the PBC patient support groups of Northern California and will recruit potential subjects verbally from these groups as well during normal scheduled presentations.

Patients may also be recruited using recruitment materials such as flyers, posters and social media ads.

b) HIPAA:

We are requesting HIPAA waiver:

- Study personnel will be accessing patients' medical records for their Standard of Care when it may become evident that a patient may qualify for the research.
- Access to PHI is necessary to confirm eligibility
- PHI will only be used to assess eligibility and will not be copied or stored anywhere.
- The protected health information will not be inappropriately reused or disclosed to any other person or entity.
- PHI accessed may include, but are not limited to past/current diagnoses and lab results.

9) Compensation to the Subjects

From the ICF:

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.

10) Study Timelines

Describe:

- The treatment phase of the study will last 24 weeks with an off-treatment follow up at Week 36.
- We anticipate enrollment to be complete after one year.
- We anticipate primary analysis to be complete after two years.

11) Study Endpoints

The primary endpoint assessment will be the biochemical response rate defined by normalization of alkaline phosphatase or decrease of alkaline phosphatase by > 40% of the Day 0 level at 24 weeks of treatment.

Secondary endpoints will include:

- Absolute and percent change in alkaline phosphatase from Day 0 to 24 weeks.
- Absolute and percent change in alanine transferase (ALT) from Day 0 to 24 weeks.
- Change in liver stiffness from Day 0 to week 24 as measured by magnetic resonance elastography.
- Change in quality of life measured by change in PBC-40 from Day 0 to week 24.
- Change in AMA titer from Day 0 to week 24
- Change in IgM level from Day 0 to week 24
- Change in CD4+CD44+CD62L- and CD8+CD44+CD62L- frequencies in PBMC from Day 0 to week 24
- Comparisons of safety assessments pre-treatment, on-treatment, and post-treatment including adverse events, laboratory observations, and physical exam findings.
- Trough concentrations of abatacept concentrations from Week 0 to Week 24
- Immunogenicity evaluated over time by measuring anti-abatacept antibodies and anti-CTLA-4-T antibodies

12) Procedures Involved

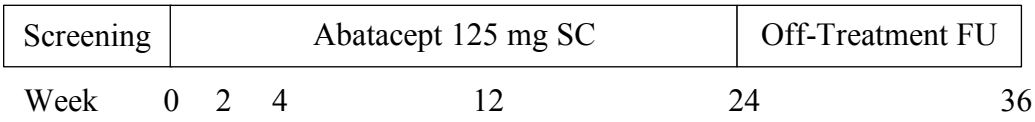
This is an open label, active treatment trial to assess the efficacy and safety of abatacept in subject with PBC who have had an incomplete biochemical response to UDCA.

In this trial, 20 subjects with PBC who have had an incomplete biochemical response to UDCA will be assigned to treatment with weekly subcutaneous injections of 125 mg of abatacept.

The treatment phase of the study will last 24 weeks with an off-treatment follow up at Week 36.

All subjects will undergo blood chemistry panel, complete blood count, INR, AMA, magnetic resonance elastography (MRE), and PBC-40 survey prior to the first dose of study drug. Baseline Mayo Risk Score and MELD score will be calculated from baseline lab values. Subjects will complete the 24 week treatment course and undergo repeat MRE and laboratory testing. Laboratory testing and assessments for adverse events will be conducted at Weeks 2, 4, 12, 24, and 36. Details are given in the Time and Events Schedule.

Figure 1. Study Design Schematic



Time and Events Schedule for Protocol [IM101-457]

Procedures	Pre-Treatment Visit	Treatment Day 1	Treatment Week 2	Treatment Week 4	Treatment Week 12	Treatment Week 24	Post-Treatment Week 36[1]
Eligibility Assessments							
Informed Consent	X						
Inclusion/Exclusion	X						
Medical History							
Safety Assessments							
Physical Exam	X					X	
Vital signs	X	X	X	X	X	X	X
Signs and Symptoms		X	X	X	X	X	X
Adverse Events		X	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	X
CBC	X	X	X	X	X	X	X
INR	X	X	X	X	X	X	X
CRP	X			X	X	X	X
AMA	X	X	X	X	X	X	X
IgG, IgM, IgA	X	X	X	X	X	X	X
ANA	X	X	X	X	X	X	X
Lipid Panel	X				X	X	X
MR Elastography	X					X	
PBC-40	X					X	
CD44+CD62L-	X				X	X	X
PK/IMG Samples[2]		X		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 recorded on the eCRF. The date and time of sample collection must be recorded so that compliance with the sampling schedule can be confirmed.

From the ICF:

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.

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.

