Perelman School of Medicine
University of Pennsylvania

A SINGLE-CENTER, OPEN LABEL, CROSS-OVER STUDY ON THE EFFECTS OF URSODEOXYCHOLIC ACID (UDCA) IN PATIENTS WITH HEPATIC SARCOIDOSIS

Principal Investigator (1)

Ethan Weinberg, MD, MS
3400 Spruce Street, 2 Dulles
Philadelphia, PA 19104
ethan.weinberg@uphs.upenn.edu

Principal Investigator (2)

K. Rajender Reddy, MD
3400 Spruce Street, 2 Dulles
Philadelphia, PA 19104
rajender.reddy@uphs.upenn.edu

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Investigational Product: *URSODEOXYCHOLIC ACID (UDCA/ursodiol) tablets, for oral use*

IRB Number: *828780*

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Table of Contents

Study Summary

Title

A single-center, open label, cross-over study on the effects of ursodeoxycholic acid (UDCA) in patients with hepatic sarcoidosis

Short Title

UDCA for Hepatic Sarcoid

IRB Number

828780

Methodology

Open label, cross-over design, pilot study

Study Duration

24 months inclusive of 12 month observational and interventional phases

Study Center

University of Pennsylvania (single-center)

Objectives

This study aims to:
1. evaluate efficacy of UDCA in: (a) improving liver function laboratory and clinical parameters, (b) improving quality of life parameters
2. monitor safety and tolerability of UDCA, as well as progression of hepatic sarcoidosis and liver disease, in patients diagnosed with hepatic sarcoidosis.

Number of Subjects

A minimum of 10 subjects are expected to be enrolled at this center. Target enrollment has been increased to 40 patients.

Main Inclusion and Exclusion Criteria

KEY INCLUSION	*KEY EXCLUSION*
-Hepatic granulomas or systemic sarcoidosis with evidence of liver involvement as denoted by any of the following: *- Elevated liver-specific ALP* *- Granulomas on liver biopsy* *- Hepatomegaly on imaging* *- Portal Hypertension*	*-hepatitis B, hepatitis C, alcohol-related liver disease, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis)* *-Currently on UDCA* *-Prior intolerance to UDCA*

Investigational Product

URSODEOXYCHOLIC ACID (UDCA), (ursodiol) tablets, for oral use

Duration of administration

For all subjects, initial 6 months will be observational; in subsequent 6 months, UDCA will be administered twice daily.

Statistical Methodology	*The primary end-point is a reduction in ALP and/or GGT from baseline. We plan to use the effect size obtained from this pilot study to launch a multi-centered study that can be adequately powered to predict a specified percentage reduction in clinical and laboratory parameters with statistical significance.*
Safety Evaluations	*Laboratory parameters, including liver function and hematology panels, will be routinely assessed to monitor safety and tolerability of UDCA during study interventional phase.*
Data and Safety Monitoring Plan	*The PI will be responsible for monitoring the data quality and the ongoing safety of subjects.*

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including *Good Clinical Practice* standards: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH).

1 Introduction

Guidelines for the treatment of hepatic sarcoid suggest waiting until a patient is symptomatic or experiencing evidence of liver dysfunction to treat. The approach to the treatment of hepatic sarcoid should be similar to two other autoimmune liver diseases: autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC). Liver decompensation can be prevented in both AIH and PBC if the disease is diagnosed and treated in the early stages. The first-line treatment for AIH is immunosuppression with corticosteroids and azathioprine; for PBC, it is UDCA. In a similar vein, patients with hepatic sarcoid may benefit from earlier initiation of therapy. Given its excellent safety profile and minimal side effects, UDCA may be the consensus first-line treatment for hepatic sarcoid, a disease that, like PBC, usually causes a cholestatic liver injury.

1.1 Background and Relevant Literature

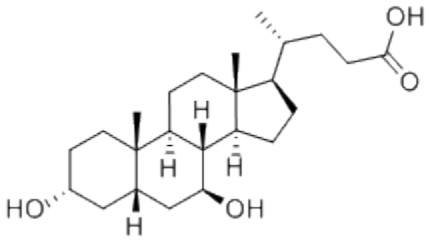
Sarcoidosis is a relatively rare, poorly defined autoimmune disease characterized by the formation of sterile granulomas in affected organs.[1] Studies over the years have implicated various genetic and environmental risk factors for development of sarcoidosis, but no single factor has been discovered to be the key initiator of the disease.[2] It is known that granuloma formation in sarcoidosis is driven by host T-cell interactions with antigen-presenting cells, but the intricacies of the immunologic events and the particular antigens responsible for perpetuating the disease remain to be determined.[1] Sarcoidosis is more prevalent in the West compared to the East, with a greater than 10-fold annual incidence of sarcoidosis seen in Northern Europe and the United States compared to Japan.[1] Within the United States, black women are at the highest risk for development of sarcoidosis, with rates three times that of Caucasian women. Overwhelmingly, the most common organs affected by sarcoidosis are the lungs, which are affected in more than 95% of patients with sarcoidosis.[3] This is followed by the skin, eyes, and liver.[3,4] In the two largest prospective cohort studies of sarcoidosis, the liver was affected in 11.5% and 17.7% of patients, respectively.[3,4] The diagnosis of hepatic sarcoid is often presumed based upon an elevated liver-specific isoenzyme of alkaline phosphatase or imaging findings suggestive of portal hypertension, hepatomegaly, or liver lesions in a patient with known pulmonary sarcoidosis; a minority of hepatic sarcoid cases are diagnosed through liver biopsy.[4]

The mainstay of treatment of systemic sarcoidosis in those with symptoms is immunosuppression with corticosteroids, which are gradually tapered over months.[5] The disease course for sarcoidosis can vary; patients who are asymptomatic can be monitored without therapy, while some require intermittent corticosteroids for flares. For those patients with persistent symptoms on corticosteroids, additional immunosuppressive or cytotoxic agents (e.g. azathioprine, methotrexate, infliximab, rituximab) are used.[5] The expert guidelines for treatment of hepatic sarcoid suggest waiting until a patient is symptomatic or experiencing evidence of liver dysfunction to treat. This approach is in opposition to the treatment of primary liver diseases in which treatment is often initiated based upon abnormal lab values even without symptoms, as symptoms of liver disease (ascites, variceal bleeding, pruritus, jaundice, and encephalopathy) often occur late in the disease.

The approach to the treatment of hepatic sarcoid should be similar to two other autoimmune liver diseases: AIH and PBC. Liver decompensation can be prevented in both conditions if the disease is diagnosed and treated in the early stages. The first-line treatment for AIH is immunosuppression with corticosteroids and azathioprine; for PBC, it is UDCA. In a similar vein, patients with hepatic sarcoid may benefit from earlier initiation of therapy. Given its excellent safety profile and minimal side effects, UDCA may be the consensus first-line treatment for hepatic sarcoid, a disease that, like PBC, usually causes a cholestatic liver injury. There have been case reports and retrospective studies documenting the beneficial effects of UDCA on hepatic sarcoid.[6–8] However, thus far, there have been no clinical trials to evaluate the efficacy of UDCA in hepatic sarcoid.

