UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN
Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.
Version date: 05/11/2011

1. PROJECT TITLE

Aramchol for HIV-associated nonalcoholic fatty liver disease and lipodystrophy

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

UCSD Medical Center-Hillcrest
Clinical and Translational Research Institute-La Jolla

4. ESTIMATED DURATION OF THE STUDY

The study is anticipated to start by March 1, 2015 and end January 1, 2018 for duration of 3 years. The recruitment phase will begin as soon as IRB approval is received.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), the progressive form of liver disease that can lead to cirrhosis and liver-related mortality in persons who drink little or no alcohol. NAFLD is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. NASH is benign in many affected individuals but can cause progressive liver injury and, indeed, may be the major cause of cryptogenic cirrhosis[1]. A subset of patients with NAFLD that have not been extensively studied are those infected with human immunodeficiency virus (HIV). Among patients with HIV infection, liver disease is one of the leading causes of death.16 Progression of liver disease in HIV is linked to metabolic derangements associated with hepatic steatosis. Till date there are no therapies for the treatment of HIV-associated NAFLD and this area remains understudied with paucity of clinical trials. Currently, there is no FDA approved treatment for HIV-associated NAFLD. Weight loss and exercise are the recommended but often difficult maintain these lifestyle changes in the long term and therefore therapeutic agents have been investigated. In this study, we propose to treat 50 patients with HIV-associated NAFLD with either aramchol or placebo for 12 weeks. After an initial evaluation, MRI liver fat distribution and full body DEXA scan, patients will receive 600 mg of Aramchol (a 200 mg/tablet and a 400 mg tablet) per day or placebo. Patients will be monitored at regular intervals for symptoms of liver disease, side effects of aramchol, and serum biochemical and metabolic indices. Patients will also be assessed for continued HIV viral load suppression and continued tolerance of antiretroviral therapy. At the end of 12weeks, patients will have a repeat medical evaluation, liver MRI and full body DEXA scan. Pre and post treatment MRI-derived liver fat content and DEXA-full body fat measurement will be compared. The primary end point of successful therapy will be improvement in hepatic steatosis measured by MRI in patients with HIV-associated NAFLD. Secondary end points will be improvement in total body fat content assessed by DEXA in patients with HIV-associated NAFLD.

6. SPECIFIC AIMS

Primary objectives:
1. To examine the efficacy of Aramchol , comparing 600 mg daily (including 200 mg tablet and 400 mg tablet) versus identical placebo in improving hepatic steatosis assessed by magnetic resonance imaging in patients with HIV-associated NAFLD

Secondary objectives:
1. To examine the efficacy of aramchol , comparing 600 mg daily (including 200 mg tablet and 400 mg tablet) versus identical placebo in improving total body fat content assessed by DEXA in patients with HIV-associated NAFLD
2. To examine the efficacy of Aramchol , comparing 600 mg daily (including 200 mg tablet and 400 mg tablet) versus identical placebo in improving serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients with HIV-associated NAFLD

Exploratory objectives:
1. To examine the efficacy of aramchol in improving imaging-based biomarkers associated with changes in NAFLD

7. BACKGROUND AND SIGNIFICANCE

Nonalcoholic fatty liver disease is the most common cause of chronic liver disease in the United States and it affects almost 30% of adults in Western countries.[1-3] With climbing obesity rates and more sedentary patient populations, the prevalence of NAFLD is increasing worldwide and is becoming the predominant cause of chronic liver disease in parts of the world.[4] NAFLD represents a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), the progressive form of fatty liver disease that can lead to cirrhosis and liver-related mortality in persons who drink little or no alcohol. NASH represents the more severe end of this spectrum and is characterized by steatosis, ballooning degeneration and lobular inflammation with or without fibrosis.[5] Long-term risks of NASH include cirrhosis, hepatocellular carcinoma and end stage liver disease requiring liver transplantation.[6, 7]

The majority of patients with NAFLD are asymptomatic. Clinical history, laboratory and radiological investigations are useful in excluding other causes of liver disease but do not permit an accurate diagnosis of NAFLD.[8] The diagnosis is usually suspected in a patient with elevated serum alanine aminotransferase (ALT) who drinks no or minimal amounts of alcohol, who has evidence of increased fat in the liver by ultrasound, CT scan or MRI, and who tests negative for the common causes of chronic liver disease. Liver biopsy is the gold standard for the accurate diagnosis of NAFLD, but inherent risks of biopsy such as pain, bleeding, and bacteremia make interval biopsies impractical in the management of this disease.

Recently, innovative imaging tools have demonstrated potential to change how we study and monitor liver disease.[9, 10] An advanced magnetic resonance imaging based biomarker, the proton-density fat fraction (MRI-PDFF), has been validated as a precise and accurate method of quantifying liver fat in NAFLD.[11-15] This provides a unique opportunity to research the progression and treatment of NAFLD without invasive procedures.

A subset of patients with NAFLD that have not been extensively studied are those infected with human immunodeficiency virus (HIV). Among patients with HIV infection, liver disease is one of the leading causes of death.[16] Progression of liver disease in HIV is linked to metabolic derangements associated with hepatic steatosis. Till date there are no therapies for the treatment of HIV-associated NAFLD and this area remains understudied with paucity of clinical trials.

Medical Therapy for NAFLD in HIV patients:

Currently, there is no FDA approved treatment for NAFLD or NASH. Additionally, there have been no significant clinical trials for HIV patients with NAFLD and there are no approved treatment options. Current treatments for NAFLD are limited to weight loss and exercise, but this is often difficult to adhere to for many patients. Therapeutic agents are being investigated but the trials thus far including ursodeoxycholic acid, metformin, clofibrate, betaine, N-acetylcystine, atorvastatin, and orlistat have demonstrated very limited benefit. Pioglitazone has been shown to be somewhat beneficial reducing liver fat but weight gain due to increased adiposity is harmful in the long run. Additionally, none of these trials were for HIV-infected patients. Further therapies for NAFLD and NASH are still under investigation.