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.

You will be expected to fast (only water is allowed) overnight before some of the blood samples are collected.

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 Day 1, Weeks 2, 4, 12 and 24 of the study. If you become pregnant during the study, **inform the study center immediately.**

13) Data and Specimen Banking

n/a.

14) Data Management and Confidentiality

STATISTICAL CONSIDERATIONS

The primary objective of this study is to evaluate whether abatacept is effective in inducing a biochemical response in PBC patients with an incomplete response to UDCA.

The secondary objectives of this study are:

- To assess the safety of abatacept in patients with PBC
- To assess effect of abatacept on liver stiffness as a measure of liver fibrosis in patients with PBC
- To determine the effects of abatacept on immunologic markers of PBC
- To assess the impact of abatacept on the quality of life in patients with PBC
- To characterize pharmacokinetics（PK）of abatacept 125mg administrated SC weekly in patients with PBC
- To assess immunogenicity of abatacept 125mg administered SC weekly in patients with PBC

Sample Size Determination

Among patients with PBC who do not have a complete biochemical response to UDCA, the probability of achieving serum liver biochemical normalization spontaneously is <5%. If abatacept is found to be ineffective among 20 enrolled subjects, the probability of observing 3 or fewer treatment responses is >98%. If abatacept is associated with a treatment success response rate of 30% or more, then the probability of **4** or more individuals responding is 89%. If these endpoints were met, pursuit of a randomized, double-blind, placebo-controlled trial would then be justified.

Populations for Analyses

The primary analysis set for efficacy and safety analyses will include all subjects who received at least one dose of study drug.

Pharmacokinetic Analysis Population: All available plasma concentration data from subjects who receive at least 1 dose of study medication and have at least 1 concentration result will be reported. However, only subjects without dose interruption will be included in the summary statistics.

Immunogenicity Analysis Population: For immunogenicity samples, included all subjects who receive at least 1 dose of abatacept and have at least 1 immunogenicity result reported.

Endpoint Definitions

The primary endpoint assessment will be the biochemical response rate defined by normalization of alkaline phosphatase or decrease of alkaline phosphatase by > 40% of the Day 0 level at 24 weeks of treatment.

Secondary endpoints will include:

- Absolute and percent change in alkaline phosphatase from Day 0 to 24 weeks.
- Absolute and percent change in alanine transferase (ALT) from Day 0 to 24 weeks.
- Change in liver stiffness from Day 0 to week 24 as measured by magnetic resonance elastography.
- Change in quality of life measured by change in PBC-40 from Day 0 to week 24.
- Change in AMA titer from Day 0 to week 24
- Change in IgM level from Day 0 to week 24
- Change in CD4+CD44+CD62L- and CD8+CD44+CD62L- frequencies in PBMC from Day 0 to week 24
- Comparisons of safety assessments pre-treatment, on-treatment, and post-treatment including adverse events, laboratory observations, and physical exam findings.
- Trough concentrations of abatacept from week 0 to week 24
- Immunogenicity evaluated over time by measuring serum anti-abatacept antibodies and anti-CTLA-4-T antibodies

Analyses

Endpoints of efficacy will be compared between Day 0 and Week 24 using paired t-test (or Wilcoxon signed rank test as indicated) for continuous variables and Chi-square test

(or Fisher's exact test) for categorical variables. For variables measured at multiple time points, Repeated Measures ANOVA will be employed. All analyses will be two-tailed and P values less than 0.05 will be considered as statistically significant.

The primary endpoint assessment will be the biochemical response rate defined by normalization of alkaline phosphatase or decrease of alkaline phosphatase by > 40% of the Day 0 level at 24 weeks of treatment. We will report the observed biochemical response rate and a 95% confidence interval for the expected biochemical response rate.

We will assess each of the secondary endpoints: absolute and percent change in alkaline phosphatase, absolute and percent change in alanine transferase (ALT), change in liver stiffness as measured by magnetic resonance elastography, change in quality of life measured by change in PBC-40, change in AMA titer, change in IgM level, and change in CD4+CD44+CD62L- and CD8+CD44+CD62L- frequencies in PBMC from Day 0 to week 24 by paired t-test or Wilcoxon signed-rank test when appropriate. Because these endpoints will be generated with these studies, to solve the problem of the above multiple significance testing, we will use the false discovery rate proposed by Benjamini and Hochberg. In addition, PK and immunogenicity of abatacept in patients with PBC will be estimated.

