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Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer

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SCHEMA

Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer

Patients with liver cirrhosis who have no evidence of hepatocellular carcinoma (HCC)

▼

Pre-Screen Chart Review – Initial determination of eligibility (Expected N=377)

Medical charts of patients who have an upcoming appointment with a study hepatologist will be reviewed for age, cirrhosis diagnosis, prior liver transplant, prior statin use, prohibited concomitant medications, previous malignancies, medical contraindications, laboratory results, and evidence of HCC from last abdominal image occurring within the past 18 months. A study information packet may be mailed to potentially eligible patients. Study hepatologist or clinical research staff will call potentially eligible patients before their scheduled appointment to introduce the study and answer questions.

▼

Screen 1* – Consent and Final determination of eligibility (Expected N=90)

Patients who are eligible based on pre-screen chart review will be consented into the trial before any research procedures are initiated. Study hepatologist will review the patient's medical history, medications, and laboratory test results and evaluate all inclusion/exclusion criteria. Patients will undergo a physical assessment; symptom assessment; ECOG performance status; blood tests; and urine pregnancy test (for women able to become pregnant) to confirm eligibility. *Patients with a MELD score >20, AST/ALT >5x ULN, or other lab results outside eligibility range; and women who are pregnant will be excluded.*

▼

Eligible, consented patients with liver cirrhosis randomized to simvastatin or placebo (Expected N=80)

Simvastatin 40 mg, daily for 6 months (N=40)	Placebo identical in color, consistency, and appearance to simvastatin 40 mg, daily for 6 months (N=40)

▼ ▼

Study Visit 1 – Baseline / initiation of the intervention (0-30 days following Screen 1)

Review medical history, medications, and laboratory test results; vital signs assessment; symptom assessment; ECOG performance status; blood draw; liver elastography (FibroScan); interviewer-administered questionnaire; food frequency questionnaire; dispense study drug and diary

▼

Study Visit 2 (30 days after initiation of the intervention)

Review medical history, medications, and laboratory test results; vital signs assessment; symptom assessment; ECOG performance status; blood draw; collect study drug and diary; assess compliance (pill count); review study diary; assess adverse events; dispense study drug and diary

▼

Study Visit 3 (3 months after initiation of the intervention)

Review medical history, medications, and laboratory test results; vital signs assessment; symptom assessment; ECOG performance status; blood draw; collect study drug and diary; assess compliance (pill count); review study diary; assess adverse events; dispense study drug and diary

▼

Study Visit 4* (6 months after initiation of the intervention)

Review medical history, medications, and laboratory test results; physical assessment; symptom assessment; ECOG performance status; blood draw; liver elastography (FibroScan); abdominal imaging; collect study drug and diary; assess compliance (pill count); review study diary; assess adverse events

▼

Endpoints – Evaluate the effect of simvastatin versus placebo after 6 months of treatment on change in:

Primary endpoint: serum AFP-L3%

Secondary endpoints:

1) serum AFP
2) serum IL-6
3) serum deoxycholic acid
4) liver stiffness
5) FIB-4 score
6) MELD score

Exploratory endpoints: other serum bile acid levels and immune markers

**Note: Screen 1 and Study Visit 4 are concurrent with standard of care visit.*

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1. OBJECTIVES

The objective of this randomized double-blinded, placebo-controlled Phase II trial is to examine the effects of simvastatin use versus placebo after 6 months of treatment on liver disease progression in 80 patients with liver cirrhosis who have a current Model for End-Stage Liver Disease (MELD) ≤ 20 and no evidence of hepatocellular carcinoma (HCC).

1.1 Primary Objectives

To evaluate the effect of a simvastatin intervention versus placebo on the change in serum AFP-L3% from baseline to 6 months following treatment initiation in patients with liver cirrhosis who have a current Model for End-Stage Liver Disease (MELD) ≤ 20.

1.2 Secondary Objectives

To evaluate the effect of a simvastatin intervention versus placebo at 6 months from baseline on the change in:

1) serum AFP;
2) serum IL-6;
3) serum deoxycholic acid;
4) liver stiffness;
5) FIB-4 score; and
6) MELD score.

1.3 Exploratory Objectives

To evaluate the effect of a simvastatin intervention versus placebo at 6 months from baseline on the change in other:

1) serum bile acid levels; and
2) serum immune markers

2. BACKGROUND

2.1 Study Disease

Hepatocellular carcinoma (HCC) is a highly lethal cancer with rising incidence and mortality rates. Approximately 33,000 HCC diagnoses were expected in 2014, and the incidence is increasing among the most rapidly of any cancer, with an age-adjusted annual increase of 3.7% and 2.9% in men and women, respectively [1]. HCC burden depends heavily on age and ethnicity. Older Hispanic men have the highest HCC incidence rate of any major demographic group, and HCC risk overall is nearly 3 times higher in Hispanics compared to non-Hispanic whites [2, 3]. Tragically, HCC has a dismal 5-year survival rate of 18%, second in lethality only to pancreatic cancer [1]. Thus, in-line with the incidence trends, HCC mortality is also increasing at the most rapid pace of any cancer and is highest in older Hispanic men [1, 2]. Targeted studies of HCC in populations consisting of a high proportion of Hispanics are needed to identify strategies to curtail the rising HCC burden.

Between 70-90% of HCCs develop in people with liver cirrhosis, and cirrhosis is considered a pre-cancer lesion [4, 5]. For a person with cirrhosis, the 5-year risk of developing HCC varies according to several influential characteristics including race/ethnicity, liver disease etiology, and severity of complications, with a cumulative HCC risk as high as 30% among patients with advanced cirrhosis [6-9]. Hispanics have a more rapid progression from cirrhosis to HCC compared to other major racial/ethnic groups [10]. Liver

transplantation is the only curative option for cirrhosis and can prevent the development of HCC if patients can be transplanted in time. Over the last decade, there has been a growing crisis of insufficient donor livers for transplantation due to the convergence of increasing need, decreasing donation, and increasing discard of sub-optimal livers, leading to a near doubling of the median transplant wait time [11]. Long wait times increase the chance for HCC development. Although patients who develop HCC are given priority on the waitlist and thus "advantaged" in the current system for liver allocation, between 10-15% of cirrhotics who develop an HCC prior to receiving a transplant have a fatal recurrence of their cancer post-transplant [12].

The rising HCC burden has been attributed to the changing etiological landscape for HCC primarily brought on by the rising obesity pandemic. Obesity and diabetes are currently the leading risk factors for HCC, followed by alcohol abuse and hepatitis C virus (HCV) [13]. Obesity (body mass index (BMI) ≥ 30) affects 34.9% of all adults and 42.5% of Hispanic adults; an overall increase of 2.8% from a decade ago [14]. Nonalcoholic steatohepatitis (NASH), the hepatic manifestation of obesity and diabetes, is twice as common in Hispanics compared to non-Hispanic whites [15]. NASH has more than doubled in incidence over the last decade, and it is projected that 25 million Americans will develop NASH by 2025, with 20% progressing to cirrhosis and/or HCC and may require liver transplantation [16-20]. In summary, there is a rising problem of HCC which poses a substantial public health problem.

2.2 Study Agent

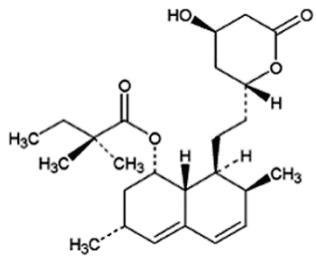


Figure 1. Molecular structure of simvastatin

Simvastatin (butanoic acid, see Figure 1) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol, and ethanol.

Simvastatin tablets for oral administration contain 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose, hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.

Simvastatin is the most commonly prescribed HMG-CoA reductase inhibitor, which has a widely accepted tolerability profile with few serious side effects [21]. Potential, but uncommon side effects include muscle, liver, and kidney problems. Elevated levels of creatine kinase and rhabdomyolysis occur in <1% of consumers, and myalgia, or muscle ache or weakness, can occur in approximately 5% of consumers [22]. In a clinical trial database in which 41,413 patients were treated with simvastatin, 60% of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses [23].

Simvastatin is prescribed for primary and secondary prevention of cardiovascular disease and thus is indicated for long-term use. We propose to administer simvastatin 40 mg daily for 6 months in this trial.

2.3 Rationale

Hypotheses:

1) Participants randomized to simvastatin will experience a decrease from baseline to 6 months in serum AFP-L3% compared to the placebo group.

2) Compared to the placebo group, participants randomized to simvastatin will have:
    a) lower serum AFP levels;
    b) lower serum IL-6 levels;
    c) lower serum deoxycholic acid (DCA) levels;
    d) less liver stiffness;
    e) lower FIB-4 score; and
    f) lower MELD score.

HCC is amenable to a chemoprevention strategy. Cirrhosis is the penultimate step of the multistage pathogenesis of HCC [4, 5]. Currently, the only clinical option for cirrhotics awaiting a transplant is to watch and wait for HCC to develop and hope that the tumor is caught early enough so that transplantation is still a viable option. In a recent paper, in a convenience sample including Child class B/C patients with chronic liver disease attending a hepatology clinic (similar to recruitment methods for this trial), the 3-year cumulative HCC incidence was 14.8%. Although the data are not presented explicitly, based on the Kaplan-Meyer plot, the cumulative incidence over the first 6-months of follow-up appears to be around 1% [8]. For this current trial, this would amount to less than 1 participant. An intervention that has the ability to delay or halt the development of HCC in the high risk setting of cirrhosis would have a major clinical impact for individual patients, better utilization of precious donor organs, and an improvement of outcomes for this liver disease cohort in aggregate. In spite of this unmet need, chemopreventive strategies for HCC have been understudied in clinical trials.

Statins and the prevention of HCC: mechanistic links and human studies. HMG-CoA reductase inhibitors, commonly known as statins, are pleiotropic drugs that also have chemopreventive properties mediated through diverse pathways [24, 25]. The potential for liver cancer prevention is particularly relevant, due to the fact that the liver is the target organ for statins and sequesters the majority of the drug. For example, statins inhibit downstream products of the mevalonate pathway including isoprenoid (e.g., farnesyl pyrophostate, geranyl pyrophosphate), a necessary post-translational modifier of the RAS oncoprotein, which promotes cell cycle progression, growth, and survival of cancer cells [26]. Statins may also suppress β-catenin, the main downstream effector of the canonical WNT signaling pathway which is commonly activated in HCC and detected in 30-90% of tumors [27-30]. Statins have also been shown to modulate the bile acid pool and reduce levels of putative hepatocarcinogenic bile acids such as deoxycholic acid (DCA) in human secretions [31-35], as well as tumor promoting cytokines (such as IL-6) in human serum. In hepatocellular carcinoma cells, statins can induce autophagy, the selective recycling of damaged cellular organelles [36]. Impaired autophagy leads to development of liver tumors [37]. Statins are also immunomodulatory, and can decrease TLR4 expression in response to LPS, which has been implicated in hepatocarcinogenesis [38]. Furthermore, statins can inhibit HCV-induced hepatocarcinogenesis by inhibiting the formation of lipid rafts and host factors necessary for HCV replication and epidermal growth factor signaling pathway increasing opportunity for HCV cellular entry [39].

There is accumulating epidemiological data supporting the notion that statins prevent HCC. A recent meta-analysis of 11 studies found that statins were associated with a significant reduction in HCC risk (HR=0.6, 95%CI=0.5-0.7) [40]. This reduced hazard of HCC has been observed in diverse populations with high and low prevalence of underlying liver disease etiologies (e.g., HCV, hepatitis B virus (HBV), and diabetes) [41-46]. The most recent and largest study to date of statins and HCC was conducted within the Clinical Practice Research Datalink of the United Kingdom and included over 1,000 HCC diagnoses

[42]. This study found that statins were associated with a significant reduction in HCC risk (OR = 0.55, 95% CI = 0.45 to 0.69), and that diabetics on a statin had a more pronounced reduction of HCC risk. While some contrasting pre-clinical studies suggest that lipophilic statins (such as lovastatin and simvastatin) might have greater chemopreventive effects due to their greater lipid solubility and membrane permeability, and others suggest that lipophobic statins (such as pravastatin) may have greater chemopreventive effects due to the ability to accumulate in cells, the observational data suggest that the reduction in HCC risk is a class effect and not specific for particular formulation of statins. Although these observational studies support the hypothesis that statins prevent or reduce the risk of HCC, these studies cannot prove a causal link. Importantly, they have been criticized for bias due to confounding by contraindication (i.e., statin prescribing patterns). Secondary analyses of randomized control trials (RCTs) of statins and cardiovascular disease have also examined HCC risk as an outcome, although the results are inconclusive [45]. These RCTs are limited in that they often were unable to account for important HCC risk factors, and were based in low HCC risk populations with inadequate follow-up time and statistical power for HCC as an outcome. An RCT with defined intermediate biomarkers of HCC in a high-risk HCC population could shed much needed light on the potential for statins to protect against, or delay the progression to, HCC.

HCC Biomarkers and Their Links to Statins

Alpha Fetoprotein (AFP) and AFP-L3%. Serum levels of AFP, a glycoprotein expressed by fetal hepatocytes or poorly differentiated HCC cells, is the most frequently used biomarker for HCC worldwide. Although the sensitivity and specificity of AFP for detecting HCC, and particularly early HCC, vary according to study population, it is clear that AFP is far from a perfect marker for HCC. Serum AFP levels may be elevated in patients with chronic liver disease in the absence of HCC or in patients with other cancers. Thus, even if one assumes best-case estimates of sensitivity and specificity, the case for surveillance by AFP, particularly for early HCC, remains weak [47]. The poor performance of AFP in detecting HCC has led to increased interest in identifying tumor markers with greater clinical utility.

An AFP glycoform may have greater utility as a biomarker for HCC than AFP. There are three AFP glycoforms that can be determined by the degree of fucosylation of the N-acetylglucosamine-linked sugar chain, based on their reactivity in lectin affinity electrophoresis (ability to bind the lectin Lens culinaris agglutinin, a carbohydrate binding protein isolated from lentil seeds). AFP-L1 is non-LCA binding and the major glycoform found in individuals with nonmalignant hepatopathy (e.g., cirrhosis or chronic HBV infection). AFP-L2 has an intermediate LCA binding capacity and is primarily produced by yolk sac tumors. AFP-L3 is produced by malignant liver cells, binds to LCA with high affinity, and is the major glycoform found in individuals with HCC [48, 49]. Because AFP-L3 is produced by malignant hepatocytes, its measurement helps distinguish non-malignant hepatic disease from HCC. Results from a large multicenter prospective study showed elevated AFP-L3% was the only biomarker that was predictive of HCC in multivariate analyses OR=5.2, p=0.0003 [50, 51], when compared against AFP and other biomarkers. Even more striking, is that the change in AFP-L3% over time was also a highly predictive marker of HCC, OR=7.2, p<0.0001 [50, 51]. The diagnostic sensitivity and specificity ranges from 36% to 66% and 77% to 95%, respectively [52, 53].