1.2 Name and Description of the Investigational Product

Ursodeoxycholic acid (abbreviated UDCA), also known as ursodiol, is available as a film-coated tablet for oral administration as 250 mg (URSO 250®), 500 mg (URSO Forte®) film-coated tablets, and Actigall 300mg capsules for oral administration. UDCA is a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. It is a bitter-tasting white powder consisting of crystalline particles freely soluble in ethanol and glacial acetic acid, slightly soluble in chloroform, sparingly soluble in ether, and practically insoluble in water. The chemical name of UDCA is 3α,7ß-dihydroxy-5ß-cholan-24-oic (C24 H40 O4). UDCA has a molecular weight of 392.56. Its structure is shown below:



1.2.1 Clinical Data to Date

A multicenter, randomized, double-blind, placebo-controlled study was conducted in the US to evaluate the efficacy of ursodeoxycholic acid at a dose of 13 to 15 mg/kg/day, administered in 3 or 4 divided doses in 180 patients with PBC (78% received QID dosage). Upon completion of the double-blind portion, all patients entered an open-label active treatment extension phase.

Treatment failure, the main efficacy end point measured during this study, was defined as death, need for liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal. After two years of double-blind treatment, the incidence of treatment failure was significantly reduced in the URSO 250® group (n=89) as compared to the placebo group (n=91). Time to treatment failure was also significantly delayed in the URSO 250® treated group regardless of either histologic stage or baseline bilirubin levels (>1.8 or <1.8 mg/dl).

Using a definition of treatment failure which excluded doubling of serum bilirubin and voluntary withdrawal, time to treatment failure was significantly delayed in the URSO 250® group. In comparison with placebo, treatment with URSO 250® resulted in a significant improvement in the following serum hepatic biochemistries when compared to baseline: total bilirubin, SGOT, alkaline phosphatase and IgM.

A second study conducted in Canada randomized 222 PBC patients to UDCA, 14 mg/kg/day or placebo, administered as a once daily dose in a double-blind manner during a two-year period. At two years, a statistically significant difference between the two treatments, in favor of UDCA, was demonstrated in the following: reduction in the proportion of patients exhibiting a more than 50% increase in serum bilirubin; median percent decrease in bilirubin, transaminases and alkaline phosphatase; incidence of treatment failure; and time to treatment failure. The definition of treatment failure included: discontinuing the study for any reason; a total serum bilirubin level greater than or equal to 1.5 mg/dl or increasing to a level equal to or greater than two times the baseline level; and the development of ascites or encephalopathy. Evaluation of patients at 4 years or longer was inadequate due to the high drop-out rate and small number of patients. Therefore, death, need for liver transplantation, histological progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritis, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal were not assessed.

A randomized, two-period crossover study in fifty PBC patients compared efficacy of URSO 250® (UDCA) in BID (two) versus QID (four) divided dosing schedules in 50 patients for 6 months in each crossover period. Mean percent changes from baseline in liver test results and Mayo risk score (n=46) and serum enrichment with UDCA (n=34) were not statistically significant with any dosage at any time interval.

This study demonstrated that UDCA (13 to 15 mg/kg/day) given BID is equally effective to UDCA given QID. In addition, URSO 250® was given as a single (once daily) versus TID (three) dosing schedules in 10 patients. Due to the small number of patients in this arm of the study, it was not possible to conduct statistical comparisons between these regimens.

In a randomized, cross-over study in sixty PBC patients, four patients (6.7%) experienced one serious adverse event each (diabetes mellitus, cyst and breast neoplasm (experienced by two patients)). No deaths occurred in the study. Forty-three patients (43, 71.7%) experienced at least one treatment-emergent adverse event (TEAEs) during the study. The most common (>5%) TEAEs were asthenia (11.7%), dyspepsia (10%), peripheral edema (8.3%), hypertension (8.3%), nausea (8.3%), GI disorders (5%), chest pain (5%), and puritius (5%). Seven patients (11.6%) reported nine events that were judged as possibly or probably related to study medication. These nine TEAEs included abdominal pain and asthenia (1 patient), nausea (3 patients), dyspepsia (2 patients) and anorexia and esophagitis (1 patient each). One patient on the BID regimen (total dose 1000 mg) withdrew due to nausea. All of these nine TEAEs except esophagitis were observed with the BID regimen at a total daily dose of 1000 mg or greater.

On the basis of clinical trial results in a total of 868 patients with radiolucent gallstones treated in 8 studies (three in the U.S. involving 282 patients, one in the U.K. involving 130 patients, and four in Italy involving 456 patients) for periods ranging from 6 to 78 months with Actigall doses ranging from about 5-20 mg/kg/day, an Actigall dose of about 8-10 mg/kg/day appeared to be the best dose. With an Actigall dose of about 10 mg/kg/day, complete stone dissolution can be anticipated in about 30% of unselected patients with uncalcified gallstones < 20 mm in maximal diameter treated for up to 2 years. Patients with calcified gallstones prior to treatment, or patients who develop stone calcification or gallbladder nonvisualization on treatment, and patients with stones > 20 mm in maximal diameter rarely dissolve their stones. The chance of gallstone dissolution is increased up to 50% in patients with floating or floatable stones (i.e., those with high cholesterol content), and is inversely related to stone size for those < 20 mm in maximal diameter. Complete dissolution was observed in 81% of patients with stones up to 5 mm in diameter. Age, sex, weight, degree of obesity, and serum cholesterol level are not related to the chance of stone dissolution with Actigall. A nonvisualizing gallbladder by oral cholecystogram prior to the initiation of therapy is not a contraindication to Actigall therapy (the group of patients with nonvisualizing gallbladders in the Actigall studies had complete stone dissolution rates similar to the group of patients with visualizing gallbladders). However, gallbladder nonvisualization developing during ursodiol treatment predicts failure of complete stone dissolution and in such cases therapy should be discontinued. Partial stone dissolution occurring within 6 months of beginning therapy with Actigall appears to be associated with a > 70% chance of eventual complete stone dissolution with further treatment; partial dissolution observed within 1 year of starting therapy indicates a 40% probability of complete dissolution. Stone recurrence after dissolution with Actigall therapy was seen within 2 years in 8/27 (30%) of patients in the U.K. studies. Of 16 patients in the U.K. study whose stones had previously dissolved on chenodiol but later recurred, 11 had complete dissolution on Actigall. Stone recurrence has been observed in up to 50% of patients within 5 years of complete stone dissolution on ursodiol therapy. Serial ultrasonographic examinations should be obtained to monitor for recurrence of stones, bearing in mind that radiolucency of the stones should be established before another course of Actigall is instituted. A prophylactic dose of Actigall has not been established.