Descriptive statistics will be used to summarize safety data to allow a comparison between pre-treatment, on-treatment, and post-treatment. Safety data, including AEs, clinical and laboratory observations and physical examination findings, and other safety related outcomes will be summarized. Summary tables of treatment-emergent AEs will be provided. A treatment emergent AE (TEAE) is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study medication. AEs will be included in the treatment-emergent analysis if the onset date is on or after the first day of dosing and up to 56 days post the last dosing day. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to study medication discontinuation and SAEs will be provided. Descriptive statistics summarizing laboratory data (hematology and chemistry) will be presented for all trial visits. Changes from pretreatment to each trial visit will also be summarized. Additional safety assessments include vital signs, physical examinations, and ECGs.

For safety assessments pre-treatment, on-treatment, and post-treatment including adverse events, laboratory observations, and physical exam findings, repeated measures analysis of variance (ANOVA) will be employed to analyze a continuous outcome variable measured at these multiple time points, and a generalized estimating equation will be used to analyze a count or binary outcome variable measured at these multiple time points in order to take into account a possible unknown correlation among outcomes obtained on the same patient.

Clinical outcomes will be assessed including death from hepatic and non-hepatic causes, liver transplantation or placement on a liver transplant list, MELD score ≥ 15, new complications of liver disease including DILI as defined above, esophageal variceal bleeding, interventions to manage variceal bleeding, ascites, hepatic encephalopathy, renal failure, spontaneous bacterial peritonitis, and hepatocellular carcinoma.

Summary statistics for abatacept concentrations from Week 0 to Week 24 will be tabulated. Lack of immunogenicity is defined as the absence of a positive antibody response generated against abatacept administered subcutaneously. The incidence of a positive response will be summarized. The data will be analyzed to assess immunogenicity and its potential effect on pharmacokinetics and safety.

Procedures for maintenance of confidentiality:

- All data and specimens will be stored on password protected computers in locked offices and in monitored freezers/refrigerators
- The data will only be stored for the duration of the study and then destroyed.
- Only authorized research personnel will have access to the data and/or specimens.
- Ultimately the PI is responsible for the transmission of data and specimens, but this duty will likely be delegated to a qualified study coordinator.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects Data Monitoring Committee

An independent multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim data reviews in order to protect subject welfare and preserve study integrity. The first DMC review will be conducted after the first 5 subjects enrolled complete through week 24. The DMC will subsequently meet after every 5 subjects complete 24 weeks of treatment and finally after the last subject enrolled completes through week 32. In addition, the DMC will receive every Serious Adverse Event (SAE) in the trial in real time and monthly listings of all Adverse Events (AEs) reported. The DMC members can request an ad hoc meeting based on their review of these safety events. Finally, if a minimum of 2 subjects in the trial either experience the same treatment-emergent Grade 3 AE or if any one subject experiences a Grade 4 or 5 AE by the MedDRA grading system, this will trigger an ad hoc meeting of the DMC to review the safety of continuing the trial. The DMC will provide recommendations as needed regarding study design and conduct. The DMC has the authority to terminate the trial early if they determine that continuing the trial puts the subjects in the trial at undue risk.

16) Withdrawal of Subjects

Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

17) Risks to Subjects

From the ICF:

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

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 are 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.

>10%:

Central nervous system: Headache (≤18%)

Gastrointestinal: Nausea

Respiratory: Nasopharyngitis (12%), upper respiratory tract infection

Miscellaneous: Infection (adults 54%; children 36%), antibody development (2% to 41%)

1% to 10%:

Cardiovascular: Hypertension (7%)

Central nervous system: Dizziness (9%)

Dermatologic: Skin rash (4%)

Gastrointestinal: Dyspepsia (6%), abdominal pain, diarrhea

Genitourinary: Urinary tract infection (6%)

Immunologic: Immunogenicity (1% to 2%)

Infection: Herpes simplex infection, influenza

Local: Injection site reaction (3%)

Neuromuscular & skeletal: Back pain (7%), limb pain (3%)

Respiratory: Cough (8%), bronchitis, pneumonia, rhinitis, sinusitis

Miscellaneous: Infusion-related reaction (≤9%), fever

<1% (Limited to important or life-threatening): Acute lymphocytic leukemia, anaphylactoid reaction, anaphylaxis, cellulitis, diverticulitis, dyspnea, exacerbation of arthritis, exacerbation of chronic obstructive pulmonary disease, hypersensitivity, hypotension, joint wear, malignant neoplasm (including malignant melanoma, malignant neoplasm of the bile duct, malignant neoplasm of bladder, malignant neoplasm of breast, malignant neoplasm of cervix, malignant neoplasm of kidney, malignant neoplasm of prostate, malignant neoplasm of skin, malignant neoplasm of thyroid, myelodysplastic syndrome, and uterine neoplasm), malignant neoplasm of lung, ovarian cyst, pruritus, pyelonephritis, rhonchi, urticaria, varicella, vasculitis (including hypersensitivity angiitis [cutaneous vasculitis and leukocytoclastic vasculitis]), wheezing

There may be other risks that are not yet known. 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.