Aramchol:

Aramchol, also known as arachidyl amido cholanoic acid, is a fatty acid bile acid conjugate (FABAC) that was created by conjugating 2 natural components, cholic acid and arachidic acid, through a stable amide bond. Aramchol inhibits stearoyl coenzyme A desaturase 1 (SCD1), a key enzyme in fatty acid synthesis. SCD1 is an endoplasmic reticulum enzyme that catalyzes the rate-limiting step in the biosynthesis of monounsaturated fatty acids from saturated fatty acids. Inhibiting SCD1 decreases synthesis and increases beta-oxidation of fatty acids, causing decreased storage of fatty acids. SCD1 has been demonstrated to be tightly associated with control of lipid homeostasis and body weight regulation. Within in vitro models, Aramchol has demonstrated significant (70% to 83%) inhibition of the SCD1 activity.[17] Additionally, Aramchol increases cholesterol efflux by stimulating the adenosine triphosphate-binding cassette transporter A1. This has demonstrated an anti-atherogenic effect in animal models with increased fecal sterol output and decreased plasma cholesterol levels in mice.[18]

Aramchol and the liver:

The three proposed mechanisms of Aramchol's effects on liver fat are 1) reducing de novo fatty acid synthesis, 2) reducing SCD1 activity, and 3) increasing beta-oxidation of fatty acids.[19] In a 2003 study by Gilat,[20] Aramchol significantly reduced hepatic fat content in animals (rats, hamsters, and mice) with a high-fat diet model. These animals gained total weight although they had less fat deposition in their liver, measured histologically, which suggests a redistribution of fat deposition in the body. The authors hypothesized that redistribution of liver fat to adipose tissue was the most likely explanation, but the mechanism was unknown.

However, additional animal studies demonstrated that FABACs have specific metabolic effects as they increase cholesterol efflux from fibroblasts and may not affect the import of dietary fat.[21] In addition, preliminary data indicate that aramchol may increase fatty acid catabolism in the liver by acting as a peroxisome proliferator-activated receptor agonist.[22, 23] These studies have proposed possible mechanisms of FABACs but further study of fatty acid and triglyceride synthesis vs. degradation in the liver are needed to identify the in vivo mechanisms of aramchol.

Effect of Aramchol on NAFLD and total body fat:
A recent study by Safadi[24] demonstrated that aramchol significantly reduced liver fat content, measured by magnetic resonance sprectroscopy (MRS), in 60 Israeli NAFLD patients after 12 weeks of 300mg aramchol per day. Their trial gave patients either 100mg or 300mg of aramchol or placebo (3 groups; n = 20/group) once daily for 12 weeks. Their primary finding was that liver fat content decreased by 12.57% (+/- 22.14% standard deviation) in the high dose aramchol group. There were no serious or drug-related adverse events in the study and the authors proposed that aramchol might be used for the treatment of fatty liver disease. In the preceding Phase I study of aramchol, dosing up to 900mg was studied and found to have a good safety profile. An international, multicenter trial is currently being conducted using a two doses of Aramchol , a 200 mg/tablet and a 400 mg tablet per day given the excellent safety profile and expectation of increased liver fat reduction at higher doses. Aramchol has not yet been studied in HIV-associated NAFLD.

Side effects of Aramchol:
Patient trials with Aramchol are limited to the Safadi study,[24] but the clinical trial demonstrated no significant adverse events in the 12-week treatment period for 58 patients that underwent the trial. The few adverse events were mild (abdominal pain, back pain, constipation) and did not cause anyone to drop out of the trial. There were no severe adverse effects. Aramchol does not induce or inhibit the CYP450 enzyme family and is not expected to have significant drug interaction. The previous studies on Aramchol were done in animal models.

Aims and Significance:
We plan to investigate the role of aramchol in patients with HIV-associated NAFLD residing in the United States and assess liver fat changes during therapy with MRI of the liver. Here we hypothesize that aramchol would lead to a greater improvement in liver fat content compared with placebo and may lead to greater improvement in total body fat content assessed by DEXA scan as compared to placebo. In this pilot study, we propose to randomize approximately 50 patients (1:1 ratio) to 600 mg of Aramchol (a 200 mg/tablet and a 400 mg tablet) per day or placebo over 12-weeks in order to evaluate changes in baseline laboratory data, total body fat content assessed by DEXA, and liver fat by MRI during therapy.

8. PROGRESS REPORT

Not applicable.

9. RESEARCH DESIGN AND METHODS

We plan to conduct a randomized, double-blind, placebo-controlled clinical trial to examine the efficacy of aramchol 600 mg daily (including 200 mg tablet and 400 mg tablet) versus identical placebo given over 12 weeks to improve HIV-associated hepatic steatosis as measured by a validated and accurate magnetic resonance imaging (MRI)-based technique. Galmed will not receive any subject or study data.

Initial Evaluation
Patients will be initially screened in the UCSD NAFLD research center clinic with history, physical examination, review of outside medical records (including HIV status) and routine blood tests. Alcohol history will be assessed in the medical interview, and the lifetime alcohol consumption will be estimated by standardized questionnaires. All patients will be asked to stop any medications being used for their liver disease, including herbal medications and vitamins. Only those meeting all inclusion criteria and avoiding all exclusion criteria will be invited to participate in the study. After the initial visit, those who meet all eligibility criteria and have no exclusion criteria will undergo more thorough evaluation with liver MRI, cardiac MRI, Ultrasound transient elastography with CAP and DEXA scan for total body fat. Patients with MRI-PDFF > 5% will be invited to participate in the study. Total screening time will be approximately 3 hours (2 hours screen visit, 10 minutes ARFI, 6-10 minutes DEXA scan, 30 minutes MR scan, 5 minutes Ultrasound transient elastography with CAP), 20 minutes Cardiac MRI scan.

Following an information session during which the primary consent document, a genetic sampling consent document and the UCSD HIPAA forms are reviewed, discussed and signed the following tests and procedures will be done shortly before starting therapy at the UCSD Medical Center, Hillcrest. If they have already been completed elsewhere as part of the patient's original diagnostic evaluation at the referring clinic they do not need to be repeated.

The following evaluation will be done shortly before starting therapy.

1. History and physical examination.

2. Blood tests. These include complete blood count (CBC with differential and platelet count), prothrombin time, INR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct and total serum bilirubin, alkaline phosphatase, albumin, total protein, fasting plasma glucose, hemoglobin A1c, C-reactive protein (CRP), creatinine phosphokinase (CPK), lactic acid, sodium, chloride, potassium, bicarbonate, blood urea nitrogen, creatinine, uric acid, calcium, phosphorus, ferritin, antinuclear antibody, antimitochondrial, antibodies if indicated, thyroid stimulating hormone (TSH), HBsAg, anti HBs, anti HAV, anti HCV, ceruloplasmin, alpha-1-antitrypsin if indicated, hemochromatosis gene test (HFE test) if indicated, alfa feto protein, fasting insulin, , Elisa HIV test if indicated, CD4 T-count, HIV PCR, CK-18 level. 1. A pregnancy test will be performed for women of childbearing age who are not using oral, barrier or surgical methods of contraception. Women who have had hysterectomies are also excluded from pregnancy testing. If the pregnancy test is positive they will not be enrolled in the study. The participants will be required to provide urine and stool samples as well.