Two placebo-controlled, multicenter, double-blind, randomized, parallel group trials in a total of 1,316 obese patients were undertaken to evaluate Actigall in the prevention of gallstone formation in obese patients undergoing rapid weight loss. The first trial consisted of 1,004 obese patients with a body mass index (BMI) ≥ 38 who underwent weight loss induced by means of a very low calorie diet for a period of 16 weeks. An intent-to-treat analysis of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, or 1200 mg/day of Actigall experienced a 6%, 3%, and 2% incidence of gallstone formation, respectively. The mean weight loss for this 16-week trial was 47 lb for the placebo group, and 47, 48, and 50 lb for the 300, 600, and 1200 mg/day Actigall groups, respectively. The second trial consisted of 312 obese patients (BMI ≥ 40) who underwent rapid weight loss through gastric bypass surgery. The trial drug treatment period was for 6 months following this surgery. Results of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, or 1200 mg/day of Actigall experienced a 9%, 1%, and 5% incidence of gallstone formation, respectively. The mean

weight loss for this 6-month trial was 64 lb for the placebo group, and 67, 74, and 72 lb for the 300, 600, and 1200 mg/day Actigall groups, respectively.

1.2.1.1 Human Pharmacokinetics

UDCA is normally present as a minor fraction of the total bile acids in humans (about 5%). Following oral administration, the majority of UDCA is absorbed by passive diffusion and its absorption is incomplete. Once absorbed, UDCA undergoes hepatic extraction to the extent of about 50% in the absence of liver disease. As the severity of liver disease increases, the extent of extraction decreases. In the liver, UDCA is conjugated with glycine or taurine, then secreted into bile. These conjugates of UDCA are absorbed in the small intestine by passive and active mechanisms. The conjugates can also be deconjugated in the ileum by intestinal enzymes, leading to the formation of free UDCA that can be reabsorbed and reconjugated in the liver. Nonabsorbed UDCA passes into the colon where it is mostly 7-dehydroxylated to lithocholic acid. Some UDCA is epimerized to chenodiol (CDCA) via a 7-oxo intermediate. Chenodiol also undergoes 7-dehydroxylation to form lithocholic acid. These metabolites are poorly soluble and excreted in the feces. A small portion of lithocholic acid is reabsorbed, conjugated in the liver with glycine, or taurine and sulfated at the 3 position. The resulting sulfated lithocholic acid conjugates are excreted in bile and then lost in feces.

Lithocholic acid, when administered chronically to animals, causes cholestatic liver injury that may lead to death from liver failure in certain species unable to form sulfate conjugates. UDCA is 7-dehydroxylated more slowly than chenodiol. For equimolar doses of UDCA and chenodiol, steady state levels of lithocholic acid in biliary bile acids are lower during UDCA administration than with chenodiol administration. Humans and chimpanzees can sulfate lithocholic acid. Although liver injury has not been associated with UDCA therapy, a reduced capacity to sulfate may exist in some individuals. Nonetheless, such a deficiency has not yet been clearly demonstrated and must be extremely rare, given the several thousand patient-years of clinical experience with UDCA.

In healthy subjects, at least 70% of UDCA (unconjugated) is bound to plasma protein. No information is available on the binding of conjugated UDCA to plasma protein in healthy subjects or primary biliary cirrhosis (PBC) patients. Its volume of distribution has not been determined, but is expected to be small since the drug is mostly distributed in the bile and small intestine. UDCA is excreted primarily in the feces. With treatment, urinary excretion increases, but remains less than 1% except in severe cholestatic liver disease.

During chronic administration of UDCA, it becomes a major biliary and plasma bile acid. At a chronic dose of 13 to 15 mg/kg/day, UDCA constitutes 30-50% of biliary and plasma bile acids.

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. It appears to have little inhibitory effect on synthesis and secretion into bile of endogenous bile acids, and does not appear to affect secretion of phospholipids into bile. With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady-state in about 3 weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodiol acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus, even though administration of high doses (e.g., 15 -18 mg/kg/day) does not result in a concentration of ursodiol higher than 60% of the total bile acid pool, ursodiol-rich bile effectively solubilizes cholesterol. The overall effect of ursodiol is to increase the concentration level at which saturation of cholesterol occurs. The various actions of ursodiol combine to change the bile of patients with gallstones from cholesterol-precipitating to cholesterol-solubilizing, thus resulting in bile conducive to cholesterol stone dissolution. After ursodiol dosing is stopped, the concentration of the bile acid in bile falls exponentially, declining to about 5% to 10% of its steady-state level in about 1 week.

1.2.1.2 Clinical Studies in Adults: Pregnancy Category B

Teratology studies have been performed in pregnant rats at oral doses up to 2,000 mg/kg/day (12,000

mg/m2/day, 22 times the recommended maximum human dose based on body surface area) and in pregnant rabbits at oral doses up to 300 mg/kg/day (3,600 mg/m2/day, 7 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to UDCA.

There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It is also not known whether UDCA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when URSO 250® and URSO Forte® are administered to a nursing mother.

There are no contraceptive requirements for males. Ursodiol was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y, TK+/-) forward mutation test, the human lymphocyte sister chromatid exchange test, the mouse spermatogonia chromosome aberration test, the Chinese hamster micronucleus test and the Chinese hamster bone marrow cell chromosome aberration test. Ursodiol at oral doses of up to 2,700 mg/kg/day (16,200 mg/m2/day, 29 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

1.2.2 Clinical Studies in Children

The safety and effectiveness of URSO 250® and URSO Forte® in pediatric patients have not been established.

1.3 Dose Rationale

The recommended adult dosage for URSO 250® and URSO Forte® in the treatment of PBC is 13-15 mg/kg/day administered in two to four divided doses with food. The URSO Forte® scored tablet can be broken in halves to provide recommended dosage. Due to the bitter taste, segments should be stored separately. Half-tablets (scored URSO Forte® 500 mg tablets broken in half) maintain acceptable quality for up to 28 days when stored in the current packaging (bottles) at 25ºC (77ºF), The recommended adult dosage for Actigall 300mg (for treatment of radiolucent gallbladder stones) is 8-10 mg/kg/day given in 2-3 divided doses. Dosing regimen should be adjusted according to each patient's need at the discretion of the physician. We will be using 250mg or 500mg tablets, or 300mg capsules for this protocol. This decision will be determined based on price, pill burden, and adherence complexity. Subjects will receive a targeted dose of 13-15 mg/kg/day in divided doses to be taken with meals. As the approach to the treatment of hepatic sarcoid in this protocol is designed to resemble that of the treatment of PBC, the targeted dose for subjects taking the Actigall 300mg capsules will also be 13-15 mg/kg/day, which remains within safe means of dosing for this formulation. For subjects in which the dosing increment does not fall into the 13-15mg/kg range, we will initiate intervention using the lower dose. For example, if a subject is 80kg, the dose range is from 1040-1200mg/kg/day. We will initiate 1000mg/day (12.5mg/kg/day in our 80kg example) rather than 1250mg/day (15.6 mg/kg/day). If the subject tolerates this lower dose well and the ALP and GGT have not reached a 20% decreased by month 9 (after 3 months of treatment), the subject will receive an additional 250mg tablet for daily administration. A dose calculation assessment will be performed at each in-person visit following UDCA administration. UDCA doses in the range of 17-23mg/kg have been used in long-term trials for PSC (PMID: 11606503, PMID:16285948). The UDCA studies in PSC demonstrated an improvement in ALP and GGT in subjects taking UDCA without an increase in adverse events from the medication.