In addition to its important use in HCC surveillance and detection, there is reason to believe that AFP-L3% may also be indicator of biological processes that predispose to HCC, making it a good target for chemoprevention. Hepatocytes are normally organized to be polar with the basolateral side facing the circulation and the apical side forming the bile canalicular network [54]. Core fucosylated glycoproteins produced by hepatocytes in the liver are sorted such that they are directed apically and secreted into the bile. Liver-derived fucosylated glycoproteins in the circulation are thought to result from loss of polarity and adhesion of hepatocytes, which is also a common feature of cancer cells. Thus, AFP-L3 in circulation

may represent this early malignant phenotype. Additionally, fucosylated proteins may be directly related to the activation of the canonical β-catenin signaling pathway, which is often activated in HCC, suggesting a direct relationship between the alteration in glycosylation with activation of known cancer pathways [55]. The fact that AFP-L3% is widely used as a serum marker for early recognition of HCC, coupled with studies illustrating that AFP-L3 reflects biological features of HCCs, opens that possibility that AFP-L3% is a marker for biological activity important in the etiology of HCC, and may serve as an intermediate marker for chemoprevention studies for HCC.

Although the evidence is lacking with respect to statin influence on AFP-L3%, there is evidence that statins can reduce AFP. In a small randomized control trial including ~80 patients with HCC, 6 months of pravastatin (40 mg/day) was associated with significantly lower AFP levels (p=0.04) and HCC diameter (p=0.03) compared to controls [56]. By extension, statin should also reduce AFP-L3% levels, and given that AFP-L3% is a more specific marker for HCC, we feel that AFP-L3% is best suited to serve as a primary endpoint for this study. We will examine AFP as a secondary endpoint.

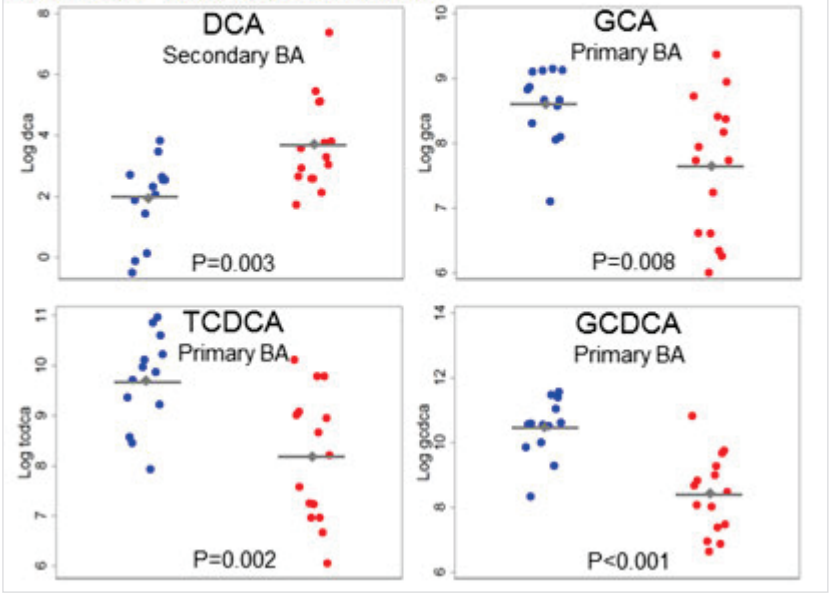
AFP and AFP-L3 will be measured simultaneously by Quest Diagnostics using an immunofluorescent liquid-phase binding assay. Ion exchange chromatography will be employed to separate AFP-L3 and non-AFP-L3 glycoforms. Fluorescence detection of the 2 chromatography fractions will be conducted. The analytic sensitivity of the assay is 0.8 ng/mL for AFP and 0.5% for AFP-L3%. The reference ranges for AFP are 1.6-4.5 ng/mL, and for AFP-L3% are 0.5-9.9 %. For cirrhotics without HCC, median AFP-L3% levels have been reported at 0.5% (25th and 75th quartiles: 0.5,1.7%) [50]. Abnormal is typically defined at >10%, and 8.4% of cirrhotics without HCC were abnormal in that prior study. In the same study, among cirrhotics who went on to develop HCC, the median for AFP-L3% was 6.1% (25th and 75th quartiles: 0.7, 21.3%). Based on a >10% cutoff, 44.1% of those who went on to develop HCC were abnormal [50].

Interleukin 6 (IL-6). It is known that the hepatic inflammatory process plays an important role in liver carcinogenesis. There is strong and consistent epidemiological evidence that elevated serum levels of IL-6 predisposes to HCC development by several years [57-60]. In healthy subjects, 14-day treatment with simvastatin (40 mg/day) resulted in a significant reduction in serum IL-6 levels [61]. The reduction of IL-6 by statin is also observed in disease states including chronic obstructive pulmonary disease and hypercholesterolemia [62, 63]. We will explore the secondary hypothesis that statins exert a suppressive effect on the key inflammatory cytokine IL-6.

Bile acids. Bile acids are the end products of cholesterol metabolism. Recently, we found that serum DCA, a secondary bile acid, was elevated in cirrhotics with HCC compared to cirrhotics without HCC, and several other bile acids were reduced in HCC cases (Figure 2). This finding with DCA is interesting in the context of a recent study reporting that DCA was necessary for hepatocarcinogenesis in a mouse model of NASH cirrhosis [64]. DCA is known to cause DNA damage by inducing mitochondrial oxidative stress, reactive oxygen species (ROS) production, and NF-kappaB (NF-kB) activation [65]. Furthermore, antioxidants have been shown to ameliorate the DCA-induced carcinogenesis [66]. Three recent studies have used global metabolomics profiling of blood to identify small molecule differences between cirrhotics with and without HCC, although the bile acid associations with HCC have been varied: DCA and taurocholic acid were elevated; lithocholic acid (LCA), glycodeoxycholic acid (GDCA), and taurochenodeoxycholic acid (TCDCA) were reduced; and glycochenodeoxycholic acid (GCDCA) and glycocholic acid (GCA) were both elevated and reduced (depending on the study) in cirrhotics with HCC compared to cirrhotics without HCC [67-69]. Prior studies have shown that statins modulate the

composition of the bile acid pool [31-35] and can lead to a reduction in the putatively hepatocarcinogenic bile acid DCA [33, 34]. We will explore the secondary hypothesis that statins modulate serum bile acid levels.

Figure 2. Plasma bile acid levels differ between cirrhotics with and without HCC. Log-transformed bile acid levels (pMoles/gram) in cirrhotics without HCC (blue dots), cirrhotics with HCC (red dots). Mean levels indicated by the gray bars. DCA=deoxycholic acid; GCA=glycocholic acid; TCDCA= taurochenodeoxycholic acid; GCDCA= glycochenodeoxycholic acid.



Liver stiffness. Recent studies have pointed to the predictive power of liver stiffness for HCC in patients with chronic hepatitis and/or cirrhosis [70-76]. Myofibroblasts are a major source of the hepatic extracellular matrix constituting the fibrous scar. Experimental studies have shown that statins can attenuate fibrosis by inhibiting activation, proliferation, and cytokine and collagen production of hepatic myofibroblasts [77, 78]. Furthermore, epidemiological studies have reported significant associations between statin use and fibrosis regression in patients with advanced fibrosis [39, 79, 80]. Reducing or reversing fibrosis and cirrhosis may create a less favorable environment for tumor development. FibroScan® examination is a non-invasive measurement of liver fibrosis. The advantage of FibroScan over biopsy is that it provides a look at the state of the liver globally, as opposed to a biopsy where only a very small sample is measured. A test result of >20 kPa (kilopascal) is generally associated with an increased HCC risk [81]. Another non-invasive measure of liver fibrosis is the Fibrosis 4 index (FIB-4) [82]. The FIB-4 index is calculated as follows: FIB-4 = (Age × AST (U/L)) ÷ (PLT (10^9/L) × (√ ALT (U/L)). High values of FIB-4 are associated with increased risk of hepatocellular carcinoma [83, 84]. Although there is limited data regarding statin use and liver stiffness, data show that statin use is significantly associated with a reduced risk of fibrosis progression among patients with chronic HCV infection [79, 85]. Thus, we will explore the secondary hypothesis that a statin intervention reduces liver stiffness as measured by FibroScan and the FIB-4 Index.

MELD. As described in Section 2.1, over the last decade the growing crisis of insufficient livers for transplantation has led to a near doubling of the transplant wait time. In addition to increasing the risk for developing HCC, this increased wait time also increases the risk for waitlist dropout due to mortality. The Model for End-Stage Liver Disease (MELD) is a validated predictor of survival among different populations of patients with advanced liver disease [86-89]. MELD score is calculated using a patient's values for serum bilirubin, serum creatinine, serum sodium, and the international normalized ratio for prothrombin time (INR). This version of the MELD calculation (MELD-Na) is the United Network for Organ Sharing (UNOS) 2016 modification of the original model to include serum sodium as a factor. The score is calculated as:

MELD = 9.57 x ln(creatinine [mg/dL]) + 3.78 x ln(total bilirubin [mg/dL]) + 11.2 x ln(INR) + 6.43
MELD-Na = 1.32 x (137 – sodium [mEq/L]) – [0.033 x MELD x (137 – sodium [mEq/L])]

If the patient has been dialyzed at least twice within the last 7 days, then the factor used for serum creatinine should be 4.0. Any value less than one is given a value of 1 (i.e., if bilirubin is 0.8 a value of 1.0 is used) to prevent the occurrence of scores below 0 (because any positive value below 1 the

natural logarithm would yield a negative result). The upper limit of serum creatinine is capped at 4.0. The lower limit of serum sodium (Na) is capped at 125, and the upper limit is capped at 137.

The major use of the MELD score has been in allocation of organs for liver transplantation, a system which was implemented in 2002. Although statin use has been associated with lower risk of mortality and transplantation in observation studies [90], the effect of a statin intervention on MELD has not been examined.

Statin Use in Cirrhosis. Statins have been used clinically for a long time, and in most settings have a very favorable toxicity profile [91]. Historically, there has been reluctance to prescribe statins to patients with preexisting liver disease due concerns of causing an elevation in liver enzymes and/or inducing diabetes [92]. However, in recent years, a benefit of statin use has proven to outweigh the potential for adverse events in the liver disease population: statins have been shown to delay liver disease progression, improve survival, reverse non-alcoholic steatohepatitis, and ameliorate metabolic syndrome [85, 93, 94]. Even so, currently, only 5% of registered liver transplant patients at Cedars-Sinai Medical Center (CSMC) are on a statin, according to their medical records. Therefore, given the overall potential benefit of statins in patients with liver disease, and the current lack of widespread clinical implementation, we are well-positioned to conduct this randomized study of statins in a low-exposure population that has a great deal to gain from its use.

3. SUMMARY OF STUDY PLAN

Design Overview. We will conduct a randomized double-blinded, placebo-controlled Phase II trial of statin to reduce disease progression in 80 patients with liver cirrhosis enrolled at four study sites: Cedars-Sinai Medical Center (CSMC), Northwestern University Feinberg School of Medicine (NWU), Georgetown University/MedStar Georgetown University Hospital (GU), and the University of Puerto Rico Comprehensive Cancer Center (UPR). We will focus on patients with a current Model for End-Stage Liver Disease (MELD) ≤ 20 to increase the likelihood that they will be healthy and transplant-free for the duration of the 6-month intervention and follow-up. Cirrhotics, given their high risk of developing HCC, have the potential to derive the maximum benefit from an intervention that could delay the progression to HCC.

Eighty patients will be randomized to simvastatin or placebo (40 in the simvastatin arm, 40 in the placebo arm). Assuming that ~10% of the study participants drop-out, we expect to have data on a final sample of 72 men and women (36 simvastatin, 36 control) completing the 6-month follow-up visit (Study Visit 4). Clinical and research measurements will be taken at baseline (Study Visit 1), month 1 (Study Visit 2), month 3 (Study Visit 3), and month 6 (Study Visit 4). The 6-month intervention duration was chosen because it corresponds to 1) mandated interval for clinical follow-up for those who are on the transplant waitlist, and 2) widely recommended interval for HCC surveillance in high risk cirrhotic patients based on tumor doubling time [95, 96]. In addition, a prior study showed that 6 months of statin intervention led to a decrease in serum AFP, which was not the case after only 3 months on statin [56].

Screening, Recruitment, and Consent. Medical charts of patients who have an upcoming appointment with a study hepatologist will be reviewed for age, cirrhosis diagnosis, prior liver transplant, prior statin use, prohibited concomitant medications, previous malignancies, medical contraindications, laboratory results, and evidence of HCC from last abdominal image (ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)) occurring within the past 18 months. If a patient's lab results in the medical record do not meet the eligibility criteria, the patient may still be considered potentially eligible because blood tests will be done for the Screen 1 visit and reviewed by a study hepatologist. An information packet that introduces the study may be mailed to potentially eligible patients approved for contact by a study hepatologist. The packet will include the study consent form (ICF), HIPAA

authorization, and IRB-approved recruitment materials (e.g., introductory letter, leaflet; each participating site will choose what materials to include). One of the study hepatologists or clinical research staff will call potentially eligible patients before their scheduled appointment to introduce the study and answer questions. Patients will be encouraged to review the consent documents with family, friends, and/or other physicians. The patient will be told that the decision to join or not join the study will not affect the medical treatment that s/he receives, and that s/he can withdraw from the study at any time. Patients who wish to participate will be consented into the trial at their next standard of care visit with a study hepatologist.