3. Routine urinalysis.

4. Detailed metabolic characterization

   a. Oral glucose tolerance test (OGTT): after an overnight fast, subjects will be given 75 grams oral glucose solution. Plasma glucose, insulin levels, and free fatty acids will be obtained from blood samples drawn at 0 and 120 minutes after the oral glucose load 26.

   b.Lipid profiles. Levels of fasting triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol, free fatty acid will be obtained after an overnight fast.

5. Estimation of body fat and fat distribution

   a.Body Mass Index (BMI): For each patient, weight (kg) and height (m) will be recorded with empty bowel and bladder. BMI is calculated by the formula: BMI = weight (kg)/ height (m)2.

   b. A trained investigator will measure waist/hip ratio at the same time as other measures are taken.

   c. DEXA scan for whole body fat

   d. Magnetic resonance imaging (MRI) of the liver: MRI is done to evaluate liver size and estimate liver fat content.

   e. MR Elastography (MRE) of the liver: MRE will be done to evaluate changes in liver stiffness before and after therapy if additional funding is available.

   f. Cardiac MRI scan: will be done to assess improvement in cardiovascular risk by lowering of pericardial fat with aramchol relative to placebo.

   j. Ultrasound transient elastography with CAP of the liver: Ultrasound transient elastography with CAP is a noninvasive test used to asses liver stiffness.

6. ARFI ultrasound measurements are made automatically by the ARFI software that is loaded on the Siemens S2000 ultrasound machine by Siemens. An ARFI ultrasound imaging examination of the abdomen will be performed. ARFI ultrasound imaging examinations will be performed without contrast agents by well-trained staff and lasts about 10 minutes long. ARFI measurements are made automatically by the ARFI software that is loaded on the Siemens S2000 ultrasound machine we will use.

Treatment Phase:

After the initial evaluation, patients who continue to fulfill all inclusion criteria will be randomized to receive 600 mg daily of Aramchol (including 200 mg tablet and 400 mg tablet) versus identical placebo orally for a total of 12 weeks. Medication diaries and a count of residual tablets will monitor patient compliance at scheduled visits. Patients will be interviewed and examined by an investigator and have blood draw at weeks 0, 4, 8, and 12 of treatment. In addition, an ARFI ultrasound imaging examination of the abdomen will be performed. At each visit particular attention will be paid to symptoms associated with the possible side effects of Aramchol and patients will complete a standardized symptom scale.

Labs to be checked during the treatment phase include:

1. Urinalysis will be done with extended blood tests.

2. Routine blood tests (Fasting specimens): CD4 counts, HIV PCR, Complete metabolic panel (CMP) and prothrombin/INR. In addition, research blood will be taken for cytokine levels and changes in lipid biomarkers.

3. Extended blood tests (Fasting specimens): Insulin, plasma glucose, lipid profile (cholesterol, triglyceride, LDL and HDL), free fatty acids (FFA), and creatinephosphokinase (CPK), lactic acid, and glycosylated hemoglobin (HbA1c). In addition, research blood will be taken for cytokine levels and changes in lipid biomarkers.
4. Stool and urine sample will be collected for analysis of changes related to the study drug.
5. If the subject consents to genetic blood sampling the specimen will be drawn at this time.

Post-Treatment Phase:
At the end of the study, patients will undergo the same evaluation as listed under the initial evaluation as above, following which treatment will be stopped. Repeat MRI of the liver, ultrasound transient elastography with CAP of the liver and full body DEXA scan will also be performed at study conclusion. It is not possible to predict the outcome of this study, but if aramchol appears to have a significant effect on liver fat by MRI and/or total body fat by, we will probably develop a follow-up protocol to assess long-term therapy with aramchol in a large multicenter study to examine the efficacy in improving liver histology. Total post treatment visit time will be approximately 3hours (30 minutes MR scan, 20 minutes cardiac MRI scan, 5 minutes ultrasound transient elastography with CAP, and 10 minutes DEXA scan).

From screening to finish, total amount of time required of a patient will be approximately 6-7 hours (2 hours screen visit, 10 minutes ARFI, 10 minutes DEXA scan, 5 minutes ultrasound transient elastography with CAP, 30 minutes week 4 and 12 visits, 30 minutes MR scan, 2 hours post-treatment visit).

Stored specimen:
The specimens (serum, plasma, urine, saliva, whole blood (DNA), PBMCs, and stool) collected as part of this study will be kept at CTF building A. The purpose of this collection is to analyze inflammatory markers associated with treatment response in patients with HIV-associated NAFLD and to elucidate the mechanism of action of aramchol in the treatment of HIV-associated NAFLD. These samples and data may be stored indefinitely. At the end of the study, the data collected will be maintained at NARF building GI offices in a locked computer file with access available to the principal and study investigators only.

All samples and data will be labeled with a code number. The name, address, social security number, date of birth and other personal identifiers will not be available on the sample, and we will not give out any information that identifies the patient to the researchers who use these samples and data. Samples may be given to other researchers for collaborative research only if said researchers have proof of IRB approval for use of stored samples.

Table I. Study design

Week	0	4	8	12
Routine blood tests	X	X	X	X
Serum/plasma banking	X	X	X	X
Extended blood tests	X		X	X
Stool/urine/DNA/saliva banking	X		X	X
Physical exam and vital sign	X		X	X
DEXA	X			X
OGTT	X			X
MRI-PDFF	X			X
MRE	X			X
Aramchol VS placebo	600 mg of Aramchol(a 200 mg/tablet and a 400 mg tablet) per day	600 mg of Aramchol(a 200 mg/tablet and a 400 mg tablet) per day	600 mg of Aramchol(a 200 mg/tablet and a 400 mg tablet) per day	Stop

Annual follow up visits:

Patients will be offered annual follow up visits if they choose to attend. At the annual follow up visit, subjects will undergo a detailed history and physical examination. Standardized questionnaires Skinner Lifetime Drinking History in addition to the Alcohol Use Disorders Identification Tests (AUDIT) will be used. A urine pregnancy test will be performed for all women of childbearing age. Women who have had hysterectomies are excluded from pregnancy testing. If the pregnancy test is positive, the patient will not be enrolled in the study. The patient will undergo full body DEXA scan, magnetic resonance elastography, and a magnetic resonance imaging for liver stiffness calculation and hepatic fat fraction, respectively.