Accidental or intentional overdosage with UDCA has not been reported. The most severe manifestation of overdosage would likely consist of diarrhea which should be treated symptomatically.
Single oral doses of UDCA at 10, 5 and 10 g/kg in mice, rats and dogs, respectively, were not lethal. A single oral dose of UDCA at 1.5 g/kg was lethal in hamsters. Symptoms of acute toxicity were salivation and vomiting in dogs, and ataxia, dyspnea, ptosis, agonal convulsions and coma in hamsters. Doses of Actigall in the range of 16-20 mg/kg/day have been tolerated for 6 to 37 months without symptoms by 7 patients. The LD50 for ursodiol in rats is over 5000 mg/kg given over 7 to 10 days and over 7500 mg/kg for mice.

2 Study Objectives

The objectives of this study are to evaluate the efficacy of UDCA in improving liver function and quality of life, and to assess the safety and tolerability of UDCA, as well as the progression of disease, in patients with hepatic sarcoidosis.

2.1 Primary Objective

- Evaluate the efficacy of UDCA in improving liver function as measured by a reduction in alkaline phosphatase (ALP) and/or gamma-glutamyl transferase (GGT) from baseline

2.2 Secondary Objectives

- Evaluate the efficacy of UDCA in improving other liver function laboratory and clinical parameters (as measured by improvements in liver function tests and Fibroscan measurements)
- Assess quality of life parameters prior to and following intervention with UDCA (as measured by improvements in patient-reported outcomes (PRO) questionnaire scores)
- Assess the safety and tolerability of UDCA, as well as disease progression (as measured by laboratory tests including liver function and hematology panels)
- Assess the effect of UDCA on the metabolic capacity of the liver as determined by the ^{13}C methacetin breath test (exploratory objective)
- Assess the effect of UDCA on other laboratory measures associated with sarcoidosis, including angiotensin converting enzyme (ACE) and soluble interleukin 2 receptor (sIL2R)
- Collect serum and plasma samples for biobanking

3 Investigational Plan

3.1 General Design

This will be a pragmatic, single-center, cross-over pilot study to evaluate the safety and efficacy of UDCA in patients subjects with hepatic sarcoidosis. For this project, potential subjects (i.e. patients with a prior diagnosis of sarcoidosis and lab/imaging findings suggestive of hepatic sarcoid) seen at Penn Medicine clinics will be identified by the study team and screened in the Hepatology clinic at the Perelman Center for Advanced Medicine. . At least ten patients will be enrolled for an expected twelve month duration. Frequency of clinical evaluations will align with standard of care monitoring of this patient population; the study-specific intervention will be the administration of UDCA (unblinded). Study-specific procedures include research labs, patient-reported outcomes questionnaires; optional biomarker retains, methacetin breath test (MBT) measurements; further details on the schedule of events for this study can be found in section 6.

NOTE: All subjects enrolled under Amendment 10 (JUN 2021) or later will NOT be included in the optional MBT sub-study.

3.1.1 Screening Visit

At the screening visit, prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed with the subject by the PI and signed and dated by the subject and the PI. For all subjects, the PI and/or study coordinator will: record medical history, record prior and current medications, record general health (including averse events and illnesses), conduct physical examination (including assessment of certain physical symptoms that are associated with liver disease), collect vital signs, perform a Fibroscan (ultrasound of abdomen to measure liver stiffness), administer quality of life (QoL) questionnaires, and collect blood samples for routine laboratory tests specific to liver function. A urine pregnancy test will be performed at screening for women of child-bearing potential (WOCBP). These subjects will also be required to confirm the use of appropriate contraceptive prior to receiving UDCA while in the study.

3.1.2 Study Observational Phase

Once the PI confirms a subject's eligibility, subject will be called by the study coordinator and asked to come back to the clinic for 4 future visits over the course of 1 year. The visits will occur approximately every 3 months, according to standard of care monitoring of this patient population.

The Day 1 and Month 3 study assessments will be observational in nature, and can be performed remotely, per standard of care for patients with hepatic sarcoidosis. During the Day 1 telephone encounter, the study coordinator will review current medications with subjects. During the Month 3 visit, for all subjects, the PI and/or coordinator will: review prior and current medications, record your general health (including averse events and illnesses), conduct physical examination, including assessment of certain physical symptoms that are associated with liver disease, collect vital signs (if visit is conducted in clinic), height and weight, and collect blood samples for routine laboratory tests specific to liver function. If visiting the clinic at Month 3 is impractical for the subject for any reason, Month 3 assessments can be conducted remotely.

3.1.3 Study Intervention Phase

Study medication will be dispensed at Month 6 to initiate the interventional phase of the study. During study visits, for all subjects, the research team will: review prior and current medications, record your general health (including adverse events and illnesses), conduct physical examination, including assessment of certain physical symptoms that are associated with liver disease, collect vital signs, height and weight, perform a Fibroscan (ultrasound of abdomen to measure liver stiffness), perform MBT (Month 6 and Month 12), administer QoL questionnaires, collect blood samples for routine laboratory tests specific to liver function, initiation of study medication (Month 6), and assess medication compliance (Month 9 and Month 12). For WOCBP, urine pregnancy testing will be performed at Month 6 and every 4 weeks while on drug. Home pregnancy testing kits will be provided for this. WOCBP will be contacted by the study coordinator every 4 weeks while on drug for reporting results of urine pregnancy tests. Subjects will be instructed to notify Dr. Weinberg or the study coordinator if they become pregnant at any time during the study, and to discontinue study drug immediately upon suspecting pregnancy. Drug will be discontinued immediately for any subject who becomes pregnant during the study. Pregnancy will not be considered an AE, nor will an elective abortion to terminate a pregnancy without medical reasons. Pregnancy outcomes will not be followed for this study.