For potentially eligible patients who may not be mailed a recruitment packet in advance of the regular clinic visit (e.g., new patients or patients added to the schedule late), a study hepatologist will introduce the study to the patient during the standard of care clinic visit. The patient may be given a study information packet to take home for review. Clinical research staff will be present at the clinic during this visit and will be available to review the materials in the information packet with the patient and answer questions about the study. Clinical research staff will follow-up with a phone call to the patient a few days later to evaluate interest in study participation and answer additional questions. Interested patients will be scheduled to sign informed consent documents with the study hepatologist or a member of the clinical research team. Patients who have had all their questions about the study answered on the day they first learn about the study, and who wish to participate, may be consented the same day they are first informed of the research.

Written consent will be obtained after all clinical options have been presented and before any research related procedures are initiated. Consented patients will undergo additional screening and testing at the clinic to confirm eligibility and safety of statin initiation. The study hepatologist will thoroughly review the patient's medical history, concomitant medications, and laboratory test results and evaluate all inclusion and exclusion criteria. Patients will undergo blood tests to confirm eligibility. If a patient's lab results are current (within the past 30 days) in the medical record and within eligibility range, blood will not be drawn for lab testing at the Screen 1 visit. Otherwise, blood will be drawn to confirm eligibility. Because statins are known to be teratogenic, women who are able to become pregnant will be required to have a urine pregnancy test. Women ≥ 50 years of age who have not had a menstrual period in the past year; and women who have had a hysterectomy, both ovaries removed, or a tubal ligation; will not be required to have a pregnancy test. Patients with a MELD score >20, AST/ALT >5x ULN, or other lab results that do not meet the eligibility criteria; and women who are pregnant will be excluded from the study. Patients who qualify for the study after the eligibility evaluations will be registered and enrolled in the study and randomized to the intervention (simvastatin or placebo).

Study Visits. There will be four study visits: Study Visit 1 (baseline measurements and initiation of the intervention) will occur 0-30 days after the eligibility screening visit; Study Visit 2 (30 days after initiation of the intervention); Study Visit 3 (3 months after initiation of the intervention); and Study Visit 4 (6 months after initiation of the intervention). Each study visit will include a medical history and medications review; vital signs and symptom assessment; ECOG performance status; and a blood draw. A risk questionnaire (interviewer-administered) and food frequency questionnaire (self-administered) will be done at baseline (Study Visit 1). A liver elastography (FibroScan) examination will be done at the baseline and 6-month visits (Study Visits 1 and 4). An abdominal image (CT, MRI, or ultrasound) will be taken at Study Visit 4.

Study Measurements. Following is a brief description of study measurements.

Medical history, medications, and laboratory test results review. Medical history, concomitant medications, and laboratory test results will be reviewed at Study Visits 1, 2, 3, and 4 by one of the study hepatologists or the clinical research staff.

Vital signs and symptom assessment. Participants will have a vital signs and symptom assessment at Screen 1 and Study Visits 1, 2, 3, and 4. Each assessment will include an interval symptom history; ECOG performance status; vital signs, including blood pressure, heart rate, and temperature; and measurement of weight. Height will be measured at Study Visit 1. A physical assessment, including assessment of liver disease sequelae (varices, ascites, and encephalopathy) will be done at Screen 1 and Study Visit 4.

Blood specimen. A blood specimen (approximately 15 mL) will be collected from patients at the Screen 1 eligibility visit for blood tests to confirm eligibility. If a patient's lab results are current (within the past 30 days) in the medical record and within eligibility range, their blood will not be drawn at the Screen 1 visit. Otherwise, the patient's blood will be drawn to confirm eligibility. A Complete Blood Count and Automated Differential (CBDF), a Comprehensive Metabolic Panel (CMPL), and Prothrombin Time (PT/INR) will be done to confirm that blood levels are within the eligibility requirements (acceptable organ function, AST/ALT ≤5x upper limits of normal, and MELD ≤ 20).

A blood specimen (approximately 10-15 mL) will be collected from each participant at Study Visits 1, 2, 3, and 4 for laboratory blood tests to monitor for potential adverse effects of the intervention. A Lipid Panel and hemoglobin A1C will be done at Study Visits 1, 3, and 4. A Complete Blood Count and Automated Differential (CBDF) and Comprehensive Metabolic Panel (CMPL) will be done at Study Visits 2, 3, and 4. Creatine Phosphokinase (CPK) will be measured at Study Visit 1. Prothrombin Time (PT/INR) will be done at Study Visit 4 to calculate the MELD score. Clinical lab results from Screen 1 and Study Visit 4 will be used to calculate the MELD and FIB-4 scores.

An additional blood specimen (20 mL) will be collected from each participant at Study Visits 1 and 4 for research purposes. Ten mL of blood will be drawn for measurement of protocol-specific biomarkers (AFP, AFP-L3%, IL-6, and bile acids) and 10 mL of blood will be drawn for DNA extraction and use in future studies.

Liver elastography (FibroScan). A FibroScan examination will be conducted at Study Visits 1 and 4. Participants will be instructed to refrain from eating for 3 hours before the FibroScan examination. The test result provides a look at the state of the liver globally, as opposed to a biopsy where only a very small sample is measured. The FibroScan will be used as a non-invasive measurement of liver stiffness.

Abdominal imaging. Abdominal imaging is done every 6 months for HCC surveillance and is standard of care in this high-risk study population. Typically, imaging occurs within a few weeks prior to the patient's clinical appointment with hepatology, and we will require that eligible patients for this trial have had imaging done (CT, MRI, or ultrasound) within 18 months prior to Study Visit 1 to assure that there is no HCC present prior to enrollment. Another abdominal image will be taken for all trial participants at Study Visit 4, which will be another standard of care procedure.

Baseline risk factor questionnaire. A structured questionnaire developed for this investigation will be administered at Study Visit 1 in either Spanish or English, according to each participant's preference. The interview will elicit information on detailed race/ethnicity; education and marital status; medical and medications history; alcoholic beverage consumption; tobacco smoking; and anthropometry including weight at different decades of life. Reporting of alcohol use is sensitive for cirrhotics, as it is a factor in their transplant eligibility. Nevertheless, prior studies have found that one-third of registered participants are active drinkers [97]. We will use a three-item alcohol questionnaire, the Alcohol Use Disorders Identification Test for Alcohol Consumption (AUDIT-C), comprised of the first three questions from the Alcohol Use Disorders Identification Test (AUDIT) proposed by the World Health Organization for the assessment of hazardous drinking in primary care, which is 83.5% accurate at identifying active alcohol

users from a liver transplant waitlist population [97].

Food frequency questionnaire (FFQ). A food frequency questionnaire (FFQ) will be administered at Study Visit 1 to capture usual diet over the last 90 days using VioScreen®, a graphical dietary assessment that has been validated against traditional paper-based FFQs, available in English and Spanish [98]. The VioScreen® is a self-administered electronic questionnaire that participants will complete online using a computer or tablet. Food items and components that are of particular interest include total fat, saturated fat, carbohydrate, dietary fiber, coffee, and antioxidants, based on prior publications reporting associations with HCC [99-112]. Please see Appendix J for VioScreen® instructions for participants.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Confirmed diagnosis of liver cirrhosis assessed by the presence of clinical signs, symptoms, body imaging (ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)), or liver biopsy

4.1.2 Age ≥18 years

4.1.3 ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix A)

4.1.4 Participants must have acceptable organ, hepatic and renal function as defined below:

Leukocytes	≥2,500/microliter
Absolute neutrophil count	≥1,500/microliter
Platelets	≥50,000/microliter
Hemoglobin	≥8 g/dL
Total bilirubin	≤3 × institutional upper limit of normal (ULN)
AST (SGOT)/ALT (SGPT)	≤5 × institutional ULN
Creatinine	≤1.5 × institutional ULN

Patients whose lab results meet the inclusion criteria after the Screen 1 blood tests will be included in the trial.

4.1.5 Women who are able to become pregnant must have a confirmed negative pregnancy test result prior to enrollment. Women ≥ 50 years of age who have not had a menstrual period in the past year; and women who have had a hysterectomy, both ovaries removed, or a tubal ligation; will not be required to have a pregnancy test.

4.1.6 The effects of simvastatin on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women who are able to become pregnant must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.1.7 Ability to understand and the willingness to sign a written informed consent document and medical release

4.1.8 Willing and able to comply with trial protocol and follow-up

4.1.9 Have had an abdominal imaging test (CT, MRI, or ultrasound) within the past 18 months

4.2 Exclusion Criteria

4.2.1 Prior or current use of statin medication

4.2.2 Current systemic use of medications known to interact with statins and potentially increase toxicity, including gemfibrozil, cyclosporine, danazol, lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine, strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, or cobicistat-containing products), or strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin)

4.2.3 History of adverse effects, intolerance, or allergic reactions attributed to compounds of similar chemical or biologic composition to simvastatin (i.e., other statin medications)

4.2.4 Current use of any other investigational agents

4.2.5 Women who are pregnant or breastfeeding. Pregnant women are excluded from this study because simvastatin is a lipid-lowering agent with the potential for teratogenic or abortifacient effects. It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with simvastatin, breastfeeding should be discontinued if the mother is treated with simvastatin.

4.2.6 Prior liver transplant

4.2.7 Prior known or suspected hepatocellular carcinoma

4.2.8 Prior cholangiocarcinoma

4.2.9 Model for End-Stage Liver Disease (MELD) >20

4.2.10 Any lab results that do not meet inclusion criteria 4.1.4 after the Screen 1 blood tests

4.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

4.2.12 History of chronic myopathy

4.2.13 Prior germ cell cancer

4.2.14 History of active malignancy within the past 5 years (excluding basal/squamous cell skin cancer or prostate cancer with a Gleason score 6 or less)

4.2.15 Known active infection with HIV

4.2.16 Medical contraindications to blood draw (e.g., hemophilia)

4.2.17 Concurrent illness which in the opinion of the investigators would compromise either the patient or the integrity of the data

4.2.18 Current excessive alcohol consumption (average alcohol consumption of more than 5 drinks per day)

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.4 Recruitment and Retention Plan

Source Population. Participants will be recruited from all eligible patients who have a confirmed diagnosis of cirrhosis assessed by the presence of clinical signs, symptoms, body imaging (ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)), or liver biopsy. Patients will not be restricted on the basis of their cirrhosis severity, but Child Pugh classification will be captured and considered in statistical analysis. We will recruit patients from hepatology clinics and will target patients who are currently waitlisted, or under evaluation, for a liver transplant. However, patients who are inactive on the waitlist, or ineligible for a transplant, will still be eligible for this trial, since many attend hepatology clinics on the same 6 month schedule as those who are waitlisted. Compared to other transplant centers in the region, patients awaiting a liver transplant at CSMC tend to be lower acuity (94% have a MELD ≤ 20 compared to 80% regionally and 85% nationally), providing the study team access to a large number of patients who are likely to remain listed and healthy for the 6 month trial duration [113]. At NWU, GU, and UPR, a smaller proportion (79%, 78%, 69% respectively) of patients listed are expected to have a MELD ≤ 20. However, among the four institutions, we will have a substantial pool of patients to select from for this trial (see Figure 3) . CSMC and NWU liver transplant waitlist candidates are all adults (≥18 years old); 95% of GU's and 98% of UPR's candidates are adults. Among the four institutions, about 65% are male, and about 81% are between 18 and 65 years old [113]. A large proportion (40%) of the CSMC liver transplant candidates are Hispanic/Latino, more than twice the national average of liver transplant candidates (18%). Coupled with a majority Hispanic/Latino liver transplant population at UPR, this provides a unique opportunity to test an intervention for a cancer that is the most burdensome to this large, growing, and understudied demographic group [113]. We will make every attempt to enroll and retain Hispanic participants, particularly Spanish monolingual participants, by using interpreters and study materials (e.g., ICFs, study information sheets, questionnaires) translated into Spanish). In 2015, 12% of patients listed for a liver transplant at CSMC indicated that Spanish was their preferred language.

Recruitment and Feasibility. Recruitment will occur over 12 months and will target patients who are attending a usual care appointment at the transplant hepatology clinics at CSMC, NWU, GU, and UPR. Most of these patients are on the waiting list for a liver transplant. Based on the most recent Scientific Registry of Transplant Recipients (SRTR) report and data on patients registered for a liver transplant during July, 2016-June, 2017, we expect that there will be approximately 187 (CSMC), 77 (NWU), 269 (GU), and 15 at UPR patients actively registered for a liver transplant at the start of the study, and that over the course of 12 months, 110 new patients will be added at CSMC, 140 at NWU, 224 at GU, and 55 at UPR [113]. Thus, over the 12-month recruitment period for this study, we will have access to 1077 patients awaiting liver transplant. Major exclusion criteria include MELD ≥20 (~30%), prior HCC or cholangiocarcinoma (~5%), prior or current use of statins (~10%), and prior liver transplant (~5%). We estimate that 15% of patients not excluded for the previously stated reasons, will be excluded for other less common reasons. Thus, we are anticipating that 65% of the source population will be ineligible for the study, leaving 377 or 35% of the source population eligible. Based on prior experiences recruiting similar patients into trials, our expectation is that we will obtain consent from ~24% of eligible patients (target n=90), and that 80 patients (21% of eligible patients) will pass the Screen 1 evaluations and be randomized to the study intervention.

We are expecting the composition of our study population to be 75% white, 16% Black or African American, and 9% Asian (Table 1).

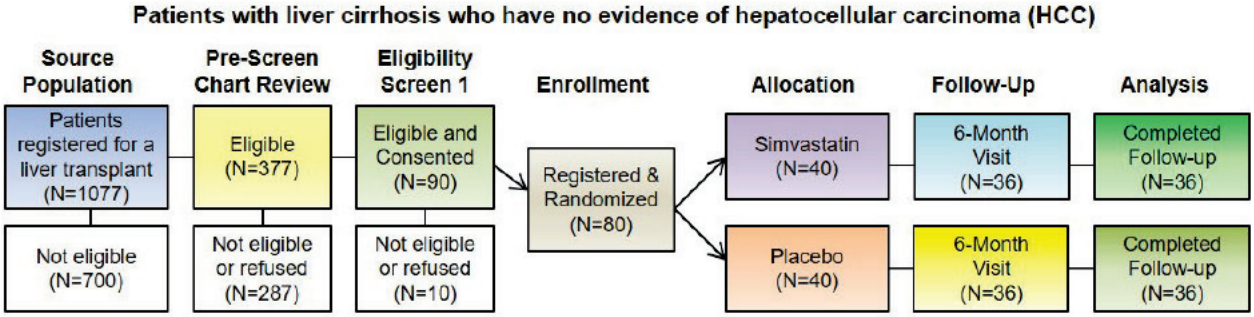
Table 1. Projected Enrollment by Race and Ethnicity

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	2	5	0	0	7
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	8	0	0	13
White	13	23	9	15	60
More Than One Race	0	0	0	0	0
Total	20	36	9	15	80

These proportions are based on recent SRTR data for the number of people awaiting transplant at CSMC, NWU, GU, and UPR and are aligned with the racial proportions of liver waitlist registrations nationally. We estimate that 30% of our study population will be Hispanic or Latino, which is greater than the proportion of Hispanics awaiting a transplant nationally (18%).