Assessment of Response and Statistical Analyses:
The primary outcome of this study will be improvement in hepatic steatosis by liver MRI. Statistical analyses will compare liver fat improvement between the treatments versus placebo-arms. It is not possible to predict what the spontaneous or therapeutic response rate will be. Thus, we predict that the spontaneous improvement rate would be zero to less than 1%. The sample size is chosen to avoid exposure of a large number of patients to 12 weeks of therapy and extensive evaluation if the study medication has no effect, but also to avoid missing a reasonably significant beneficial effect. We will require a sample size of 22 patients in each arm to have a power 90% (or higher) with a β of 0.05. We expect that Aramchol therapy group would have at least 6% reduction in liver fat compared to baseline as compared to 1% or less improvement in the placebo group. These estimates are also based upon our recent trial using MRI-PDFF as an accurate and reproducible marker of hepatic steatosis.[12] We expect to enroll up to 55 patients in this study and randomize at least 50 of them to either treatment or placebo arm for a full 12weeks with follow up evaluations. Clinical trials of experimental medications have had variable dropout rates. Our pilot studies of metformin had less than 9% dropouts, and all remaining patients underwent follow up evaluation and liver biopsy. In the randomized-controlled trial of colesevelam versus placebo, we had a 10% drop rate. Therefore, we expect less than a 10% drop out. Dropouts would be considered non-responders based upon intention to treat analysis. A modified intention to treat analysis will be done in which we will exclude the patients who dropped out before getting the week 12 exit evaluation.
Secondary outcomes will be assessed comparing pre-treatment to 12-weeks outcomes on therapy using parametric or non-parametric tests as indicated. The major secondary outcomes to be evaluated are:
1. Total body fat via DEXA scan
2. Serum ALT and AST values.
3. Lipid profiles.

We will compare the changes in the mean difference in the MRI-PDFF determined fat fraction between the treatment arm and the placebo arm at the co-localized region of interest. A two-tailed t-test would be utilized to compare the differences between the two groups. A two-tailed p-value of less than 0.05 is considered statistically significant. We will also conduct segment-to-segment changes in liver fat before and after treatment. We may perform internal validation by comparing MRI-PDFF with magnetic resonance spectroscopy between the two treatment arms in selected cases.

10.   HUMAN SUBJECTS

In this study, we propose to randomize up to 50 patients with HIV-associated NAFLD to either aramchol or placebo for 12weeks. We plan to enroll a total of 56 patients, Spanish and English speaking participants will be included. We are expecting some drop outs prior to randomization and a dropout of a small number of patients because of intolerance to aramchol.

Inclusion criteria:
1. Age at entry at least 18 years.
2. And at least one of the following risk factors for more severe liver disease.
   a. Hypertiglyceridemia based upon ATP-III guidelines
   b. Increased LDL cholesterol or increased total cholesterol based on ATP-III guidelines
   c. Decreased HDL cholesterol based upon ATP-III guidelines
   d. Serum alanine (ALT) aminotransferase that are above the upper limits of normal. 19 or more in women and 30 or more in men.
   e. Overweight as defined as BMI: $25 < 30 \text{ kg/m}^2$
   f. Obesity as defined BMI $\geq 30 \text{ kg/m}^2$

g. Hyperuricemia based upon A TP-III guidelines

h. Prediabetes or Diabetes by American Diabetes Association Criteria

3. Lipodystrophy will be confirmed on both clinical and radiologic assessment and defined as:

   a. Clinical history and/or exam by the study physician with signs of either facial, temporal, upper or lower extremity lipoatrophy

   b. Documented abdominal fat accumulation with presence of hepatic steatosis on MRI (defined below)

4. Evidence of hepatic steatosis or liver fat ($\geq 5\%$) by MRI.
5. History of HIV documented by a previously positive HIV elisa or PCR
6. Stable HIV infection as defined by the following parameters: Stable antiretroviral (ART) regimen for at least 12 weeks prior to study inclusion
   a. CD4 count of less than 200
   b. Detectable viral load
   c. Changes to ART regimen in the preceding 12 weeks
   d. Lack of alternative ART regimens should the patient virologic breakthrough
   e. History of opportunistic infection in the preceding 12 months
7. Written informed consent.

Exclusion criteria:
8. Evidence of another form of liver disease.
   a. History of hepatitis B as defined as presence of hepatitis B surface antigen (HBsAg).
   b. History of hepatitis C as defined by presence of hepatitis C virus (HCV) RNA in serum.
   c. History of autoimmune hepatitis as defined by anti-nuclear antibody (ANA) of 1:160 or greater and liver histology consistent with autoimmune hepatitis or previous response to immunosuppressive therapy.
   d. History of autoimmune cholestatic liver disorders as defined by elevation of alkaline phosphatase and anti-mitochondrial antibody of greater than 1:80 or liver histology consistent with primary biliary cirrhosis or elevation of alkaline phosphatase and liver histology consistent with sclerosing cholangitis.
   e. History of wilson disease as defined by ceruloplasmin below the limits of normal and liver histology consistent with Wilson disease.
   f. History of alpha-1-antitrypsin deficiency as defined by alpha-1-antitrypsin level less than normal and liver histology consistent with alpha-1-antitrypsin deficiency.
   g. History of hemochromatosis as defined by presence of 3+ or 4+ stainable iron on liver biopsy and homozygosity for C282Y or compound heterozygosity for C282Y/H63D.
   h. Drug-induced liver disease as defined on the basis of typical exposure and history.
   i. Bile duct obstruction as shown by imaging studies.
9. History of excess alcohol ingestion, averaging more than 30 gm/day (3 drinks per day) in the previous 10 years, or history of alcohol intake averaging greater than 10 gm/day (1 drink per day or 7 drinks per week) in the previous one year.
10. Contraindications to MRI:
    a. The subject has any contraindication to MR imaging, such as patients with pacemakers, metallic cardiac valves, magnetic material such as surgical clips, implanted electronic infusion pumps or other conditions that would preclude proximity to a strong magnetic field.
    b. The subject has a history of extreme claustrophobia
    c. The subject cannot fit inside the MR scanner cavity
11. Decompensated liver disease, Child-Pugh score greater than or equal to 7 points