3.1.4 *Follow Up Phase (Optional)*

Subjects will have the option to remain on UDCA after study completion if it can be obtained through prescription outside of the trial. PI will continue to follow all of these patients in hepatology clinic after completion of the trial as clinically indicated. Data will be collected for an additional 12 months.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

To evaluate the efficacy of UDCA in improving liver function, the following laboratory parameters will be assessed:

1. Reduction in ALP and/or GGT from baseline

3.2.2 Secondary Study Endpoints

1. safety and tolerability of UDCA in patients with hepatic sarcoidosis (liver function tests will be monitored alongside reporting of adverse events)
2. efficacy of UDCA in the improvement of liver stiffness as a clinical parameter of liver function (Fibroscan stiffness readings (in kPa) will be monitored)
3. Changes in quality of life parameters prior to and following intervention with UDCA (PRO questionnaire scores will be assessed for improvements)
4. Changes in the ^{13}C-methacetin breath tests in all subjects prior to and following intervention with UDCA (exploratory endpoint)
5. Changes in ACE and sIL2R

4 Study Population and Duration of Participation

A minimum of ten adult patients with a prior diagnosis of sarcoidosis and lab/imaging findings suggestive of hepatic sarcoid will be enrolled for a twelve-month comprehensive observational and interventional period. Subjects will have the option to continue being followed for another year; thus the study will last approximately 24 months, cumulative of recruitment, enrollment, data collection, and analysis.

4.1 Eligibility Criteria

Study Eligibility Criteria

Inclusion	Exclusion
1. Male or female, at least 18 years of age, and able to provide written informed consent 2. Systemic sarcoidosis with evidence of liver involvement as denoted by any of the following: - Elevated liver-specific alkaline phosphatase - Granulomas on liver biopsy - Hepatomegaly on imaging - Portal Hypertension (via imaging or endoscopy) OR granulomas on liver biopsy (not attributable to infection) AND elevated liver-specific alkaline phosphatase 3. Stable dose of immunosuppressant ≥ 6 months (with the exception of changes in prednisone less than or equal to 20 mg or prednisone equivalent) 4. If cirrhotic, absence of hepatocellular carcinoma as indicated by imaging within 6 months of screening	1. Female who is pregnant, planning to become pregnant during the study, or breastfeeding 2. Clinically significant abnormalities, co-morbidities, or recent alcohol/drug abuse that make the subject an unsuitable candidate 3. hepatitis B, hepatitis C, alcohol-related liver disease, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis) 4. Currently on or prior intolerance to UDCA 5. Receipt of any investigational product within a time period equal to 10 half-lives of the product, or 6 weeks (whichever is longer), to study drug administration 6. Current evidence of hepatic decompensation (variceal bleeding, hepatic encephalopathy, or ascites). In the event potential participant is post-transplant, no evidence of hepatic decompensation since transplantation

4.2 Subject Recruitment

Potential subjects will be recruited from Penn Medicine clinics as well as remote clinics. The PI and study team will identify study candidates; referrals from physicians or the subjects themselves will be accepted and further assessed for eligibility by the PI during a screening visit which will take place in the Hepatology clinic at the Perelman Center for Advanced Medicine.

4.3 Duration of Study Participation

The expected duration of the subjects' participation is initially 12 months. Monitoring for an additional 12 months will be optional.

4.4 Total Number of Subjects and Sites

It is approximated that 15 subjects will need to be screened in order to produce 10 evaluable subjects.

4.5 Vulnerable Populations:

All subjects to be recruited in this trial will be referred to us by their physician. Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. No mentally disabled or economically disadvantaged persons will be enrolled. Only subjects able to provide informed consent autonomously will be eligible for enrollment. Penn students or employees will not be directly targeted or excluded. In the event that Penn students or employees present for screening, they will be informed that their decision regarding whether or not to participate will in no way impact their standing at the University.

5 Study Intervention (UDCA)

During the second 6 months of the study, all subjects will receive open-label UDCA 250mg or 500mg tablets, or 300mg capsules. This will be obtained through prescription and initiated at the Month 6 visit. Subjects will take this medication twice daily as instructed for 6 months, as described above. If the subject is taking a sequestrant, the UDCA would need to be taken 5 hours apart from it (because bile acid sequestrants, such as cholestyramine, can bind UDCA). Bile acid sequestrants and estrogen can lower

the therapeutic effect of UDCA, but these are not contraindications to taking UDCA. More information on the study medication, UDCA, can be found in section 1.2 as well as the package insert for Ursodiol.

5.1 Description

See section 1.2 and 1.3, as well as the package inserts for Ursodiol for more information.

5.2 Intervention Regimen

Dosing for study participants with mild liver disease:
After at least 3 months of treatment and if subject weighs more than 200 lbs., PI may decide to increase dose of study drug based on a review of lab results and ability to tolerate the study drug. Dose would be increased to two tablets (500mg) with breakfast and one tablet (250mg) with dinner. If subject is on the 300mg option, their dosage would be calculated accordingly using these models.

Dosing for study participants with moderate liver disease:
If during the screening period of the study, it is determined that subject has moderate liver disease, subject may receive corticosteroids (per standard of care). If subject is already taking corticosteroids, dose may be increased.

5.3 Receipt

At the Month 6 visit, a 3-month supply of drug will be prescribed by study investigator and obtained through insurance and filled at pharmacy of choice. Subjects will be prescribed another 3-month supply at Month 9 visit. Subjects will take this medication as instructed and return to the clinic at Month 9 and Month 12 for routine care visits, inclusive of dosing compliance assessment.

5.4 Storage

UDCA will be stored at 20C to 25C (68F to 77F) and dispensed in a tight container.

5.5 Preparation and Packaging

Each URSO 250® elliptical, biconvex, film-coated tablet, white, engraved with "URS785", contains 250 mg of UDCA. Available in bottles of 100 tablets (NDC 58914-785-10) and 500 tablets (NDC 58914-785-50). Each URSO Forte® elliptical, biconvex, scored, film-coated tablet, white, engraved with "URS790", contains 500 mg of ursodiol. Available in bottles of 100 tablets (NDC 58914-790-10) and 500 tablets (NDC 58914-790-50).
Actigall Capsules are opaque white and pink capsules imprinted “ACTIGALL” on one half and “300 mg” on the other half of the capsule in black. Bottles of 100 are supplied with child-resistant closures. (NDC 0023-6145-01)

5.6 Administration, Accountability, and Subject Dosing Compliance Monitoring

The investigator or his/her designated and qualified representatives will prescribe study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. At the start of the study, each subject should receive counseling regarding the importance of dosing compliance. At visits following the initiation of dosing, study site personnel will assess subject compliance by asking subjects if any doses were missed. Treatment compliance will be based on the subjects’ responses, as recorded in source.