In an effort to minimize participant burden and increase the likelihood of enrollment and follow-up, we will "piggy-back" two out of four study visits onto usual care appointments, and we have chosen non-invasive primary and secondary endpoints (blood tests and FibroScan). Thus, based on our large eligible source population, low participant burden of study activities, and importance of our objectives to our hepatology colleagues and their patients, our recruitment goal of 80 patients over 12 months is highly feasible. Assuming that ~10% of the study participants drop-out, we expect to have data on a final sample of 72 men and women (36 simvastatin, 36 control) completing the 6-month follow-up visit (Figure 3).

Figure 3. Trial Profile



Pre-Screen Medical Chart Review – Initial determination of eligibility and recruitment. Patients who have an upcoming usual care appointment with a study hepatologist will be identified and pre-screened for eligibility based on the most updated information in their medical charts, prior to their visit. The medical records will be reviewed by the clinical research staff to determine initial eligibility as specified in the inclusion and exclusion criteria. Medical charts will be reviewed for age, cirrhosis diagnosis, prior liver transplant, prior statin use, prohibited concomitant medications, previous malignancies, medical contraindications, laboratory results, and evidence of HCC from last abdominal image (ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)) occurring within the past 18 months. The research staff will notify the study hepatologist that a patient is potentially eligible for the trial based on the pre-screen evaluation. The hepatologist will review the eligibility information and notify research staff whether the patient may be considered for participation. An information packet that introduces the study may be mailed to potentially eligible patients who may be

considered for participation. The packet will include the study consent form (ICF), HIPAA authorization, and IRB-approved recruitment materials (e.g., introductory letter, leaflet; each participating site will choose what materials to include). One of the study hepatologists or clinical research staff will call potentially eligible patients before their scheduled appointment to introduce the study and answer questions. Patients will be encouraged to review the consent documents with family, friends, and/or other physicians. The patient will be told that the decision to join or not join the study will not affect the medical treatment that s/he receives, and that s/he can withdraw from the study at any time. Patients who wish to participate will be consented into the trial at their next standard of care visit with a study hepatologist.

For potentially eligible patients who may not be mailed a recruitment packet in advance of the regular clinic visit (e.g., new patients or patients added to the schedule late), a study hepatologist will introduce the study to the patient during the standard of care clinic visit. The patient may be given a study information packet to take home for review. Clinical research staff will be present at the clinic during this visit and will be available to review the materials in the information packet with the patient and answer questions about the study. Clinical research staff will follow-up with a phone call to the patient a few days later to evaluate interest in study participation and answer additional questions. Interested patients will be scheduled to sign informed consent documents with the study hepatologist or a member of the clinical research team. Patients who have had all their questions about the study answered on the day they first learn about the study, and who wish to participate, may be consented the same day they are first informed of the research.

We estimate that 377 of the patients registered for a liver transplant during the 12-month recruitment period will be potentially eligible. Cirrhotics who are eligible and not listed for transplant may also be recruited.

Screen 1 Consent and Final determination of eligibility. The study hepatologist will review the study details and answer any questions regarding the proposed trial after all clinical options have been presented to the patient. After the patient's questions have been answered, the study hepatologist will obtain signatures on the consent documents from patients who are eligible based on the pre-screen chart review and wish to volunteer for the study. Patients for whom Spanish is their preferred language will be consented using a version of ICF translated into Spanish, administered by an interpreter. The patient will carefully review and sign the study consent form and HIPAA authorization. Copies of each form will be given to the patient and placed in the medical record. Participants who sign consent will be provided a copy of Appendix D (Food and Medications to Avoid During Your Participation in the Study). We anticipate that we will obtain consent from 90 patients. Written consent will be obtained before any research related procedures are initiated. After consent has been obtained, a final assessment of eligibility will be conducted. Consented patients will undergo additional screening and testing to confirm eligibility and safety of statin initiation.

The study hepatologist will thoroughly review the patient’s medical history, concomitant medications, and laboratory test results and evaluate all inclusion and exclusion criteria. A blood specimen will be collected from patients for blood tests to confirm eligibility. If a patient’s lab results are current (within the past 30 days) in the medical record and within eligibility range, their blood will not be drawn at the Screen 1 visit. Otherwise, the patient’s blood will be drawn to confirm eligibility. A Complete Blood Count and Automated Differential (CBDF) (for leukocytes, neutrophils, platelets, and hemoglobin), a Comprehensive Metabolic Panel (CMPL) (for liver enzymes (AST/ALT) and for total bilirubin, creatinine, and sodium (required for calculation of the MELD score)), and Prothrombin Time (PT/INR) (required for calculation of MELD) will be done to confirm that blood levels are within the eligibility requirements (acceptable organ function, AST/ALT 3≤5x upper limits of normal, and MELD ≤ 20). Because statins are known to be teratogenic, women who are able to become pregnant will be required to

have a urine pregnancy test. Women ≥ 50 years of age who have not had a menstrual period in the past year; and women who have had a hysterectomy, both ovaries removed, or a tubal ligation; will not be required to have a pregnancy test. Patients with a MELD score >20, AST/ALT >5x ULN, or other lab results that do not meet the eligibility criteria; and women who are pregnant will be excluded from the study. Following eligibility screening, and prior to Study Visit 1, consented patients who qualify for the study after the eligibility evaluations will be registered and enrolled in the study and randomized to the intervention (simvastatin or placebo).

There will be four study visits. Study Visit 1 (baseline measurements and initiation of the intervention) will occur 0-30 days after the Screen 1 eligibility visit. Follow-up visits will be scheduled at 1 month (± 14 days), 3 months (± 14 days), and 6 months (± 30 days) after initiation of the intervention to avoid protocol violations. Study visits will coincide whenever practicable with usual care appointments to reduce travel time and to increase compliance with the study protocol. Participants will receive $50 when they complete the Screen 1 testing and $100 at the completion of each study visit for their time, transportation, parking, and other expenses related to the study. Participants who complete the entire study – the Screen 1 eligibility testing and four study visits – will receive $450.

Compensation schedule

Screen 1	Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4
$50	$100	$100	$100	$100

The participant will be contacted by telephone 5-7 days prior to the scheduled study visit to confirm or reschedule his/her visit. If a study participant misses his/her visit study visit, s/he will be called promptly to reschedule. The study coordinator will have a database which tracks active participants who do not have a scheduled visit or who have missed their targeted visit date. Study visits will be rescheduled for up to 2 months until the participant is considered lost to follow-up.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

Eighty participants with liver cirrhosis will be randomized into one of 2 groups: 40 participants will receive 40 mg simvastatin per day and 40 participants will receive a placebo identical in color, consistency, and appearance to simvastatin 40 mg. Simvastatin and placebo will be provided as over-encapsulated tablets. Dosing will extend for 6 months.

- Agent(s): Simvastatin and placebo
- Daily dose(s) and regimen(s) for each agent: One 40 mg capsule per day
- Duration for each agent: Daily treatment for 6 months

The usual recommended dose of simvastatin is 10-40 mg/day, and the toxicity and tolerability are comparable for 20 mg and 40 mg [23]. In a prior published trial of patients with chronic hepatitis or cirrhosis, statin dosing began at 20 mg and was titrated up to 40 mg, and no serious side effects or discontinuation of therapy were noted [56]. Thus, we feel that a 40 mg dose will be well-tolerated by the participants in this trial.

5.2 Study Agent Administration

Patients will self-administer the 40 mg capsule of simvastatin or placebo daily in the evening. Patients will be instructed to take the study agent at bedtime or with an evening meal. Each participant will be given/shipped one bottle of 120 capsules at Study Visit 1 (90-day supply + buffer) and one bottle of 120 capsules (90-day supply + buffer) at Study Visit 3 (Month 3).

5.3 Run-in Procedures

None.

5.4 Contraindications

Patients are advised not to consume any form of grapefruit (e.g., juice, fruit, grapefruit seed extract, dietary supplements containing grapefruit) while on simvastatin as grapefruit may increase the blood levels of simvastatin [114]. Participants enrolled in the study will be instructed to avoid all forms of grapefruit.

The combined use of simvastatin with systemic formulations of gemfibrozil, cyclosporine, danazol, lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine, or strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and cobicistat-containing products) is contraindicated due to an increased risk for myopathy. Patients will be screened for contraindications to simvastatin prior to enrollment in the study. Patients with known active infection with HIV will be excluded from the study. Patients will be advised not to use contraindicated medications during the study and will be excluded if systemic use of any contraindicated medication is unavoidable. Concomitant medications will be reviewed at study visits and during follow-up telephone calls. Participants will be closely monitored for symptoms and side effects to the study drug and will be instructed to call the study doctor immediately if they have a serious adverse reaction.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included.

5.6 Dose Modification

No dose modifications are planned. The study agent will be stopped in the event of an AE ≥ grade 3 considered possibly, probably, or definitely related to the study agent. The study agent will be restarted after resolution. One of the common side effects of statin medication is myalgia (muscle pain with normal Creatine Phosphokinase (CPK) level), and rarely this is associated with statin myopathy (muscle weakness or other muscle injury with or without elevation in CPK level). In randomized controlled trials of standard dose statin therapy, the risk is very low (<1%). We will measure levels of CPK in the blood drawn at the first study visit to establish a patient-specific reference for this indicator of muscle toxicity. During the trial, if the participant reports unexplained muscle pain or weakness, CPK will be tested again to check for elevation.

The study agent will be permanently discontinued in subjects experiencing grade 3 or greater myopathy (unexplained muscle symptoms *and* CPK > 5 times ULN) or hepatotoxicity (ALT or AST > 5 times

ULN) that is considered possibly, probably, or definitely related to the study agent. The study agent will be permanently discontinued in subjects experiencing the following grade 2 hepatotoxicities considered possibly, probably, or definitely related to the study agent: (1) hemorrhage requiring medical attention, and (2) symptomatic fistulas. All other grade 2 hepatotoxicities can be restarted after resolution.

Because dose modification could lead to lack of dose homogeneity that may impair the research objectives, we will stop the intervention in patients who initiate drugs that require dose modifications of simvastatin below 40 mg: lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, or ranolazine.

5.7 Adherence/Compliance

Compliance will be measured by pill counts and patient diaries. For telehealth visits, we will ask participants to photograph unused pills for remote pill counts and patient pill diaries and compliance will be assessed remotely. Compliance is defined as 85% of the total dose over the entire study period. A participant diary will be used to monitor daily compliance (Appendix C). Participants will be instructed to record the time the study drug was taken each day in the diary, as well as any potential side effects. Diaries will be reviewed and compliance will be assessed at Study Visits 2-4.

Phone calls will be made to study participants every four weeks (± 7 days) to monitor compliance. Participants will be asked if they missed any doses of medication, and the dates of all missed doses will be recorded. The study agent diary will be reviewed with participants at every visit. Participants who report having taken < 85% of the study drug doses between phone calls, or whose pill count at a study visit reveals < 85% compliance, will be called every two weeks (± 3 days) to monitor compliance.

The participant will be asked at registration if they would like to receive reminder emails or text messages regarding the study medication. Messages will be sent daily for the first week; in following weeks, messaging will be targeted to participants having difficulty remembering their dose. In addition, phone calls will be made to all study participants during the week before their final visit (Visit 4) to remind them to take the study drug every day until the last study visit. Participants will also be reminded to bring any leftover study drugs and the study diary with them to each visit.

Capsule counts will be performed at Study Visits 2, 3, and 4 to assess compliance. If less than 85% of the dose has been consumed during the study period, the subject will be considered non-compliant. All participants that receive a study agent for any period of time will be evaluable for toxicity.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND# [redacted] (Exempt), IND Sponsor: NCI/Division of Cancer Prevention)

Simvastatin (Zocor) 40 mg and simvastatin placebo will be supplied by NCI, DCP. Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, and catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. It is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol, and ethanol. Simvastatin tablets for oral administration contain 40 mg of simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose,

hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.

Information on the placebo will be provided when available.

6.2 Reported Adverse Events and Potential Risks

The most common reported adverse events (incidence ≥5.0%) are upper respiratory infection, headache, abdominal pain, constipation, and nausea. Other adverse events reported in clinical trials (<5%) were diarrhea, rash, dyspepsia, flatulence, and asthenia.

Persistent increases in serum transaminases (to more than 3× the ULN) have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated.

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness, or weakness with creatine kinase above ten times the ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment. The risk of myopathy, including rhabdomyolysis, is dose related. The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, the antidepressant nefazodone, cobicistat-containing products, or grapefruit-containing products. Combination of these drugs with simvastatin is contraindicated. If short-term treatment with strong CYP3A4 inhibitors is unavoidable, therapy with simvastatin must be suspended during the course of treatment.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including simvastatin.

6.3 Availability

Simvastatin and matching placebo are investigational agents supplied to investigators by DCP, NCI. Simvastatin 40 mg and matching placebo will be supplied as over-encapsulated tablets for oral administration. Simvastatin and matching placebo will be packaged with 120-count 40 mg capsules per bottle. Each participant will be given/shipped one bottle at Study Visit 1 and one bottle at Study Visit 3 (Month 3). Please see the NWU2015-06-03 pharmacy manual for shipping procedures.

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of NCI Central IRB (CIRB) approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each

Organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing, and final disposition of study agent. This responsibility has been delegated to the study pharmacists: Annie Yi, Pharm.D., Investigational Drug Pharmacist at Cedars-Sinai Medical Center; Jane Regalado, Pharm. D., Investigational Drug Pharmacist at Northwestern Memorial Hospital; Khang Ho, Pharm.D. at Georgetown University, and Elsa Pedro, Pharm.D. at the University of Puerto Rico. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

Simvastatin and placebo will be packaged by NCI, DCP.