12. History of gastrointestinal bypass surgery or ingestion of drugs known to produce hepatic steatosis including corticosteroids, high-dose estrogens, methotrexate, tetracycline or amiodarone in the previous 6 months.
13. Recent use (within the last 90 days) of medications to treat hepatic steatosis such as pioglotazone (or medications in the same class) or vitamin E.
14. Use of cyclosporine, alfentanyl and fentanyl on a chronic basis
15. Use of simvastatin and lovastatin at a dose of 40 mg once daily or higher.
16. Use of the following medications for more than 3 consecutive days: rifampicin, carbamazepine, phenytoin, enzalutamide and St John's wort
17. Use of clarithromycin, verapamil, diltiazem, itraconazole, difluconazole, ciprofloxacin, and grapefruit juice on a chronic basis (> 3 days consecutive days)
18. Use of Aramchol or agents in the same class.
19. HbA1c > 9 or uncontrolled diabetes.
20. Significant systemic or major illnesses other than liver disease, including congestive heart failure, coronary artery disease, cerebrovascular disease, pulmonary disease with hypoxia, renal failure (defined as GFR < 45 or CKD IIIB), organ transplantation, serious psychiatric disease, malignancy that, in the opinion of the investigator would preclude treatment with Aramchol and adequate follow up.
21. Active substance abuse, such inhaled or injection drugs within the previous three months.
22. Pregnancy or inability to practice adequate contraception in women of childbearing potential.
23. Nursing mothers
24. History of hepatocellular carcinoma: alpha-fetoprotein levels greater than 200 ng/ml and/or liver mass on imaging study that is suggestive of liver cancer.
25. HIV specific exclusions:
    a. CD4 count of less than 200 in the previous 6 months
    b. Detectable viral load in the previous 6 months
    c. changes to ART regimen in the preceding 12 weeks
    d. History of opportunistic infection in the preceding 6 months
    e. AIDS wasting syndrome
26. Symptoms of uncontrolled gastrointestinal disorders involving motility, gastric acid or gastric emptying or malabsorption.

    a. Disorders including but not limited to peptic ulcer disease, gastroesophageal reflux, severe dyspepsia, gastroparesis, chronic diarrhea, chronic constipation, gall bladder disease, pancreatitis, severe lactose intolerance and celiac disease.

    b. Patients who have used anticholinergic or other drugs known to affect gastrointestinal motility within 7 days prior to dosing and throughout the study will also be excluded

27. Patients with hypersensitivity to Aramchol or to any of the excipients in the tablets or with hypersensitivity to cholic acid or bile acid sequestrants

28. Any other condition, which, in the opinion of the investigators would impede competence or compliance or possibility hinder completion of the study.
29. Women who are pregnant or may become pregnant

11. RECRUITMENT

Enrollment of patients may be initiated once IRB approval is acquired and will continue until June 2015.

English speaking and Spanish speaking patients will be recruited from the following populations:
• Primary care and internal medicine clinics
• Tertiary referral clinics at the Hillcrest Campus and Perlman Clinics:
    - GI/Liver clinic
    - Liver transplant clinic

- Owen clinic
- Bariatric surgery clinic
- Lipid disorders clinic

- Physicians taking care of the patients would provide information regarding the study (flyer and stamped consent form will be used to provide information regarding the study) and then either refer the patient to our clinic or ask the patient to directly contact the PI or research team.
- Patient would be given information regarding possible studies in HIV-associated NAFLD in liver clinic by their providers. We would ask the patient to call or email the PI or research team to further discuss the study, if they are interested.
- In addition, potential subjects will also be recruited by newspaper advertisements and fliers posted on the UCSD campus bulletin in order to have enough participants to study the desired aims. Volunteers who appear to be a good match for the study will receive study announcement material that excludes any direct study contact information (email/phone). Contact information of interested participants only will be released to the research study team. Patients who are interested in the study can call our office to speak to the study team to find out more information about the study.

12.   INFORMED CONSENT

Adult consents have been uploaded to the UCSD HRPP web site for approval. Subjects will be provided consent either by the participating investigator while at their clinic visit or will be given contact information for the research team and told to contact them if they are interested in participating. All signed consents will be maintained in marked binders, secured in locked filing cabinets within private administrative offices at UCSD Medical Center, Hillcrest. Offices are accessible to study staff only.

Sub Investigator Dr. Irine Vodkin is fluent in Spanish. She will be the one to explain the study to participants that prefer Spanish or are Spanish speaking only.

There is a separate optional component of the study where subjects will be asked to donate a blood sample for genetic research. Subjects will be offered the opportunity to review, discuss and sign the consent at their scheduled visit. All questions will be answered at this time and throughout the study. Declining to give a genetic sample does not prohibit the participant from participating in the study.

13.   ALTERNATIVES TO STUDY PARTICIPATION

Currently there are no FDA approved therapies for HIV-associated NAFLD. The alternative to study participation is not to participate in this study.

14.   POTENTIAL RISKS

The risks and discomforts of frequent phlebotomy: To document changes in levels of biochemical markers of liver disease and to monitor the metabolic effects and toxicities of aramchol, frequent blood sampling will be required. Patients will have 4 venipunctures during the treatment period of the study. Each venipuncture will remove 15 to 50 ml of blood. However, no more than 1.5 ml/kg will be drawn from any one person during a four-week period. Blood collection by venipuncture is associated with mild discomfort, and the possibility of localized bruising, phlebitis, or extravasation. The risk of infection or fainting is extremely small.

The risks and discomforts of HIV testing: Patients will sign a standard consent for HIV testing for this study.
Risks and discomforts of Oral Glucose Tolerance Test (OGTT): There will be two OGTT's during this protocol, one at the beginning and one after 12 weeks of treatment with Aramchol. The purpose of this test is to assess insulin sensitivity, insulin secretion as well as free fatty acid metabolism. The patients will have an intravenous catheter placed in the arm and be given 75mg of glucose as an oral solution. Subjects occasionally complain of nausea and rarely may vomit and there is a small risk of rebound hypoglycemia. Repeat blood draw will be done at 2 hours. Total amount of blood that will be drawn for glucose and insulin measurements during this test will be 100 to 120 ml. No more than 6 ml/kg of blood will be drawn from any one person during a four-week period

The risks and discomforts of other tests:

a. MRI of abdomen and liver. Patients will undergo two MRI examinations of the liver during this study. Each session will be completed within 30 minutes. While serial MRI scanning is thought to be safe, the procedure may cause anxiety in some patients since current equipment used at the Clinical Center uses a closed tube. Patients will be offered sedatives such as Valium if they express worry about being in a closed space.