6 Study Procedures

Schedule of study assessments

Activity	Screening (CV)	Month 0 (PC)	Month 3 (CV/PC)	Month 6 (CV)	Month 9 (CV/PC)	Month 12 (CV)	Month 18 follow-up (CV)	Month 24 follow-up (CV)
Informed consent	X*					X*		

Demographics & medical history (including assessment of liver disease)	X							
Urine pregnancy test for WOCBP	X*			X*	X*	X*		
Physical exam & vital signs	X		X	X	X	X	X	X
Fibroscan	X			X*		X	X*	X
^{13}C-methacetin breath test (optional sub-study)***				X*		X*		
QoL questionnaire	X*			X*		X*	X*	X*
Concomitant medication assessment	X	X*	X	X	X	X	X	X
Adverse event assessment		X*	X*	X*	X*	X*	X*	X*
Drug initiation				X*				
Weight-based daily dosage calculation *(if in-person visit)*					X	X	X	X
Drug accountability & adherence assessment					X*	X*	X*	X*
Blood draw: clinical laboratory assessments:** -LFP -CBC -GGT	X		X	X	X	X	X	X
Blood draw: research lab assessments: -ACE -sIL2R -optional research samples	X*			X*		X*	X*	X*

**Research specific activity*
***Subjects can have labs drawn at the laboratory of their choice*
CV = clinic visit; PC = phone call; QoL = Quality of Life
LFP = liver function panel; CBC = complete blood count; GGT = gamma-glutamyl transferase
**** **NOTE: All subjects enrolled under Amendment 10 (JUN 2021) or later will NOT be included in the optional MBT sub-study.***

6.1 Screening

The following procedures are completed during the screening visit:

- Informed Consent
- Record medical history, which includes questions about social history, smoking, alcohol use, and disease history
- Record prior and current medications
- Record general health (including averse events and illnesses)
- A physical examination, including assessment of certain physical symptoms that are associated with liver disease
- Quality of Life questionnaire
- Vital signs, which include blood pressure, heart rate, breathing rate, body temperature, will be measured. height and weight may also be recorded
- A Fibroscan (ultrasound scan of abdomen to measure the stiffness of liver). *Fibroscan results available within a month of screening may be used in place of a repeat at screening*

- Blood samples will be collected for routine & research laboratory tests (about 3 tablespoons, 30 mL) and to test for liver function
- Urine pregnancy test for women of child-bearing potential

6.2 Study Observational Phase

Assessmentsduring the observational phase will include the following procedures:

- Review prior and current medications
- Record general health (including adverse events and illnesses)
- A physical examination, including assessment of certain physical symptoms that are associated with liver disease*
- Vital signs, which include blood pressure, heart rate, breathing rate, body temperature, will be measured. height and weight may also be recorded*
- Blood samples will be collected for routine laboratory tests (about 2 tablespoons, 20 mL) and to test for liver function

  *if in-person clinic visit is conducted

6.3 Study Intervention Phase

Clinic visits during the interventional phase will include the following procedures:

- Review prior and current medications
- Record general health (including adverse events and illnesses)
- A physical examination, including assessment of certain physical symptoms that are associated with liver disease
- Quality of Life questionnaire
- Vital signs, which include blood pressure, heart rate, breathing rate, body temperature, will be measured. height and weight may also be recorded
- A Fibroscan (ultrasound scan of abdomen to measure the stiffness of liver)
- Blood samples will be collected for routine & research laboratory tests (about 3 tablespoons, 30 mL) and to test for liver function
- MBT performed (month 6 and month 12) if subject has consented to optional sub-study
- Study drug instruction (month 6)
- Study drug compliance assessment
- Weight-based daily dosage calculation
- Urine pregnancy test for women of child-bearing potential

6.4 End of Study/Early Termination Visit

If subjects complete the interventional phase of the study, or decide to end participation, an End of Study visit will include the following:.

- Review prior and current medications
- Record general health (including adverse events and illnesses)
- A physical examination, including assessment of certain physical symptoms that are associated with liver disease
- Quality of Life questionnaire
- Vital signs, which include blood pressure, heart rate, breathing rate, body temperature, will be measured. height and weight may also be recorded
- A Fibroscan (ultrasound scan of abdomen to measure the stiffness of liver)
- MBT performed if subject has consented to optional sub-study
- Blood samples will be collected for routine laboratory tests (about 2 tablespoons, 20 mL) and to test for liver function

- Study drug compliance assessment

6.5 Follow Up Phase (Optional)

Subjects will have the option to remain on UDCA after study completion if it can be obtained through prescription outside of the trial. Subjects will be seen at 2 additional clinic visits which will consist of the following:

- Review prior and current medications
- Record general health (including adverse events and illnesses)
- A physical examination, including assessment of certain physical symptoms that are associated with liver disease
- Quality of Life questionnaire
- Vital signs, which include blood pressure, heart rate, breathing rate, body temperature, will be measured. height and weight may also be recorded
- A Fibroscan (ultrasound scan of abdomen to measure the stiffness of liver)
- Blood samples will be collected for routine laboratory tests (about 2 tablespoons, 20 mL) and to test for liver function
- Study drug compliance assessment (when applicable)
- Weight-based daily dosage calculation

6.6 Unscheduled Visits

Unscheduled/safety visits may be conducted at any time and may repeat assessments. This is not common but may be necessary to ensure subjects overall health and safety. Similarly, in case of any important findings from study laboratory tests, physical exams or any side effects that may be related to the study drug, PI may follow up for as long as necessary/until the condition or side effect stabilizes, resolves, or is no longer of concern. Follow-up may include any additional assessments needed to understand the nature or cause of the event and may include collection of additional blood samples, other assessments, or consultation with other healthcare professionals.

6.7 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the PI for lack of adherence to intervention or study procedures or visit schedules, AEs, or upon the development of varices, ascites or encephalopathy, doubling of serum bilirubin, marked worsening of fatigue or pruritus, inability to tolerate the drug, or voluntary withdrawal. . The PI may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will be asked to have one final visit to collect investigational product and to follow up regarding adverse events.

Requirements for stopping the study:

The study will be stopped if there is a pattern seen of adverse events related to the MBT test among the subjects. Since this is a small pilot study if serious adverse events related to the MBT test are seen in one subject the study will be stopped.

Stopping Criteria for Administration of MBT Test:

- Prior occurrence of any adverse events related to 13C-Methacetin solution and device
- Change in subject's health which makes continued participation unsafe. PI will see subject prior to administration of test.
- Subject has not followed the pre-requisites for taking the MBT test (e.g., requirements for fasting, caffeine consumption, general anesthesia, use of excluded medications).

Early Termination of the Breath Test:

Key personnel will be trained how to terminate the breath test early if a subject is unable to complete the full 75 minutes of breath collection. In the following situations, the breath test collection will be terminated:

- The subject vomits.
- The subject has to be disconnected from the nasal cannula/ collection device for more than 1 minute due to an urgent procedure.
- The subject is inadvertently disconnected from the BreathID® MCS device.
- The BreathID® MCS device malfunctions.