Each bottle will be labeled with a one-part label identifying study specific information, such as study title, DCP protocol number, dosing instructions, recommended storage conditions, the name and address of the distributor, randomization number, and a caution statement indicating that the agent is limited by United States law to investigational use only and the agent should be kept out of reach of children.

6.7 Storage

The DCP Drug Repository, MRIGlobal, will distribute the study agent directly to each participating site. Study agents will be stored in a safe, secure, temperature monitored limited access drug storage area specifically for research medication at the Research Pharmacy at each site. Study agents shall be maintained at a controlled room temperature [between 15-30°C] by the Research Pharmacy at each site and once dispensed, the subjects will be instructed to store the drug in their homes protected from light, heat, and moisture. MRIGlobal will be notified in the event of a temperature excursion below 15°C or above 30°C for 24 hours continuously. MRIGlobal will evaluate the temperature excursions on a case-by-case basis.

6.8 Registration/Randomization

1. A study coordinator must upload into the Northwestern Clinical Trials Management System, a signed and complete informed consent along with HIPAA authorization and a completed eligibility form for each participant identified as eligible to be entered into the study.
2. All participants must be registered in the Northwestern University Robert H. Lurie Comprehensive Cancer Center Clinical Trials Management System (CTMS). Participants must not start protocol treatment prior to registration in the Lurie Cancer Center CTMS.
3. After registration in the CTMS, participants will be assigned a participant identification number and a randomization number when applicable.
4. An NCPC Quality Assurance Monitor will submit the following into the REDCap Randomization Information Form: (1) Study Number, (2) Site, (3) Pharmacist Email(s), (4) Participant ID, (5) Participant Initials, and (6) Randomization Date.
5. An Automatic Treatment Assignment Notification email will be sent to the research pharmacist(s) containing: (1) Study Number, (2) Site, (3) Participant ID, (4) Participant Initials, (5) Randomization Date, and (6) Treatment Assignment.
6. The clinical research coordinator(s) will receive a Confirmation of Registration containing the PID via email.
7. The following people will have a copy of the un-blinded randomization log: the study statistician at NU, the Quality Assurance Team at NU, and the Investigational Pharmacists at each site. The following people will have access to the REDCap study project containing randomization information: the study statistician at NU and the Quality Assurance Team at NU. The study statistician will set up randomization blocks.

When possible, the study coordinator will notify an NCPC Quality Assurance Monitor and/or send an email to ncpc@northwestern.edu prior to registering a participant. Prior notification is required for participant randomizations outside the normal business hours of Monday-Friday 9:00am-5:00pm CT.

6.9 Blinding and Unblinding Methods

The research pharmacist will manage the investigational agent. The blind will be maintained through the effort of the research pharmacist, and the pharmacy. Unblinding will only occur when it is deemed medically necessary, and will only take place after consultation with the NCI, DCP Task Order Monitor. If the NCI Task Order Monitor cannot be reached and the participant requires emergency care, the Study Chairman may authorize the site PI to break the blind. The date and reason for breaking the blind must be submitted by the site PI to the Study Chairman and the NCI Task Order Monitor as soon as possible.

The NCI Medical Monitor must be notified that the blind has been broken. The NCI CIRB and the IRB at the site where the blind is broken will also be notified.

DCP Medical/Task Order Monitor
Luz Maria Rodriguez, MD, FACS
NCI/Division of Cancer Prevention
9609 Medical Center Dr.
Rm 5E-228
Bethesda, MD 20892
Telephone (240) 276-7039
Fax (240) 276-7848
Email: rodrigul@mail.nih.gov

6.10 Agent Destruction/Disposal

At the completion of investigation, all unused study agent will be destroyed according to local institutional procedures. Destruction records must be provided to MRIGlobal at the end of the study.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Procedure	Pre-Screen[1]	Screen 1[2^]	Study Visit 1[3]	Study Visit 2[4]	Study Visit 3[5]	Study Visit 4[6^]	Follow-Up
Assess eligibility (review inclusion/exclusion criteria) and recruitment	X	X					
Informed Consent and HIPAA authorization		X					
Abdominal imaging (CT, MRI, ultrasound)[7]	X					X	
Review study requirements	X	X	X	X	X		
Review medical history, medications, and laboratory test results	X	X	X	X	X	X	
Blood hematology: Complete Blood Count and Automated Differential (CBDF)		X	X	X	X	X	
Blood chemistry: Comprehensive Metabolic Panel (CMPL)		X	X	X	X	X	
Blood test: Prothrombin Time (PT/INR)		X				X	
Urine pregnancy test[8]		X					
Registration and randomization to simvastatin or placebo		X					
Demographics (race, ethnicity, education)			X				
Assess symptoms and ECOG performance status		X	X	X	X	X	
Physical assessment, assess liver disease sequelae		X				X	
Vital signs assessment, measure weight		X	X	X	X	X	
Blood test: Lipid Panel			X		X	X	
Blood test: Hemoglobin A1C (HbA1C)			X		X	X	
Blood test: Creatine Phosphokinase (CPK)			X				
Collect blood specimen for research[9]			X			X	
Conduct liver elastography (FibroScan)			X			X	
Interviewer-administered risk questionnaire			X				
Self-administered VioScreen® food frequency questionnaire[11]			X				
Dispense study agent and diary			X	X	X		
Collect study agent and diary				X	X	X	
Review study diary				X	X	X	
Assess compliance (pill count)				X	X	X	
Assess adverse events				X	X	X	X
Telephone contact[10]	X	X	X	X	X	X	X
^ Screen 1 and Study Visit 4 are concurrent with standard of care visit.							

Procedure	Pre-Screen[1]	Screen 1[2^]	Study Visit 1[3]	Study Visit 2[4]	Study Visit 3[5]	Study Visit 4[6^]	Follow-Up

[1] Medical chart review for patients who are liver transplant candidates and have an upcoming appointment with a study hepatologist to determine initial eligibility; recruitment of potentially eligible patients
[2] Obtain consent of potentially eligible patients; thorough review of patient's medical history, concomitant medications, and laboratory test results; evaluation of inclusion and exclusion criteria; and assessments for final determination of eligibility. Screen 1 eligible/consented patients will be registered and randomized to the intervention (simvastatin or placebo).
[3] Study Visit 1 (baseline measurements/initiation of the intervention) will occur 0-30 days after Screen 1.
[4] Study Visit 2 will occur 1 month (± 14 days after initiation of the intervention.
[5] Study Visit 3 will occur 3 months (± 14 days) after initiation of the intervention.
[6] Study Visit 4 (last day of study intervention) will occur 6 months (± 30 days) after initiation of the intervention.
[7] Abdominal imaging results will be reviewed during pre-screen medical chart review to determine initial eligibility. An abdominal image (CT, MRI, or ultrasound), which is a standard of care procedure for the study population, will be taken at Study Visit 4. The abdominal imaging may be done up to the end of follow-up for the study (3 months after completion of Study Visit 4 [Visit 4 ± 3 months]).
[8] Because statins are known to be teratogenic, women able to become pregnant will be required to have a urine pregnancy test. Women ≥ 50 years of age who have not had a menstrual period in the past year; and women who have had a hysterectomy, both ovaries removed, or a tubal ligation; will not be required to have a pregnancy test. Women who are pregnant will be excluded from the study.
[9] Blood collection for research: A 20 mL blood specimen will be collected from each participant at Study Visits 1 and 4 for research purposes. Ten mL of blood will be drawn for measurement of protocol-specific biomarkers (AFP, AFP-L3%, IL-6, and bile acids) and 10 mL of blood will be drawn for DNA extraction and use in future studies.
[10] Telephone contact with patients during the screening period to assess eligibility, introduce the study, and answer questions. Telephone contact every four weeks (± 7 days) during the intervention to assess compliance and adverse events. Follow-up telephone contact on days 30 ± 7, 60 ± 7, and 90 ± 7 after completion of Study Visit 4 to assess adverse events.
[11] Please see Appendix J for VioScreen® instructions for participants.

7.2 Pre-Study Evaluation and Baseline Testing

7.2.1 Pre-Screen Medical Chart Review – Initial determination of eligibility and recruitment

Patients who have an upcoming usual care appointment with a study hepatologist will be identified and pre-screened for eligibility based on the most updated information in their medical charts, prior to their visit. The medical records will be reviewed by the clinical research staff to determine initial eligibility as specified in the inclusion and exclusion criteria. Medical charts will be reviewed for age, cirrhosis diagnosis, prior liver transplant, prior statin use, prohibited concomitant medications, previous malignancies, medical contraindications, laboratory results, and evidence of HCC from last abdominal image (ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)) occurring within the past 18 months. If a patient's lab results in the medical record do not meet the eligibility criteria, the patient may still be considered potentially eligible because blood tests will be done at the Screen 1 visit. The research staff will notify the study hepatologist that a patient is potentially eligible for the trial based on the pre-screen evaluation. The hepatologist will review the eligibility information and notify research staff whether the patient may be considered for participation. An information packet that introduces the study may be mailed to potentially eligible patients who may be considered for participation. The packet will include the study consent form (ICF), HIPAA authorization, and IRB-approved recruitment materials (e.g., introductory letter, leaflet; each participating site will choose what materials to include). One of the study hepatologists or clinical research staff will call potentially eligible patients before their scheduled appointment to introduce the study and answer questions. Patients will be encouraged to review the consent documents with family, friends, and/or other physicians. The patient will be told that the decision to join or not join the study will not affect the medical treatment that s/he receives, and that s/he can

withdraw from the study at any time. Patients who wish to participate will be consented into the trial at their next standard of care visit with a study hepatologist.

For potentially eligible patients who may not be mailed a recruitment packet in advance of the regular clinic visit (e.g., new patients or patients added to the schedule late), a study hepatologist will introduce the study to the patient during the standard of care clinic visit. The patient may be given a study information packet to take home for review. Clinical research staff will be present at the clinic during this visit and will be available to review the materials in the information packet with the patient and answer questions about the study. Clinical research staff will follow-up with a phone call to the patient a few days later to evaluate interest in study participation and answer additional questions. Interested patients will be scheduled to sign informed consent documents with the study hepatologist or a member of the clinical research team. Patients who have had all their questions about the study answered on the day they first learn about the study, and who wish to participate, may be consented the same day they are first informed of the research.

7.2.2 Screen 1 – Consent, Final determination of eligibility, Registration, and Randomization

The study hepatologist will review the study details and answer any questions regarding the proposed trial after all clinical options have been presented to the patient. After the patient's questions have been answered, the study hepatologist will obtain signatures on the consent documents from patients who are eligible based on the pre-screen chart review and wish to volunteer for the study. Patients for whom Spanish is their preferred language will be consented using a version of ICF translated into Spanish, administered by an interpreter. The patient will carefully review and sign the study consent form and HIPAA authorization. Copies of each form will be given to the patient and placed in the medical record. Written consent will be obtained before any research related procedures are initiated. Participants who sign consent will be provided a copy of Appendix D (Food and Medications to Avoid During Your Participation in the Study).

After consent has been obtained, a final assessment of eligibility will be conducted. Consented patients will undergo additional screening and testing to confirm eligibility and safety of statin initiation.

1. The study hepatologist will thoroughly review the patient’s medical history, concomitant medications, and laboratory test results.
2. All inclusion and exclusion criteria will be evaluated for the patient.
3. Symptom assessment and ECOG performance status
4. Physical assessment including vital signs, measurement of weight, and assessment of liver disease sequelae (varices, ascites, and encephalopathy)
5. A blood specimen (approximately 15 mL) will be collected from patients for blood tests to confirm eligibility. If a patient’s lab results are current (within the past 30 days) in the medical record and within eligibility range, their blood will not be drawn at the Screen 1 visit. Otherwise, the patient’s blood will be drawn to confirm eligibility. A Complete Blood Count and Automated Differential (CBDF) (for leukocytes, neutrophils, platelets, and hemoglobin), a Comprehensive Metabolic Panel (CMPL) (for liver enzymes (AST/ALT) and for total bilirubin, creatinine, and sodium (required for calculation of the MELD score)), and Prothrombin Time (PT/INR) (required for calculation of MELD) will be done to confirm that blood levels are within the eligibility requirements (acceptable organ function, AST/ALT ≤5x upper limits of normal, and MELD ≤ 20). See Appendix E for Clinical Laboratory Minimum Test Requirements.
6. Women who are able to become pregnant will be required to have a pregnancy test because statins are known to be teratogenic. Women ≥ 50 years of age who have not had a menstrual

period in the past year; and women who have had a hysterectomy, both ovaries removed, or a tubal ligation; will not be required to have a pregnancy test.

Patients with a MELD score >20, AST/ALT >5x ULN, or other lab results that do not meet the eligibility criteria; and women who are pregnant will be excluded from the study. Following eligibility screening, and prior to Study Visit 1, consented patients who qualify for the study after the eligibility evaluations will be registered and enrolled in the study and randomized to the intervention (simvastatin or placebo). The Screen 1 MELD calculation will be used as the baseline MELD score, and Screen 1 lab values for AST, ALT, and platelets (PLT) will be used to calculate the baseline FIB-4 score.