b. MRE is a type of MR imaging where the images indicate tissue stiffness. MRE imaging involves placing a vibrating paddle over the abdomen while images are being obtained. This is an FDA-approved procedure when used clinically, but is considered to be investigational in this study. These vibrations have been reported to be well tolerated by patients. (14) However, the vibrating paddle could be uncomfortable to some subjects, and so subjects will be instructed to tell the MR technologist if the vibrations become uncomfortable, and the MRE part of the examination will be discontinued.

c. Cardiac MRI (without contrast). Patients will undergo two Cardiac MRI examinations during this study. Each session will be completed within 20 minutes. While serial MRI scanning is thought to be safe, the procedure may cause anxiety in some patients since current equipment used at the Clinical Center uses a closed tube. Patients will be offered sedatives such as Valium if they express worry about being in a closed space.

d. The ARFI ultrasound imaging method to be used for this study is investigational, and is considered to be of minimal (i.e., non-significant) risk. This investigational imaging method has the same safety precautions built into it as the ones that are used clinically, and so the method we will use is considered by the FDA to be of minimal risk and of similar safety as the sequences that are approved by the FDA for clinical use. As per 63 FR 216:60364-60367, ultrasound is considered a (Category 4) minimal risk procedure because it involves the "collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves ...", for which "examples include … ultrasound …".

The conventional ultrasound imaging that will be performed in this study is the same as is used clinically. When it is used clinically it is FDA approved; however, for the purposes of this research study it will be considered to be investigational and not FDA approved since we are using it for research. Possible effects of ultrasound imaging on nursing mothers have not been examined. Therefore, nursing mothers will be excluded.

e. Reproductive risks:

Although ultrasound and magnetic resonance imaging are routinely performed in pregnancy in clinical practice. We will take a conservative approach as potential effects of ultrasound and MRI imaging on human embryonic or fetal development may not have been examined. Therefore, women of childbearing potential, including those who have had a tubal ligation, will be required to take a urine pregnancy test and have negative results before enrolling into study.

f. Unforeseeable risks:

Although serious injury to organs or death have never been attributed to ultrasound imaging or MRI, it is possible that currently unforeseen side effects, including serious injury to organs or death may occur. Also, because this is an investigational study, there may be some other unknown risks that are currently unforeseeable. The subject will be informed of any significant new findings.

g. Dual energy x-ray absorptiometry (DEXA) body composition assessment will be obtained using the Hologic Discovery W densitometer with APEX software (Hologic, Inc., Bedford, MA). The DEXA systems assess body composition by measuring the differential absorption of x-ray at two frequencies to separate tissue into fat, lean, and bone mineral. A whole body composition DEXA scan last approximately 6 minutes and the radiation dose is 9 mrem (0.09 mSv) for two DEXA scan, one at screening and one at the post treatment phase.

h. Ultrasound transient elastography with CAP is a noninvasive procedure to measure liver density. There are no known direct risks from the Ultrasound transient elastography with CAP medical device which uses ultrasound waves. However, you may feel minor discomfort or minor soreness over the area where the ultrasound probe contacts the abdomen. There is a small risk of allergic reaction to the gel used during the procedure. Ultrasound gel is water-based. There is no radiation exposure and the CAP measure is simply an additional calculation.

Side effects due to Aramchol: Patient trials with Aramchol are limited to the Safadi study[24], but the clinical trial demonstrated no significant adverse events in the 12-week treatment period for 58 patients that underwent the trial. The few adverse events were mild (abdominal pain, back pain, constipation) and did not cause anyone to drop out of the trial. There were no severe adverse effects. The previous studies were done in animal models. Due to the paucity of clinical trials to evaluate side effects of Aramchol, we will encourage patients to notify staff of any adverse reactions and we will monitor patients via physical exams and laboratory testing at regular intervals to ensure patient safety.

Dosage modification and discontinuation of Aramchol: patients will be monitored for side effects and the toxicity will be ranked as Grades 1 to 4. We will use the common toxicity criteria (CTC), version 4.0, for scoring adverse events during

therapy. Specific scoring of toxicity for the major safety parameters to be followed in this study is shown in Table II. The criteria for grading leukocytes, platelets, prothrombin time, partial thromboplastin time, bilirubin, ALT, and AST are modified slightly from the CTC version 4.0 because these factors are likely to be abnormal before therapy in patients with chronic liver disease.   An adverse event is defined as any adverse change from the patient's baseline (pre-treatment) condition. These include current illness during the course of the study, regardless of the illness being considered unrelated to treatment. Patients will also be monitored closely for antiretroviral therapy tolerance and continued virologic suppression of HIV.

- Dose modification of Aramchol**:** If any grade 2 adverse events (anemia, elevated serum CPK, hypoglycemia, decrease in serum bicarbonate, elevation in liver transaminases, elevation in bilirubin, anorexia, nausea, diarrhea) occur and persist on repeat testing for one week, Aramchol will be reduced 600 mg daily (including 200 mg tablet and 400 mg tablet) versus identical placebo to 300 mg daily and the patient will be closely monitored. If the adverse event resolves and in retrospect is not believed to be due to Aramchol, the drug will be restarted at the dose of 600 mg daily (including 200 mg tablet and 400 mg tablet) versus identical placebo. If the adverse event recurs or persists for 2 weeks despite this dose reduction, Aramchol will be stopped.
- Discontinuation of Aramchol**:** In this study, discontinuation of Aramchol will be based upon the scoring of adverse events as shown in the table below. Factors that will lead to discontinuation of Aramchol include pregnancy, any one of the grade 3 or 4 adverse events or any adverse event, which, in the opinion of the investigator, places the patient at increased risk. Factors specific to the HIV population which will lead to discontinuation of aramchol will include: development of HIV viremia, decrease in CD4 T-cell count below 200, any evidence of increased antiretroviral toxicity (lactic acidosis, as well as grade 3 or 4 myalgia, CPK elevation or LFT abnormalities), and any aramchol related side effects that interfere with adherence to antiretroviral therapy. Aramchol will not be restarted unless another cause for the abnormality or symptom is found.