Should an interruption in breath collection due to removal of the cannula or its disconnection occur during the administration of the MBT and the device cannot compute the delta over baseline results, the test may be repeated at a different date (minimum time allowed before repeating is 24 hours) provided the subject still qualifies and is willing to repeat testing. If the interruption occurred at the beginning of the Breath Test (during baseline breath collection) and before ingestion of the 13C-Methacetin solution, the test can be repeated immediately.

6.7.1 Data Collection and Follow-up for Withdrawn Subjects

If subjects withdraw from the study, the information that was collected before withdrawal will still be used. No new information will be collected without subject permission except to follow up on safety events that might have happened during the study.

6.8 Clinical Laboratory Tests

Category	*Tests*
Hematology	*RBC, hemoglobin, hematocrit, platelet count, WBC with differential*
Liver associated tests (Hepatic function panel)	*SGOT/AST, SGPT/ALT, total Bilirubin, GGT, ALP, Albumin*

6.9 Optional Research Blood Sample Collection

Subjects who provide informed consent for the collection and use of their blood samples for future research will have samples collected every 6 months during the course of their study participation. All samples will be de-identified prior to being stored. Subjects who do not consent to this optional collection will still be able to participate in the rest of the study.

6.10 Efficacy Evaluations

Standard of care laboratory tests for liver function*: See 3.2.1, 6.7*

FibroScan® as a standard of care measure for liver stiffness *(3.2.2):*
Transient elastography is a non-invasive, reproducible method for measuring liver stiffness that correlates with liver fibrosis and will be measured using FibroScan® (manufacturer Echosens). An ultrasound transducer probe is mounted on the axis of a vibrator; vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing a wave that propagates through the underlying tissue. The propagation velocity of the wave is then measured. The velocity is directly related to tissue stiffness; the stiffer the tissue, the faster the wave propagates

Methacetin Breath Test for liver metabolic capacity *(3.2.2, optional, exploratory):*
The ^{13}C-methacetin breath test (MBT) is a noninvasive tool to assess liver microsomal capacity to metabolize the nonradioactive ^{13}C-labeled Methacetin. The Breath Test System consists of the BreathID® Molecular Correlation Spectrometry (MCSTM) device and a test kit containing a

breath collection nasal cannula and a nonradioactive isotope 13C-methacetin solution. The BreathID MCS device measures and computes the $^{13}CO_2/^{12}CO_2$ ratio in the subject's exhaled breath in real time. Additional details for the procedure are provided in Appendix 5 (16.5).

Subjects will be asked to sit in a chair with a nasal cannula (a small tube) attached to the BreathID MCS device placed inside their nostrils while breathing normally. The BreathID MCS device will measure the subject's baseline carbon dioxide production for approximately 10 minutes (up to 25 minutes), after which the subject will be administered 1 cup of a solution of a 75 mg Methacetin pre-dissolved in water. Methacetin is exclusively broken up in the liver and turns into carbon dioxide and acetaminophen. The subject will remain sitting in a chair with the nasal cannula in their nose breathing in a normal fashion for another 60 minutes while the BreathID MCS device measures carbon dioxide production. The MBT will be performed at screening, Month 6, and Month 12 for this protocol.

6.11 Safety Evaluations

Laboratory tests for liver function and adverse event reporting: See 3.2.2.

7 Statistical Plan

7.1 Primary Endpoint

The primary end-point is a reduction in ALP and/or GGT from baseline.

7.2 Secondary Endpoints

To assess the safety and tolerability of UDCA in patients with hepatic sarcoidosis, liver function tests will be monitored alongside reporting of adverse events.
To assess efficacy of UDCA in the improvement of liver stiffness as a clinical parameter of liver function, Fibroscan stiffness readings (in kPa) will be monitored.
To assess quality of life parameters prior to and following intervention with UDCA, PRO questionnaire scores will be assessed for improvements.
To assess changes in metabolic capacity of the liver, 13C-methacetin breath tests will be analyzed and resulted in all subjects prior to and following intervention with UDCA (exploratory endpoint).

7.3 Sample Size and Power Determination

This is a descriptive, pilot study of UDCA in subjects with hepatic sarcoid. We aim to enroll at least ten subjects over two years. We will use the effect size obtained from this pilot study to launch a multi-centered study that can be adequately powered.

7.4 Statistical Methods

The primary end-point is a reduction in ALP and/or GGT from baseline. We plan to use the effect size obtained from this pilot study to launch a multi-centered study that can be adequately powered to predict a specified percentage reduction in clinical and laboratory parameters with statistical significance.

7.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

7.4.2 Efficacy Analysis

See 7.1.

7.4.3 Safety Analysis

See 7.2.

7.5 Subject Population(s) for Analysis

All-treated population: Any subjects enrolled into the study that received at least one dose of investigational product.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:
Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.
Adverse events will be collected at each study visit. The start and stop date(s) of the event(s) (if known), and relationship to study drug (UDCA), to methacetin or, MBT procedure will also be collected.

Anticipated AEs related to the study drug are listed in the package insert for UDCA/ursodiol.
There are no anticipated AEs with methacetin.

8.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

All subjects taking part in the optional MBT substudy will be monitored for AEs for 24 hours following MBT administration. This assessment will be conducted remotely; subjects will be contacted by phone one day following MBT administration.

8.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized by the PI (as definitely related, probably related, possibly related, unlikely or unrelated).

8.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

In accordance with Abbreviated IDE requirements outlined in 812.150(b)(1)-(3) & (5)-(10) & 812.150(a)(1), (2), (5), & (7), any unanticipated adverse device effects will be reported to IRB and FDA (21 CFR 812.3s).

8.4.1 Follow-up report

If SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.4.2 Investigator Reporting: Notifying the Penn IRB

It is the responsibility of the PI to oversee the notification of adverse events to the IRB.

8.4.3 Investigator reporting: Notifying the FDA

It is the responsibility of the PI to report all unanticipated, related and serious adverse events to the FDA.

8.5 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

8.5.1 Data and Safety Monitoring Plan

The PI is responsible for ensuring protocol adherence, regulatory oversight and reporting, data collection, and protection of research subjects. The PI is also responsible for evaluating factors external to the study, including scientific or therapeutic developments in the disease or investigational agent/procedure that may

influence study subject safety; the PI will allocate adequate time for such monitoring activities. Some PI responsibilities may be delegated to study team members, but ultimately the PI is accountable for all study activities. Yearly progress reports will be submitted to the IRB.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Data Collection and Management

All patient and study documents will be kept confidential. The research team will be responsible for the confidentiality of the data associated with subjects enrolled into this study in the same manner they are responsible for the confidentiality of any patient information within their spheres of responsibility. All forms and submitted records used for abstraction of the study data will be de-identified to maintain subject confidentiality. All study staff will identify patients by the patient identifier number generated at the first visit. The investigator and institution will permit study-related monitoring, audits, IEC/IRB review and regulatory inspection, providing direct access to source data documents. Participants grant permission to share research data with these entities in the consent document. Federal regulations govern the protection of patients' rights relative to data confidentiality and use of research data. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with the University of Pennsylvania IRB and federal requirements for compliance with HIPAA.