7.2.3 Study Visit 1 – Baseline Testing and Initiation of the intervention

Study Visit 1 (Baseline measurements) will occur 0-30 days after the Screen 1 eligibility visit. The following procedures will be performed during this visit:

1) Review of medical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Vital signs assessment, including blood pressure, heart rate, and temperature; and measurement of height and weight
4) Blood collection for clinical labs (approximately 10 mL). Laboratory blood tests will be done for a Lipid Panel, hemoglobin A1C, and Creatine Phosphokinase (CPK) to establish baseline levels prior to initiating the study agent. CBDF and CMPL lab results from the Screen 1 eligibility visit will be used to establish patient-specific references prior to initiation of therapy. If blood tests were not done at the Screen 1 visit for a CBDF and CMPL; and lab results within 30 days prior to this visit for these tests are not available in the medical record, a CBDF and CMPL will be done at this visit. See Appendix E for Clinical Laboratory Minimum Test Requirements.
5) Blood collection for research (20 mL). Ten mL of blood will be collected for measurement of protocol-specific biomarkers (AFP, AFP-L3%, IL-6, and bile acids) and 10 mL of blood will be drawn for DNA extraction and use in future studies.
6) Liver elastography (FibroScan). A FibroScan examination will be conducted. Participants will be instructed to refrain from eating for 3 hours before the FibroScan examination. The FibroScan will be used as a non-invasive measurement of liver stiffness.
7) Interviewer-administered baseline questionnaire to obtain demographic information (detailed race and ethnicity, education); medical and medications history; alcoholic beverage consumption; tobacco smoking; and anthropometry (Appendix F)
8) Food frequency questionnaire (FFQ). The VioScreen® graphical dietary assessment will be self-administered to capture usual diet over the last 30 days.
9) Review of study requirements
10) Dispense the study agent (one bottle of 120 capsules) and review instructions for how to take it
11) Dispense and review the study diary

7.3 Evaluation During the Study Intervention

7.3.1 Study Visit 2

Study Visit 2 will occur 1 month (± 14 days) after initiation of the intervention. The following procedures will be performed during this visit:

1) Review of medical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status

3) Vital signs assessment, including blood pressure, heart rate, and temperature; and measurement of weight
4) Blood collection for clinical labs (approximately 10 mL). Laboratory blood tests will be done for a CBDF and CMPL to monitor for potential adverse effects of the intervention. If lab results within 30 days prior to this visit for CBDF or CMPL are available in the medical record, the blood test(s) will not be repeated. See Appendix E for Clinical Laboratory Minimum Test Requirements.
5) Review of study requirements
6) Collect study agent and diary
7) Assess compliance (pill count)
8) Review study diary
9) Assess adverse events
10) Dispense study agent (same bottle that was brought to the visit/collected for pill count) and diary

7.3.2 Study Visit 3

Study Visit 3 will occur 3 months (±14 days) after initiation of the intervention. The following procedures will be performed during this visit:

1) Review of medical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Vital signs assessment including blood pressure, heart rate, and temperature; and measurement of weight
4) Blood collection for clinical labs (approximately 10 mL). Laboratory blood tests will be done for a CBDF, CMPL, Lipid Panel, and hemoglobin A1C to monitor for potential adverse effects of the intervention. If lab results within 30 days prior to this visit for any of these tests are available in the medical record, the blood test(s) will not be repeated. See Appendix E for Clinical Laboratory Minimum Test Requirements.
5) Review of study requirements
6) Collect study agent and diary
7) Assess compliance (pill count)
8) Review study diary
9) Assess adverse events
10) Dispense study agent (one new bottle of 120 capsules) and diary

7.3.3 Telephone Calls and Email/Text Messages

Study participants will be followed during the intervention via telephone calls every four weeks (± 7 days) by the clinical research staff to assess compliance and adverse events. Participants who report having taken < 85% of the study drug doses between phone calls, or whose pill count at a study visit reveals < 85% compliance, will be called every two weeks (± 3 days) to monitor compliance. In addition, participants will receive a phone call the day before each scheduled study visit to remind them to bring any leftover study drugs and the study diary with them to the visit if it occurs in person. For remote visits patients will be reminded to photograph their study diary and any unused study agent. Study participants will also be called during the week before their final visit (Visit 4) to remind them to take the study drug every day until the visit appointment.

Participants who opt to receive reminders for study medication intake via email or text messages will be contacted by the study staff during the first week of study and further as needed. The study staff will send emails or text messages on cellular phone; participants will be encouraged to respond to these messages indicating if the study drug has been taken. These responses will be used to assess compliance and will be reviewed during phone contacts. For participants who miss more than one dose of the study drug in a week, the email/text reminders will continue further into dosing period. Since agent compliance is very important during the final week of the intervention, text/email messages will be sent to all study participants who opt to receive these reminders.

The following information with be collected during the telephone calls:

- Compliance review: participants will be asked if they missed any doses of the study medication, and the dates of all missed doses will be recorded.
- Concomitant medications review
- Adverse events: participants will be asked if they have experienced any of the following symptoms to assess adverse events:
    - Upper respiratory infection
    - Headache
    - Abdominal pain
    - Constipation
    - Nausea
    - Vomiting
    - Mild muscle aches
- Additional symptoms experienced by participants will be recorded to assess adverse events

7.4 Evaluation at Completion of the Study Intervention

7.4.1 Study Visit 4

The final study visit will occur 6 months (± 30 days) after initiation of the intervention. Study Visit 4 is concurrent with a standard of care visit. The following procedures will be performed during this visit:

1) Review of medical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Physical assessment including vital signs, measurement of weight, and assessment of liver disease sequelae (varices, ascites, and encephalopathy)
4) Blood collection for clinical labs (approximately 15 mL). Laboratory blood tests will be done for a CBDF, CMPL, Lipid Panel, and hemoglobin A1C to monitor for potential adverse effects of the intervention; and for measurement of Prothrombin Time (PT/INR) to calculate the MELD score. Clinical lab results (AST, ALT, and platelets (PLT)) will also be used to calculate the FIB-4 score. If lab results within 30 days prior to this visit for any of these tests are available in the medical record, the blood test(s) will not be repeated. See Appendix E for Clinical Laboratory Minimum Test Requirements.
5) Blood collection for research (20 mL). Ten mL of blood will be collected for measurement of protocol-specific biomarkers (AFP, AFP-L3%, IL-6, and bile acids) and 10 mL of blood will be drawn for DNA extraction and use in future studies.
6) Liver elastography (FibroScan). A FibroScan examination will be conducted. Participants will be instructed to refrain from eating for 3 hours before the FibroScan examination. The FibroScan will be used as a non-invasive measurement of liver stiffness.

7) Abdominal imaging. An abdominal image (CT, MRI, or ultrasound) will be taken for standard of care HCC surveillance. The abdominal imaging may be done up to the end of follow-up for the study (3 months after completion of Study Visit 4 [Visit 4 ± 3 months]).
8) Collect study agent and diary
9) Assess compliance (pill count)
10) Review study diary
11) Assess adverse events

7.5 Post-intervention Follow-up Procedures

Clinical research staff will make follow-up telephone calls to study participants on days 30 ± 7, 60 ± 7, and 90 ± 7 after completion of Study Visit 4 to assess symptoms and adverse events.

7.6 Methods for Clinical Procedures

Blood specimen. A blood specimen (approximately 15 mL) will be collected from each participant at the Screen 1 eligibility visit for blood tests to confirm eligibility. If a patient's lab results are current (within the past 30 days) in the medical record and within eligibility range, their blood will not be drawn at the Screen 1 visit. Otherwise, the patient's blood will be drawn to confirm eligibility. Clinical labs will be done for a Complete Blood Count and Automated Differential (CBDF), a Comprehensive Metabolic Panel (CMPL), and Prothrombin Time (PT/INR). The CBDF includes tests for leukocytes, neutrophils, platelets, and hemoglobin; test results will be used to establish acceptable organ function necessary for trial eligibility. The CMPL includes tests for liver enzymes (AST/ALT); and for total bilirubin, creatinine, and sodium for calculation of the MELD score. Prothrombin Time is required for calculation of MELD. The CMPL and PT/INR test results will be used to confirm that blood levels are within the eligibility requirements (acceptable organ function, AST/ALT ≤5x upper limits of normal, and MELD ≤ 20).

A blood specimen (approximately 10-15 mL) will be collected from each participant at Study Visits 1, 2, 3, and 4 for blood tests to monitor for potential adverse effects of the intervention. The date and time of the blood draw and the participant's last meal will be recorded. A Lipid Panel and hemoglobin A1C will be done at Study Visits 1, 3, and 4. A CBDF and CMPL will be done at Study Visits 2, 3, and 4. Creatine Phosphokinase (CPK) will be measured at Study Visit 1. Prothrombin Time (PT/INR) will be done at Study Visit 4 to calculate the MELD score. See Appendix E for Clinical Laboratory Minimum Test Requirements.

The CMPL and CBDF test results will be utilized to screen for any issues that could be related to an adverse event or affect eligibility for continuation in the trial. It is the consensus of the liver expert panel that obtaining baseline liver enzymes (AST/ALT) and monitoring them is optimal in the care of statin-treated patients [115]. CBDF and CMPL lab results from the Screen 1 eligibility visit (blood collected at most 30 days prior to Study Visit 1) will be used to establish patient-specific references prior to initiation of therapy. If blood tests were not done at the Screen 1 visit for a CBDF and CMPL; and lab results within 30 days prior to Study Visit 1 for these tests are not available in the medical record, a CBDF and CMPL will be done at Study Visit 1. The Lipid Panel includes tests for cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides. Since the study agent is a cholesterol lowering agent, we feel that it is important to establish baseline lipid levels prior to initiating the study agent (Study Visit 1) and monitor lipids at Study Visits 3 and 4 (3- and 6-month visits). Hemoglobin A1C is used to assess glucose control in insulin-dependent diabetics whose glucose levels are very labile and in whom single blood glucose measurements may not accurately reflect the level of control present over the preceding few weeks. Glucose and hemoglobin A1C will be used for monitoring adverse events (incident diabetes) during the trial. CPK will be tested to establish a baseline for

monitoring myopathy, a rare complication associated with the study agent (<1%). We will measure levels of CPK at Study Visit 1 to establish a patient-specific reference for this indicator of muscle toxicity. If the participant reports unexplained muscle pain or weakness during the trial, CPK will be tested again to check for elevation.

An additional blood specimen (20 mL) will be collected from each participant at Study Visits 1 and 4 for research purposes. The blood will be drawn into one 10 mL red top serum vacutainer tube for measurement of protocol-specific biomarkers (AFP, AFP-L3%, IL-6, deoxycholic acid, and other serum bile acids and immune markers), and one 10 mL lavender top EDTA tube for DNA extraction and use in future studies.

Liver elastography (FibroScan). A FibroScan examination will be conducted at Study Visits 1 and 4. Participants will be instructed to refrain from eating for 3 hours before the FibroScan examination. The FibroScan will be used as a non-invasive measurement of liver stiffness. Patients will be placed in a supine position with the right hand at the most abducted position for right intercostal scanning. The probe will be placed over a small amount of water based gel with slight pressure, and ten effective measurements will be made at the same location such that the interquartile range is less than 30%. The median measurement will be employed as the result of the test, provided as a number between 1.5 and 75 kPa (the stiffer the liver, the higher the number). The test result provides a look at the state of the liver globally, as opposed to a biopsy where only a very small sample is measured. The test takes about 10 minutes, and the result is delivered immediately at the end.

Abdominal imaging. Abdominal imaging is done every 6 months for HCC surveillance and is standard of care in this high-risk study population. At CSMC and UPR, computed tomography (CT) with contrast and ultrasound are alternated every 6 months. At NWU and GU, magnetic resonance imaging (MRI) is done every 6 months. Typically, imaging occurs within a few weeks prior to the patient's clinical appointment with hepatology, when the Screen 1 eligibility assessments will be conducted. Another standard of care abdominal image will be taken for all trial participants at Study Visit 4. The abdominal imaging may be done up to the end of follow-up for the study (3 months after completion of Study Visit 4 [Visit 4 ± 3 months]).

Biomarkers. AFP and AFP-L3% will be assessed for each participant by Quest Diagnostics using a liquid-phase binding assay system. Serum IL-6 expression and other serum immune markers will be assessed by Olink Explore Proximity Extension Assay (PEA) (Waltham, MA). All samples will be run in a single batch after all participants have completed their 6-month study visit. Deoxycholic acid and other serum bile acids will be measured using liquid chromatography coupled with mass spectrometry (LC-MS/MS) utilizing Agilent 1290 UHPLC/Sciex QTRAP 6500+, triple quadrupole linear ion trap mass spectrometer by Metabolon® (Durham, NC) in a single batch at the end of the study.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

The overall objective of this trial is to examine the effects of simvastatin use versus placebo at 6 months from baseline (Study Visit 1) on liver function in high-risk patients with liver cirrhosis who have a current Model for End-Stage Liver Disease (MELD) ≤ 20 and no evidence of hepatocellular carcinoma (HCC). Participants will be on the study drug from Study Visit 1 until the last study visit (Study Visit 4 at 6 months). Primary and secondary endpoints are measured in blood samples.

8.1 Primary Endpoint

The primary endpoint is change in serum AFP-L3% from baseline to 6 months following treatment initiation. We hypothesize that participants randomized to simvastatin will experience a decrease from

baseline to 6 months in serum AFP L3% compared to the placebo group. In the treatment group, we expect change of 2.8%, with standard deviation=5.3% in both groups (or smaller). A 2.8% decline is clinically relevant given that prior studies report higher differences (7.9%) in AFP-L3% between cirrhotics without HCC and cirrhotics who progress to HCC [50].

8.2 Secondary and Exploratory Endpoints

Secondary endpoints include additional measures of liver function and disease progression. Changes in secondary endpoints from baseline to 6 months follow-up will be compared between the simvastatin and placebo groups using a similar approach to the main endpoint.

8.2.1 Change in serum AFP. We hypothesize that participants randomized to simvastatin will experience a decrease from baseline in serum AFP levels compared to the placebo group.

8.2.2 Change in serum IL-6. We hypothesize that participants randomized to simvastatin will experience a decrease from baseline in serum IL-6 compared to the placebo group.

8.2.3 Change in serum deoxycholic acid (DCA) levels. We hypothesize that participants randomized to simvastatin will experience a decrease from baseline in serum DCA (deoxycholic acid) levels compared to the placebo group.

8.2.4 Change in liver stiffness. We hypothesize that participants randomized to simvastatin will experience a decrease from baseline in liver stiffness compared to the placebo group.

8.2.5 Change in FIB-4 score. We hypothesize that participants randomized to simvastatin will experience a decrease from baseline in FIB-4 score compared to the placebo group.

8.2.6 Change in MELD score. We hypothesize that participants randomized to simvastatin will experience a decrease from baseline in MELD score compared to the placebo group.

Exploratory endpoints include additional measures of other serum bile acids and immune markers. Differences in exploratory endpoints from baseline to 6 months follow-up will be compared in the simvastatin and placebo groups using a similar approach to the main endpoint.

8.2.7 Change in serum bile acids.

8.2.8 Change in serum immune markers.

8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, AE or serious adverse event (SAE), inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. See Section 5.6. Dose Modification for additional off-agent criteria. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

As described in section 7.5, clinical research staff will make follow-up telephone calls to the participant on days 30 ± 7, 60 ± 7, and 90 ± 7 after the participant discontinues the study agent to assess symptoms and adverse events. Standard of care data (medical history, concomitant medications, laboratory test results, imaging results) will continue to be collected via review of the participant's electronic medical record at the time points specified in the Schedule of Events. If feasible, we will conduct a research visit

to collect final measurements for participants who permanently discontinue the study agent early. An end-of-study research visit will be conducted 6 months (± 30 days) after initiation of the statin intervention (Study Visit 4). The procedures that will be performed during the end-of-study visit are described in section 7.4.1 Study Visit 4.