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.

18) Potential Benefits to Subjects

From the ICF:

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.

19) Vulnerable Populations

n/a.

20) Multi-Site Research

n/a

21) Community-Based Participatory Research

n/a.

22) Sharing of Results with Subjects

Results will not be shared with patients; however information regarding the progress of the trial will be available on clinicaltrials.gov.

23) Setting

UC Davis Medical Center, Main Hospital, 2315 Stockton Blvd., Sacramento, CA 95817

And

UC Davis Medical Center Ticon 1, 2000 Stockton Blvd, Suite 100, Sacramento, CA 95817

- *Patients will be recruited from the GI/Hepatology clinic.*

All research procedures will be performed at the above mentioned addresses.

24) Resources Available

All staff has also been delegated research specific responsibilities by the PI who is compliant and up to date with all required training.

Role	*Research Duties*
Principal Investigator	Determination of eligibility, consent, f/u evaluations, supervision of all study personnel and procedures.
Co-Investigator/ Sub-Investigator	Perform PI functions if PI absent Consent, determination of eligibility, f/u evaluations
Study Coordinator	Consent, CRFs, patient visits, study protocol compliance, documentation, IRB communication

- *We should have no problem reaching the goal of 20 patients.*
- *Each coordinator is tasked with 2-4 studies depending on study complexity and availability. This ensures that coordinators are able to devote adequate and ample time to each study.*
- *We are a clinical trial research clinic only consisting of patients rooms, a laboratory and office space.*
- *The main hospital is across the street should urgent medical attention be needed.*
- *All research staff are CITI trained and have been delegated authority to conduct the research by the PI according to their job descriptions.*
- *All research staff are delegated by the PI to perform any clinical trial and are trained extensively on the protocol by self and the sponsor.*

25) Prior Approvals

n/a

26) Provisions to Protect the Privacy Interests of Subjects

Potential subjects will be approached by the PI to gauge interest in participating. If the subject declines, no other attempts will be made.

In order to help the subjects feel at ease, all conversations will be discreet and will occur in private patient areas.

Only the PI and research staff is permitted to access information about the subject in regards to the study.

27) Compensation for Research-Related Injury

If patients 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.

28) Economic Burden to Subjects

Subjects are not responsible for any costs.

29) Consent Process

- Consent will take place at UC Davis Medical Center, Ticon 1, 2000 Stockton Blvd.,Suite 100, Sacramento, CA 95817.
- Subjects will have all questions answered before signing the consent form.
- Patients will be re-consented if changes to the protocol affect their study involvement or the risks change.
- The PI will be following "SOP: Informed Consent Process for Research (HRP-090)."

HIPAA Authorization for Research

HIPAA Authorization form will be presented to patients or their legally authorized representative.

30) Process to Document Consent in Writing

The PI will be following "SOP: Written Documentation of Consent (HRP-091)."

31) Drugs or Devices

- *Identify of the holder of the IND/IDE/Abbreviated ID:* **Bristol Myers Squibb**
- *The UC Davis Investigational Pharmacy will be handling all investigational drug(s) for the trial in accordance with their SOPs for storing, handling and dispensing.*
- *Patients will be given cooler bags to accommodate the study drug on their way from the clinic to their homes.*

- *Explain and/or provide reference material for procedures that will follow and comply with FDA sponsor requirements for the following:*

	Applicable to:		
FDA Regulation	***IND studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	*X*	*X*	
• Electronic Records and Signatures			
21 CFR 54	*X*	*X*	
• Financial Disclosure by Clinical Investigators			
21 CFR 210	*X*		
• Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs			
21 CFR 211	*X*		
• Current Good Manufacturing Practice for Finished Pharmaceuticals			
21 CFR 312	*X*		
• Investigational New Drug Application			
21 CFR 812		*X*	*X*
• Investigational Device Exemptions			
21 CFR 820		*X*	
• Quality System Regulation			

21 CFR 11- All study related activities take place at UC Davis medical center using UC Davis computers that comply with this regulation
21 CFR 54- The PI does not have a financial conflict of interest.
21 CFR 210- Please refer to the sponsor's Investigator's Brochure/package insert
21 CFR 211- Information not available to us. IRB may contact the sponsor if needed.
21 CFR 312- Sponsor has applied for and received an IND for the experimental drug.
21 CFR 812 – n/a
21 CFR 820 – n/a