- REDCap will be used to enter source data as eCRFs
- PI and coordinator will have access to PHI
- Data will be stored indefinitely
- All safeguards will be used to ensure privacy. Subjects will only be seen by the investigators and coordinators in a private, research designated clinic room in the GI clinic and will not be identified to anyone in the clinic practice as anything other than a patient.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

See 8.5.1

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the University of Pennsylvania Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

11.1 Risks

Study drug: UDCA

There are risks, discomforts, and inconveniences associated with any study. All of the risks associated with taking the study drug may not currently be known. See package insert for comprehensive information on UDCA, inclusive of the adverse reactions observed in placebo-controlled clinical trials for PBC, as well as the side effects reported during postapproval use of UDCA. Subjects may have side effects from taking UDCA in this study and will be checked at each study visit for side effects. The side effects reported by patients receiving UDCA in clinical trials may have occurred due to other reasons; because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The side effects reported after the FDA approval of UDCA were reported voluntarily from a population of uncertain size; it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Additionally, in a randomized, cross-over study in sixty PBC patients, seven patients (11.6%) reported nine adverse reactions: abdominal pain and asthenia (1 patient), nausea (3 patients), dyspepsia (2 patients) and anorexia and esophagitis (1 patient each). One patient on the twice a day regimen (total dose 1000 mg) withdrew due to nausea. All of these nine adverse reactions except esophagitis were observed with the twice a day regimen at a total daily dose of 1000 mg or greater. However, an adverse reaction may occur at any dose.

Venipuncture:

When blood samples are taken from a vein, there may be some minor pain and risk of bruising at the needle site. Sometimes a person may become dizzy or faint when blood is drawn and there is a rare possibility of infection.

Data confidentiality:

All safeguards will be used to ensure privacy. Subjects will only be seen by the investigators and the research team in a private research designated clinic room in the GI clinic and will not be identified to anyone in the clinic practice as anything other than a patient. All patient and study documents are kept confidential. The research team of Drs. Reddy and Weinberg will be responsible for the confidentiality of the data associated with subjects enrolled into this study in the same manner they are responsible for the confidentiality of any patient information within their spheres of responsibility. All forms and submitted records used for abstraction of the study data will be identified by coded identifiers to maintain subject confidentiality. All study staff will identify patients by the patient identifier number generated at the study site. The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review and regulatory inspection(s), providing direct access to source data documents. Participants grant permission to share research data with these entities in the consent document. Federal regulations govern the protection of patients' rights relative to data confidentiality and use of research data. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with the University of Pennsylvania IRB and federal requirements for compliance with HIPAA.

11.2 Benefits

The information that is obtained during this study may be useful scientifically and thus be helpful to others with the same condition in the future. The subject may or may not benefit from being in this study but their participation in this research study may benefit future patients with the same disease or condition. Subjects' condition may get better, it may get worse, or it may stay the same.

11.3 Risk Benefit Assessment

Risks associated with UDCA, including the risks of AEs and hepatic laboratory abnormalities classify this study as greater than minimal risk, but appear limited and manageable based on its administration in patients with PBC. Given the potential for improving liver enzymes and function, the risk-benefit balance is favorable. Incorporation of the MBT to this protocol does not introduce significant risk, as determined by the sponsor-investigator and confirmed by the IRB.

11.4 Informed Consent Process / HIPAA Authorization

The study physician will explain the study to the subject, and answer all questions regarding the study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the study physician, and any other signatories necessary. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's study chart. An entry will also be made in the subject's chart to document the informed consent process. Sample informed consent form is attached to initial submission.

12 Study Finances

12.1 Funding Source

The study is supported by the Autoimmune Liver Diseases Pilot Research grant awarded to Ethan Weinberg by the American Association for the Study of Liver Diseases (AASLD).

Exalenz Bioscience will provide device and device-associated materials required for conducting the MBT.

12.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

12.3 Subject Stipends or Payments

Subjects will be reimbursed up to $50 per completed visit for expenses incurred from study required clinic visits. Additionally, subjects will not be charged for optional breath test. Subjects will be responsible for the cost (e.g. any deductible, co-insurance, or co-payments) of standard of care medical services including fibroscan and all laboratory tests being assessed, The cost of the study medication will also be billed to subject/insurance in the usual manner when UDCA is prescribed for cholestatic conditions and subjects will be responsible for paying any deductible, co-insurance, or co-payments. In the unanticipated event that insurance does not cover UDCA and/or laboratory evaluations, sponsor-investigator may consider allotting study funds for these.

13 Publication Plan

We will make our results available to the community of scientists interested in the treatment of hepatic sarcoidosis. In addition, we welcome collaboration with other scientists who could make use of the results and make recommendations that will advance the study aims and understanding of hepatic sarcoidosis. Our plan includes, but is not limited to, activities such as presentations at national scientific meetings, lectureships, development of web-based tools and resources, and educational presentations for health care providers interested in the treatment of hepatic sarcoidosis.

14 References

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15 Attachments

- Informed Consent Form and HIPAA Authorization – v. 20-JUN-2018
- Package Insert – UDCA (URSO 250/500)
- Package Insert – Allergan Actigall (URSODIOL, USP capsules)
- Quality of Life questionnaires:
- - PROMIS Fatigue 7b
- - PROMIS Fatigue 13a
- - PROMIS Physical Function 10b
- - PROMIS Pool v1.0 Dyspnea
- Prospective Reimbursement Analysis – UDCA
- IND Exemption/IDE determination letter – 6-FEB-2018
- Appendix 16.5: Measurement of Liver Metabolic Function with the Methacetin Breath Test
- BreathID® MCS Device Investigator's Brochure – 17-OCT-2017

16 Appendix

16.1 Reference for Safety Reporting Section- Common Definitions for Developing and Adverse Event Tracking and Serious Adverse Event Reporting Protocol

16.2 Expedited FDA Reporting Requirements

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/ IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is all:
  – *associated with the use of the study drug, and*
  – *unexpected, and*
  – *fatal or life-threatening,*
- ***Within 15 calendar days***
  Any study event that is:
  – *associated with the use of the study drug, and*
  – *unexpected, and*
  – *serious, but not fatal or life-threatening*
  -or-
  – *a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).*

Additional reporting requirements
Sponsors are also required to identify in IND/IDE safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Applicable events can be reported to the FDA using Form FDA3500A or in narrative format. The report must be sent to the correct division. Specific information that must be included in the reports can be found in 21 CFR 312.32 or in 21 CFR 812.150.

16.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

16.4 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

16.5. Measurement of Liver Metabolic Function with the MBT (optional sub-study)