Table II. Scoring of toxicity for dose modification

Adverse events	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life threatening consequences; urgent intervention indicate	Death
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; parenteral intervention	Life-threatening consequences; urgent intervention indicated	Death

			indicated; allergy-related edema/angioedema; hypoten		
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL		
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L;	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/	Hgb <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L;	Life-threatening consequences; urgent intervention indicated	Death

	<LLN - 100 g/L		transfusion indicated		
Leukocytes (cell/mm3)	3300 to 9600	2500 to 3300	2000 to 2500	1000-2000	<1000
Platelet count per mm3	154,000 to 345,000	70,000 to 150,000	50,000 to 70,000	10,000 to 50,000	<10,000
Prothrombin time	11.8 to 14.7	14.8 to 16	16.1 to 18	>18	-
Activated partial thromboplastin time prolonged	23.4 to 34.5	35.6 to 42	42 to 50	>50	-
Alkaline phosphatase (U/L)	37-116	117-250	401 - 400	401-600	>600
ALT (U/L)	Baseline-<1.5 times baseline	>200 and > 1.5 X baseline	300-400 and > 2 x baseline	401-800 and > 3x baseline	>800
AST (U/L)	Baseline-<1.5 times baseline	>200 and > 1.5 X baseline	300-400 and > 2 x baseline	401-800 and > 3x baseline	>800
Total Bilirubin (mg/dL)	0.1 to 1	1.1 to 1.5 and direct bilirubin >0.5	1.5 to 5 and direct bilirubin > 1	5.1 to 10	>10
Albumin (g/dL)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
CPK increased (U/L)	2.5 x above baseline	CPK2.5 x - 5 x x above baseline	>5 x - 10 x above baseline	>10 x baseline	-
Glucose (mg/dL)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life threatening consequences; seizures	Death
Creatinine (mg/dL)	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicate	Death

Table II. Scoring of toxicity for dose modification**.** Scoring of toxicity from the CTC Version 4.0, with modifications for leukocytes, platelets, prothrombin time, partial thromboplastin time, ALT, AST and bilirubin. Normal ranges for values at UCSD center are used.

Potential Loss of Confidentiality: All means will be employed to ensure that there is not a loss of confidentiality. Although study material will be kept private and inside a locked cabinet there is a slight possibility that a breach of confidentiality may occur. A special code de-identifying the research subject from the data and specimens collected will be assigned to all research subjects and their study material. Only the P.I. and their research team will be able to link the research subject to

the assigned code. It still may be possible, but highly unlikely, that the information in the research records could become known outside of the research setting.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Data and Safety Monitoring:
The principal investigator and research coordinator of this protocol will monitor data and safety regularly at weekly meetings. These meetings are separate from regular clinical rounds and consist of review of all study patients including flow sheets of major safety and efficacy measurements. The rationale for not using an outside data and safety monitoring committee is that this is a small, single center study using a FDA approved medication that has been associated with few severe side effects. All measurements and tests are well established in clinical medicine. Yearly reports are made to the UCSD IRB regarding safety and efficacy.

Adverse Event Reporting
All serious adverse events will be reported to the UCSD IRB and Galmed within 7 days. Unexpected and related fatal or life-threatening events will be reported within 48 hours and reports will be sent to the FDA, MEDWATCH program (telephone 1-800-FDA-1088; or via the Internet at www.fda.gov/medwatch/index.html) and Galmed Pharmaceutical.

Informed Consents
All consents will be stored in well-marked binders in locked file cabinets located in private offices at UCSD Medical center. Databases with identifying information will be secure as they will be password protected and encrypted. Staff will be trained in HIPAA guidelines and confidentiality issues.

Patient Privacy: To help us protect the privacy of the research subjects, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which will allow us to resist any demands for health information, with a few exceptions as explained below. The Certificate protects us from being forced to disclose information that may identify research subjects, even if by a court subpoena. We are also protected from demands for information made by federal, state, local civil, criminal, administrative, legislative, or other sources. However, the Certificate cannot be used to resist a demand from the U.S. Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration. All data and study forms will be in secured locations (locked room or cabinet) and access is limited to study personnel. Subject names are not used; instead a name code is assigned upon enrollment. Release of data to persons or organizations outside study personnel will require written consent of the subject.

MRI Findings: Liver MRI (Fat fraction) sequence and Cardiac MRI (without contrast) do not provide detailed information regarding other organs within the abdomen cavity and is mainly dedicated to the liver or cardiovascular region. However, if there are any unexpected findings on the liver MRI and/or Cardiac MRI, we would utilize following protocol to safeguard patient interest. A trained radiologist will read all MRI images. All abnormal findings will be communicated to the PI by the radiologist. Dr. Loomba (PI) is a gastroenterologist and a transplant hepatologist at UCSD and routinely provides consultation to other services regarding abnormal imaging findings and is therefore, well versed with the management of these findings. He would clinically correlate the significance of any unexpected MRI findings. These findings will be discussed with the patient by the study investigator and a follow-up plan will be established and documented. If the patient desires, this information will be released to the referring physician or any provider or entity that the patient would like us to send the information. PI would be available to discuss the findings with the patient or their health care providers and assist in providing adequate follow-up. These abnormal findings would be systematically recorded and reported at yearly renewals and in the final manuscript.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

All study data will be kept confidential. No publication or written reports will link subject data with a name or any individual protected health information. Protected health information will not be re-used or disclosed for other purposes. Computer data file entry and access will require a password.

Research subjects will have control over access to themselves (privacy) and how study data will be managed and used (confidentiality).

Privacy will be provided for all contact with research subjects during recruitment, informed consent, ultrasound and MRI scanning, and any other contact with subjects that may occur by ensuring privacy at our facility (210 Dickinson Street) where we have adequate dedicated space – a separated waiting room and a private examination room, each with doors that close. Subjects will also have access to, and will use a private bathroom / changing room to change into and out of a gown.

Confidentiality will be assured by allowing review in this study of medical records and imaging studies only by study investigators who are directly involved in reviewing or capturing this information. Captured information will be stored in a de-identified form. Data will be accessed at workstations at require secure login and password access, in the CTF building. Research records with personal health information will be kept in locking file cabinets in rooms that are locked after hours and which are only accessible to authorized personnel during working hours. The 408 Dickinson building where the MRIs are performed is itself locked after hours. Security of medical records is maintained as per University of California Medical Center policy, UCSD IRB security policies, and study personnel, all who have been CITI IRB trained. Security policy in the 408 Dickinson building is further maintained by Mark Wood MSc, dedicated on-site information technology and security officer, who will control computer access to medical records. De-identification of data will be done and data labels and study ID would be used. The data key to de-identified data will be the enrollment log for this study, which will be stored in a secure, locked filing cabinet in the CTF building. Identifiers will be kept in a separate file, which will be password protected until this study is concluded, at which time they will be destroyed.

17. POTENTIAL BENEFITS

Potential benefits include possible improvement in liver profile, insulin resistance, and metabolic profile for the patient. The research subject's liver disease may improve because of treatment with the study drug. However, the research subject may receive no benefit. The research subject may help future patients by providing important information about the treatment of HIV-associated NAFLD. The research subject may benefit from health information obtained during the physical exams, laboratory tests, and other study procedures. At the research subject's direction, we will provide the results of any procedures done to screen him/her for this study to their liver care provider.

18. RISK/BENEFIT RATIO

The PI believes that the there is a favorable risk/benefit ratio as risks associated with treatment with Aramchol, data collection and confidentiality does not outweigh potential benefits to the discovery of potential treatments for HIV-associated NAFLD. There are currently no approved treatments for NAFLD/NASH. Data collection and blood draws are procedures being performed as outlined in the study protocol and all efforts will be made to minimize any risk to the research subject. Staff will have HIPAA certification training.

19. EXPENSE TO PARTICIPANT

There is no expense to the research subjects.

20. COMPENSATION FOR PARTICIPATION

Participants will be paid $25 each at the first visit and at weeks 4 and 8. $50 at the completion of the study at week 12.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Dr. Rohit Loomba is an adult gastroenterologist and transplant hepatologist at UCSD Medical Center. He is a licensed physician in the state of California with full privileges at UCSD Medical Center. He has full privileges at UCSD medical center to conduct liver biopsies and also manage patients with chronic liver disease. Dr. Loomba has completed training relevant to clinical research including HIPAA certification, and Ethics training. He holds a Master's Degree in Health Sciences in Clinical Research from Duke University School of Medicine. Copies of licenses and certification are maintained at the Department of Medicine.

Dr. Claude Sirlin, an American Board of Radiology certified radiologist, has two licenses: a CA medical license, and a fluoroscopy operator license. Dr. Sirlin has completed training relevant to clinical research including Human Subjects certification, HIPAA certification, and Ethics training.

Dr. Saima Aslam is an adult infectious disease specialist at UCSD Medical Center and the director of the solid organ transplant infectious diseases service. She is a licensed physician in the state of California with full privileges at UCSD

Medical Center. Dr. Aslam has completed training relevant to clinical research including HIPAA certification, and Ethics training. Copies of licenses and certification are maintained at the Department of Medicine.

Dr. Edward Cachay is an adult infectious disease specialist at UCSD Medical Center and the director of the solid organ transplant infectious diseases service. He is a licensed physician in the state of California with full privileges at UCSD Medical Center. Dr. Cachay has completed training relevant to clinical research including HIPAA certification, and Ethics training. Copies of licenses and certification are maintained at the Department of Medicine.

Irine Vodkin is a UCSD fellow in gastroenterology and is board certified in California. Dr. Vodkin has privileges at UCSD medical Center. She has completed training relevant to clinical research through the Clinical Research Enhancement Supplemental Training program. Copies of licensure and certification are maintained in the UCSD Department of Medicine.

Daniel Lee is an adult infectious disease specialist at UCSD Medical Center, he director of the Owen lipid/lipodystrophy clinic. He is a licensed physician in the state of California with full privileges at UCSD Medical Center. Dr. Lee has completed training relevant to clinical research including HIPAA certification, and Ethics training. Copies of licenses and certification are maintained at the Department of Medicine.
Ahilan Arulanandan is a UCSD resident in gastroenterology and is board certified in California. Dr. Arulanandan has privileges at UCSD medical Center. He has completed training relevant to clinical research through the Clinical Research Enhancement Supplemental Training program. Copies of licensure and certification are maintained in the UCSD Department of Medicine.

Lisa Richards, NP is a Hepatology nurse practitioner at the UCSD Medical Center. She has special expertise as the nurse practitioner for the UCSD NAFLD clinic. Her licenses and degrees are held at the gastroenterology unit UCSD Medical Center.

Emily Rizo, NP is a Hepatology nurse practitioner at the UCSD Medical Center. She has special expertise as the nurse practitioner for the UCSD NAFLD clinic. Her licenses and degrees are held at the gastroenterology unit UCSD Medical Center.

Shirin Bassirian will serve as a study coordinator acting under the supervision of the PI, will assist in the execution of the proposed research, including arranging logistics; perform recruitment activities, enroll and consent patients, disburse monetary compensation to patients, serve as first-contact liaison and perform administrative tasks as needed. She has completed training relevant to clinical research including Human Subjects certification, HIPAA certification, and ethics training. Copies of licensure and certification are maintained in the UCSD Department of Medicine.

Phirum Nguyen and Carolyn Hernandez, will serve as the backup study coordinators acting under the supervision of the PI, will assist in the execution of the proposed research, including arranging logistics; perform recruitment activities, enroll and consent patients, disburse monetary compensation to patients, serve as first-contact liaison and perform administrative tasks as needed. She has completed training relevant to clinical research including Human Subjects certification, HIPAA certification, and ethics training. Copies of licensure and certification are maintained in the UCSD Department of Medicine.

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23. FUNDING SUPPORT FOR THIS STUDY

This is an investigator-initiated study not solicited by the sponsor company Galmed Pharmaceutical. Funding is provided by Galmed Pharmaceutical under investigator initiated studies program.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Application has been submitted to the FDA. IND# 128222

26. IMPACT ON STAFF

Lisa Richards, NP is seasoned clinician, licensed and certified to perform physical exams and appropriate medical procedures and case manage quality of care. The certified study coordinator and other key personnel at the UCSD Medical center have been trained or will be trained for their role in the study on-site.

Emily Rizo, NP is clinician, licensed and certified to perform physical exams and appropriate medical procedures and case manage quality of care.

27. CONFLICT OF INTEREST

A conflict of interest has been disclosed. Dr. Loomba follows the IRC recommended management strategy in order to manage the conflict of interest. Recompensed activities with Galmed Pharmaceutical during the course of study will be discontinued.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Subject must be able to consent to the study. Based upon past experience, we expect that the population of patients we will be including in this protocol will be competent to give informed consent. If the investigator feels that the decision-making capacity to consent to be a part of this study is insufficient, then a post-consent quiz will be administered after the consent form has been explained to the subject. The post consent quiz will be submitted to HRPP for review. If the subject is unable to answer any of the questions in the post-consent quiz, any information not clearly understood from the consent form will be repeated or explained in greater detail. If there is any concern by an investigator that a potential research participant has a condition or circumstance that is associated with a possible decrease in decision-making capacity, that subject will not be included in the study.

Version date: May 11, 2011