8.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons:

- Adverse Event
- Death
- Disease Progression
- Lost to follow-up/Participant Withdrawal
- Participant Refused Follow-up
- Physician Decision
- Protocol Defined Follow-up Completed
- Protocol Violation
- Study Complete
- Ineligible
- Other

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

Continuous assessment of the 40 mg dose of simvastatin will be ongoing to ensure safety and toxicity monitoring at this dose. Accrual will be stopped if 30% or more of study participants come off the study agent due to serious adverse events probably or definitely related to the agent, after at least 15 patients have been registered. Toxicity will be reviewed to determine whether accrual to the study should be permanently stopped.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

AFP and AFP-L3% will be measured by Quest Diagnostics on two specimen-visits per participant using a liquid-phase binding assay system. Samples will be sent to Quest from serum samples collected at Study Visits 1 and 4. All samples will be run in a single batch after all participants have completed their 6-month study visit. Ion exchange chromatography will be employed to separate AFP-L3 and non-APR-L3 glycoforms. The analytic sensitivity of the assay are 0.8 ng/mL for AFP, and 0.5% for AFP-L3. The reference ranges for AFP are 0-15 ng/mL, and for AFP-L3 are 0-9.9%.

Serum IL-6 and other serum immune marker expression will be assessed by Olink (Waltham MA) on two specimen-visits per participant. Samples will be run in Olink Explore, a biomarker platform that uses Proximity Extension Assay (PEA) technology combined with an innovative new readout methodology based on Next Generation Sequencing (NGS). This will be completed in a single batch once all participants have completed their 6-month study visit, and both samples from the same participant will be batched onto the same analytic plate.

Serum deoxycholic acid and other serum bile acids will be measured using Metabolon® (Durham, NC) Bile Acid targeted panel and assays. Metabolon® applies a specific combination of liquid chromatography

coupled with mass spectrometry technology (LC-MS/MS) utilizing Agilent 1290 UHPLC/Sciex QTRAP 6500+, triple quadrupole linear ion trap mass spectrometer in a single batch. Metabolon's® Bile Acid Panel was chosen for bile acid testing given Metabolon's® significant experience [118-120]. The Liquid Chromatograph Mass Spectrometer is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography with the mass analysis capabilities of mass spectrometry. Scheduled multiple reaction monitoring (MRM) is performed with optimized collision energies, de-clustering potentials, and collision cell exit potentials for the individual analytes. All analytes are quantified against 6-point calibration curves using internal standards.

Liver Stiffness will be assessed by liver elastography (FibroScan®) examination at Study Visits 1 and 4. Participants will be instructed to refrain from eating for 3 hours before the FibroScan examination. FibroScan examination is a non-invasive measurement of liver fibrosis that uses a patented technique called Vibration Controlled Transient Elastography (VCTE™) to measure the elasticity of the liver. VCTE allows non-invasive measurement of liver shear wave speed in m/s which is correlated with the elasticity of the liver tissue (stiffness) in kPa. As the shear wave passes through the liver, it is affected by the amount of scarring (fibrosis), and this is interpreted to give an accurate global assessment of the stage of fibrosis (fibrosis staging). FibroScan uses a button shaped probe with an ultrasound transducer that is placed at the skin surface. The probe generates a series of mechanical pulses (shear waves) that travel through the liver. The FibroScan measures the velocity of the shock wave, which correlates with the stiffness of the liver. Patients will be placed in a supine position with the right hand at the most abducted position for right intercostal scanning. The probe will be placed over a small amount of water based gel with slight pressure, and ten effective measurements will be made at the same location such that the interquartile range is less than 30%. This data is automatically processed by the on-board computer and the liver stiffness is displayed on the computer screen. The median measurement will be employed as the result of the test, provided as a number between 1.5 and 75 kPa (the stiffer the liver, the higher the number). A test result of >20 kPa is generally associated with an increased HCC risk [81]. The advantage of FibroScan over biopsy is that it provides a look at the state of the liver globally, as opposed to a biopsy where only a very small sample is measured. The test takes about 10 minutes, and the result is delivered immediately at the end.

9.2 Comparable Methods

Proposed methods represent standard technology for measuring the study biomarkers.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

1) Study blood tests will be done for a Complete Blood Count and Automated Differential (CBDF), a Comprehensive Metabolic Panel (CMPL), Prothrombin Time (PT/INR), a Lipid Panel, hemoglobin A1C, and Creatine Phosphokinase (CPK) at the clinical or local laboratories at each study site; or the blood tests will be done at an external CLIA-certified clinical laboratory as required by the participant's health insurance carrier.

2) At CSMC, specimen processing and aliquoting of blood samples collected for protocol-specific biomarker testing and for use in future studies will be performed by the CSMC Biobank & Translational Research Core Laboratory. Along with general supplies, the laboratory is fully equipped with the following instrumentation: Refrigerated Centrifuge, Ambient Centrifuge, -20ºC Freezer, -80ºC Freezer, 32ºF Refrigerator, laboratory hood, water bath, Vortex Machine, calibrated pipettes, dry ice, and supplies. Freezers and refrigerators are on daily temperature monitoring and records are meticulously kept and stored for

documentation. These main instruments are also on red outlet plugs such that they trigger backup generator electricity in case of a black out. All instrumentation is calibrated prior to use and maintained yearly by the Biomedical Engineering Services department.

3) At NWU, specimen processing, aliquoting, and shipping of blood samples collected for protocol-specific biomarker testing and for use in future studies will be performed by Northwestern University Clinical and Translational Sciences Institute Clinical Research Unit and Core Lab. The lab is IATA, CAP and CLIA certified and has 570 square feet of space for both clinical and research specimen processing and analytical work (RIA; ELISA). The Core lab also has a 65 square-foot walk-in cold room for assay incubation and freezer storage at -30°C and -70ºC. It accepts specimen submission 24 hours a day, 365 days a year, utilizes the "Freezerworks" bar code and inventory system and provides shipment of ambient and frozen research samples.

4) At GU, specimen processing, aliquoting, and shipping of blood samples collected for protocol-specific biomarker testing and for use in future studies will be performed by the Georgetown Clinical Research Unit (GU-CRU) located on 7th floor East Wing of the Main Building, Georgetown University Hospital. This location is central to the medical center, and is convenient for investigators, clinicians, staff, patients and families. The GU-CRU is equipped to provide around-the-clock support for research studies, seven days a week. The GU-CRU provides 10 patient-care rooms and occupies approximately 5411 square feet of space. It has the flexibility to support inpatient or outpatient services, thereby maximizing use of all rooms (2 are dedicated for cognitive testing; 4 are dedicated for outpatient testing; 4 are for mixed inpatient/outpatient use). The CRU is equipped with freezer storage at -30°C and -70ºC. It accepts specimen submission 24 hours a day, 365 days a year, utilizes the "Freezerworks" bar code and inventory system and provides shipment of ambient and frozen research samples.

5) At the UPR, specimen processing, aliquoting, and shipping of blood samples collected for protocol-specific biomarker testing and for use in future studies will be performed by the NIH-funded Biomedical Laboratory of the PR Clinical & Translational Research Consortia (Medical Sciences Campus). The lab is IATA, CAP and CLIA certified and has 500 square feet of space for both clinical and research specimen processing and analytical work (RIA; ELISA). The Core lab also has a freezer storage at -70ºC, -20C and refrigerators. It accepts specimen submission during business hours Monday to Friday from 7 am to 5 pm. After hour services are available upon request.

6) Measurement of serum AFP and AFP-L3% will be performed by Quest Diagnostics Nichols Institute. Quest is the world's leading provider of diagnostic testing services, serving about half of the physicians and hospitals in the U.S., with a medical and scientific staff of more than 700 M.D.s and Ph.D.s. Quest has strong logistics capabilities, including approximately 3,000 courier vehicles and 20 aircraft that collectively make tens of thousands of stops daily. Quest Diagnostics Nichols Institute focuses on specialized and highly complex laboratory testing and plays a key role in Quest Diagnostics research and development efforts, performing tests rarely done in most routine or hospital laboratories.

7) Measurement of serum IL-6 and other immune marker expression will be performed by Olink Proteomics, Inc. in Waltham, MA.

8) Measurement of serum deoxycholic acid and other bile acids will be performed at Metabolon®.

10.2 Collection and Handling Procedures

Research study staff at CSMC, NWU, GU, and UPR will receive specific instructions for collection, processing, and shipment of specimens.

Blood specimen. A blood specimen (approximately 15 mL) will be collected from each participant at the Screen 1 eligibility visit for blood tests to confirm eligibility. If a patient's lab results are current (within the past 30 days) in the medical record and within eligibility range, their blood will not be drawn at the Screen 1 visit. Otherwise, the patient's blood will be drawn to confirm eligibility. Clinical labs will be done for a Complete Blood Count and Automated Differential (CBDF), a Comprehensive Metabolic Panel (CMPL), and Prothrombin Time (PT/INR). The CBDF includes tests for leukocytes, neutrophils, platelets, and hemoglobin; test results will be used to establish acceptable organ function necessary for trial eligibility. The CMPL includes tests for liver enzymes (AST/ALT); and for total bilirubin, creatinine, and sodium for calculation of the MELD score. Prothrombin Time is required for calculation of MELD. The CMPL and PT/INR test results will be used to confirm that blood levels are within the eligibility requirements (acceptable organ function, AST/ALT ≤5x upper limits of normal, and MELD ≤ 20).

A blood specimen (approximately 10-15 mL) will be collected from each participant at Study Visits 1, 2, 3, and 4 for blood tests to monitor for potential adverse effects of the intervention. The date and time of the blood draw and the participant's last meal will be recorded. A Lipid Panel and hemoglobin A1C will be done at Study Visits 1, 3, and 4. A CBDF and CMPL will be done at Study Visits 2, 3, and 4. If blood tests were not done at the Screen 1 visit for a CBDF and CMPL; and lab results within 30 days prior to Study Visit 1 for these tests are not available in the medical record, a CBDF and CMPL will also be done at Study Visit 1. Creatine Phosphokinase (CPK) will be measured at Study Visit 1. Prothrombin Time (PT/INR) will be done at Study Visit 4 to calculate the MELD score. See Appendix E for Clinical Laboratory Minimum Test Requirements.

An additional blood specimen (20 mL) will be collected from each participant at Study Visits 1 and 4 for research purposes. The blood will be drawn into one 10 mL red top serum vacutainer tube for measurement of protocol-specific biomarkers (AFP, AFP-L3%, IL-6, and bile acids), and one 10 mL lavender top EDTA tube for DNA extraction and use in future studies. The blood will be transported to the research laboratories at CSMC, NWU, GU, and UPR, and processed within two hours of collection. The vacutainer tubes will be centrifuged as specified in the Laboratory Manual. After centrifugation, vials will be prepared from the blood specimens for research testing. Specimen aliquots from NWU, GU, and UPR will be packaged and shipped overnight on dry ice to CSMC. Aliquots will be stored at -80ºC until analyses, DNA extraction, and use in future studies.

10.3 Shipping Instructions

Blood samples collected for laboratory blood tests (Complete Blood Count and Automated Differential (CBDF), Comprehensive Metabolic Panel (CMPL), Prothrombin Time (PT/INR), Lipid Panel, hemoglobin A1C, and Creatine Phosphokinase (CPK)) will be transported to the clinical laboratories at each study site for processing and testing; or the blood will be drawn and tested at an external CLIA-certified clinical laboratory as required by the participant's health insurance carrier.

Blood samples collected for research will be transported to the designated research laboratories at CSMC, NWU, GU, and UPR for processing.

At CSMC, research study staff will transport the blood samples to the Biobank & Translational Research Core Laboratory for processing:

Cedars-Sinai Biobank & Translational Research Core Laboratory
Steven Spielberg Building, Room 110
8723 W. Alden Drive
Los Angeles, CA 90048
Telephone: (310) 423-9379

At Northwestern, research study staff will transport the blood samples to the NWU Clinical and Translational Sciences Institute Clinical Research Unit and Core Lab:

Clinical Research Unit Core Lab
251 E. Huron, Feinberg Pavilion
Suite 10-754
Chicago, IL 60611
Telephone: (312) 227-4083

At Georgetown University, blood will be drawn and processed at the Clinical Research Unit:

Clinical Research Unit
Georgetown University Medical Center
7 East, Main Bldg., M7309
3800 Reservoir Road, NW
Washington DC 20007
Telephone: 202-444-2639
Fax: 202-444-1505

At the University of Puerto Rico, research study staff will transport the blood samples to the Puerto Rico Clinical and Translational Research Consortium:

Puerto Rico Clinical and Translational Research Consortium
1st Floor University Hospital Medical Sciences Campus
PO Box 365067
San Juan PR 00936-5067

Processed blood samples collected for research at NWU, GU, and UPR (blood specimen aliquots) will be shipped to the CSMC specimen manager. Please see the study's Laboratory Manual for the shipping address.

The CSMC specimen manager will package and ship serum samples for measurement of AFP and AFP-L3% to Quest Diagnostics. Shipping address for Quest Diagnostics:

Quest Diagnostics
Nichols Institute
33608 Ortega Highway
San Juan Capistrano, CA 92675-2042
Telephone: (949) 728-4000

The CSMC specimen manager will package and ship serum samples for measurement of bile acids to Metabolon®. Shipping address Metabolon®:

Metabolon Sample Acceptance
617 Davis Drive, Suite 400
Morrisville, NC 27560
Telephone: (919) 572-1711

The CSMC specimen manager will transport serum samples for measurement of serum immune markers to Olink Proteomics, Inc. Shipping address for Olink:

Olink Proteomics, Inc.
130 Turner St.
Building 2, Suite 230
Waltham, MA 02453
Telephone: (617) 393-3933

All processed blood samples will be shipped overnight in dry ice. All samples will be shipped on Monday or Tuesday in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify, and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)

- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the participant dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0 as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

DCP Medical/Task Order Monitor
Luz Maria Rodriguez, MD, FACS
NCI/Division of Cancer Prevention
9609 Medical Center Dr.
Rm 5E-228
Bethesda, MD 20892
Telephone (240) 276-7039
Fax (240) 276-7848
Email: rodrigul@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to the following within 48 hours of learning of the event using the fillable PDF SAE Report Form.

- DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com
- DCP Medical Monitor, Dr. Luz Rodriguez (rodrigul@mail.nih.gov)
- Northwestern Cancer Prevention Consortium (ncpc@northwestern.edu)

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the CIRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. All SAEs will be followed according to standard of care. SAEs possibly, probably, or definitely related to the study agent will be followed until resolved.

12. STUDY MONITORING

12.1 Data Management

Data will be managed by the study statistician, Dr. Kocherginsky according to standard operating procedures, which meet the guidelines of DCP Requirements for Data Management and which follow the Data Management Plan that Northwestern University has on file with the Division of Cancer Prevention, NCI. Source data verification will be performed by the Northwestern Cancer Prevention Consortium. The Consortia 2012 Data Management Plan, submitted as part of a contract agreement with the NCI (HHSN261201200035I), was approved.

Clinical data will be reported to Northwestern University through the Lurie Cancer Center Clinical Trials Management System (CTMS), which will be the database of record.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRFs) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used by Northwestern University to create the electronic CRFs (e-CRFs) screens in the CTMS-RDC application. Site staff will enter data into the e-CRFs for transmission to DCP according to DCP standards and procedures.

All specimen results that are batch analyzed will be collected and stored on excel spreadsheets. The excel spreadsheets will constitute the database of record.

12.3 Source Documents

All source documents will be collected and stored by the research staff at the site of accrual. Any data recorded directly in CTMS that constitute no prior written or electronic record of data, will be specifically identified as source data. Questionnaires completed in person may be completed on the paper and entered into CTMS.

12.4 Data and Safety Monitoring Plan

A comprehensive Data Safety and Monitoring Plan has been submitted by Northwestern University, approved by the DCP, and is on file there. Any future changes will be forwarded for review.

This trial is subject to review by the Lurie Cancer Center Data Monitoring Committee (DMC). Semi-

Annual reports, SAEs, and protocol deviations will be reviewed by the DMC at bi-weekly meetings. This trial is also subject to possible annual audits by the Lurie Cancer Center Clinical Trials Audit Committee (CTAC).

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies, and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This is a randomized double-blinded, placebo-controlled Phase II trial of statin to evaluate the impact of statin treatment on disease progression in 80 patients with liver cirrhosis who have a current Model for End-Stage Liver Disease (MELD) ≤ 20 and no evidence of hepatocellular carcinoma (HCC). The primary objective of this study will be to demonstrate that statins will improve liver function in high-risk patients. The primary outcome is change from baseline (Study Visit 1) at 6 months in AFP-L3%. Secondary outcomes will include additional measures of liver function (serum AFP, IL-6 and DCA levels, liver stiffness, FIB-4 score, and MELD score).

13.2 Randomization/Stratification

Patients will be randomized by the study statistician at Northwestern University. Randomization will be carried out among consented patients meeting the Screen 1 eligibility criteria at each site (CSMC, NWU, GU, and UPR) with a 1:1 ratio for simvastatin and placebo assignment.

13.3 Accrual and Feasibility

Sample size: Intervention = 80 (40 statin: 40 placebo) randomized sample; Analytic sample = 72 (36:36)

after 10% drop-out. The expected accrual rate is 6-7 participants per month across four study sites, and the planned recruitment duration is 12 months. We anticipate that all evaluable participants will have completed all study procedures within 24 months. Power and precision arguments are provided below.

Accrual was calculated based on the number of liver transplant candidates actively registered at CSMC, NWU, GU, and UPR at a given time in addition to the number of new candidates expected to be registered over a 12-month period. Cirrhotics who are eligible and not listed for transplant may also be recruited.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary outcome for this study is change from baseline to 6 months in AFP-L3%. Power calculations are presented in Table 2. In the treatment group, we expect change of 2.8 over 6 months, and in the placebo group we expect a change of 0, with standard deviation=5.3 in both groups (or smaller). For a Phase II study we have an acceptable alpha of 10%. For the primary endpoint, AFP-L3%, we will consider changes D(T) and D(P) for D=After-Before, for simvastatin (T) and placebo (P) groups, respectively. We will use a nonparametric two-sample Wilcoxon-Mann-Whitney test to address the hypothesis H0: mean [D(T)] =mean [D(P)] versus H1: means[D(T)] > mean [D(P)] and report a defined one-sided p-value. If p<0.1 we will consider this to be evidence of an effect of simvastatin on AFP-L3%. If p>0.1 we will report the actual means and the corresponding confidence intervals observed and declare the trial had failed. If we observe: mean[(D(P)] > mean[D(T)] which would be unexpected, we will declare the trial failed and discuss possible explanations for the observed situation, which would suggest possibly adverse effect of the treatment. We are expecting less than 1 participant to progress to HCC in either the placebo or treatment arms during the course of the study [8].

Table 2. Numeric Results for Mann-Whitney Test

Power	N1	N2	Ratio	Alpha	Beta	Mean1	Mean2	S1	S2
0.81	36	36	1	0.1	0.19	2.8	0	5.3	5.3

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1>Mean2.
The standard deviations were assumed to be unknown and unequal.

13.5 Secondary and Exploratory Objectives, Endpoints, Analysis Plans

For the continuous secondary endpoints (serum AFP, IL-6, serum DCA, liver stiffness, FIB-4 score, and MELD score) and exploratory endpoints, we will consider D(T) and D(P) as well as percent change relative to baseline, namely, D(T)/B(T) and D(P)/B(P). Biomarker levels at baseline and 6 months, as well as changes from baseline to 6 months, will be summarized using descriptive statistics and graphical methods. ANCOVA models with post-treatment value as the outcome, and treatment group and baseline value as predictors will be used to examine treatment differences. In these models, the estimated coefficient for treatment is the difference between the mean change scores of each arm [116]. Model fit will be assessed using standard model diagnostics including residual plots, influence statistics, and model assumptions such as normality and equivariance, will be verified. Potential outliers will be identified and reasons for extreme values will be investigated. Biomarker values may be transformed, e.g. logarithmically, to satisfy the normality assumption. Interaction between treatment group and baseline will be tested. Additional models that further adjust for other baseline characteristics, including routine clinical tests that have been shown to be strongly predictive of HCC diagnosis in prospective cohorts of cirrhosis such as higher alkaline phosphatase [6], lower platelets [6, 71, 73, 117], lower albumin [73, 118], and lower prothrombin activity [119]. We will also consider clinical variables representing important HCC risk factors captured through the epidemiological questionnaire (Appendix F), including body mass index, current alcohol use, and current dietary fat, carbohydrate, fiber, coffee, and antioxidants [99-112]. The change in variable criterion will be used to identify confounders for our final models. Model selection will be performed using the purposeful model selection approach [120], resulting in a parsimonious model that includes adequate control for confounding. Adjusted treatment effects will be

reported.

Analyses will be performed with R statistical software. All analyses will be conducted on an intention to treat basis (all randomized participants will be included in the assigned group) and will begin with univariate cross-sectional statistics for profiling the study population and bivariate tabulations as a preliminary step to possible model building. We will not control for overall Type I error due to small number of observations and the preliminary nature of the study.

13.6 Reporting and Exclusions

We are anticipating a small proportion (10%) of drop-outs due to health deterioration, transplantation, or death. We are proposing to exclude patients with high MELDs to reduce this possibility. The median time to transplantation from waitlist registration nationally is approximately 16 months, thus we feel that the risk of transplantation in the newly registered patient population with low MELDs is very low [113]. Among patients who are already on the waitlist, there is certainly a risk for drop-out due to transplantation over a 6-month period, but we do not anticipate that this will be greater than 10%. We also anticipate some contamination from the simvastatin intervention to placebo due to non-compliance and this will be monitored and managed through blood tests. We do not expect cross-over from the placebo to the intervention group as participants will be aware that they might be on statins already and would not want to jeopardize their safety and care. However, the 2013 ACC/AHA clinical guidelines for prescription of statins may also influence drop-outs among participants who wish to reduce the risk of cardiovascular disease [121]. These guidelines recommend targeting men and women with cardiovascular disease, LDL cholesterol $\geq$ 190 mg/dL, and persons 40-75 years with diabetes or a 10-year cardiovascular disease risk $\geq$ 7.5%. Most of these people would not meet the eligibility criteria for study participation. The drop-out rate is expected to be 10% from baseline to 6 months follow-up.

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of simvastatin. Presence or absence of toxicity will be registered as a binary variable. Comparison of assumed underlying rates between groups will be performed using Fisher's exact test, and exact confidence intervals will follow the Clopper-Pearson method.

13.8 Evaluation of Response

Changes in AFP-L3% will be evaluated for all randomized participants.

13.9 Interim Analysis

There will be no planned interim analyses.

13.10 Ancillary Studies

Not applicable.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with

regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in Good Clinical Practice for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the NCI Central IRB (CIRB). Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation.

14.4 Informed Consent

All potential study participants will be given a copy of the CIRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, CIRB, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, CIRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Place, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

All research related costs associated with participating in this study will be paid for, and will not be the responsibility of the participant. Participants will receive $50 when they complete the Screen 1 testing and $100 at the completion of each study visit for their time, transportation, parking, and other expenses related to the study. Participants who complete the entire study – the Screen 1 eligibility testing and four study visits – will receive $450.

It is possible that a research injury or illness may result from participating in this study. Any expenses incurred as a result of research related injury will be the responsibility of the study participant and/or their insurance carrier.

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CONSENT FORM

Consent Form

Study Title for Study Participants: A Study Testing Simvastatin to Prevent Liver Cancer in People with Liver Cirrhosis

Protocol Title: NWU2015-06-03, Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer

Principal Investigator: Marc T. Goodman, Ph.D., M.P.H.

Sponsored By: National Cancer Institute (NCI)

Introduction

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the research. This document has important information about the reason for the study, what you will do if you choose to be in this research study, and the way we would like to use information about you and your health.

Please take your time to make your decision about volunteering. You may discuss your decision with your friends and family. You can also discuss this study with your health care team. If you have any questions, you can ask your study doctor for more of an explanation. You should only agree to participate in this study when you are comfortable enough with the information so that you can make an informed decision about joining.

What is the usual approach to managing my liver cirrhosis?

You are being asked to take part in this research study because you have liver cirrhosis (scarring of the liver which results in abnormal liver function). People who have liver cirrhosis may be treated for the underlying cause of their cirrhosis, such as treatment for viral hepatitis B or C infections, weight loss, or alcohol dependency. Also, people who have liver cirrhosis may be treated for complications due to their cirrhosis including drainage of excess body fluids and medications to treat infections and other health problems associated with cirrhosis. When cirrhosis is advanced and liver function is very poor, a liver transplant may be the only treatment option. People who have liver cirrhosis are at increased risk for liver cancer. People who are at increased risk for liver cancer and choose not to participate in a study are followed closely by their doctor to watch for the development of cancer.

What are my other choices if I do not take part in this study?

- You may choose to have the usual approach described above;
- You may choose to take part in a different study, if one is available; or
- You may choose to do nothing.

Why is this study being done?

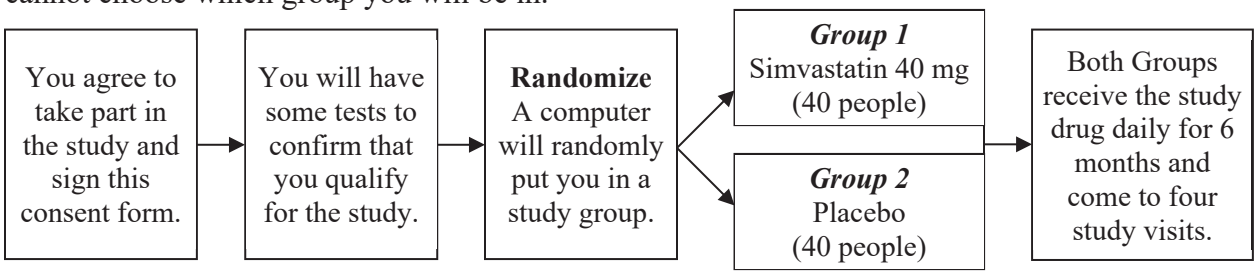
The purpose of this study is to compare the safety and effects of simvastatin in people with liver cirrhosis who are at an increased risk for liver cancer. In this study, you will get either

simvastatin 40 mg daily or placebo daily, a pill that looks like simvastatin 40 mg but contains no medication. Simvastatin is approved by the U.S. Food and Drug Administration (FDA) to reduce the risk for heart attack, stroke, and chest pain in patients who have heart disease or risk factors for heart disease such as smoking, high blood pressure, low high-density lipoprotein (HDL), or family history of early heart disease. It is also approved to lower the risk for heart attack or stroke in patients with type 2 diabetes and risk factors such as diabetic eye or kidney problems, smoking, or high blood pressure. However, simvastatin is not approved by the FDA to decrease the risk of liver cancer. Simvastatin is considered "investigational" (a study drug) in this study. Studies show that simvastatin lowers the risk of heart disease not only by decreasing cholesterol, but also by decreasing inflammation. We believe that this anti-inflammatory effect of simvastatin may help patients with liver cirrhosis. There will be about 80 people taking part in this study at Cedars-Sinai Medical Center, Northwestern University Feinberg School of Medicine, Georgetown University/MedStar Georgetown University Hospital, and the University of Puerto Rico.

What are the study groups?
This study has two study groups. Group 1 will receive simvastatin 40 mg daily, and Group 2 will receive a placebo daily. There will be 40 people in Group 1 and 40 people in Group 2.

A computer will randomly put you in a study group—like a coin toss—to decide what group you get placed into. This is done because no one knows if one study group is better, the same, or worse than the other group. Once you are put in a group, you cannot switch to the other group.

Neither you nor your doctor will know if you are receiving simvastatin or placebo. Your doctor cannot choose which group you will be in.



How long will I be in this study?
Your participation in the study will last 9 months. You will receive the study drug (either simvastatin 40 mg or placebo) daily for 6 months, and your doctor will continue to watch you for side effects and follow your condition for three months after you stop taking the study drug. If you stop taking the study drug early, your doctor will continue to watch you for side effects for 3 months.

What extra tests and procedures will I have if I take part in this study?
If you agree to participate in this study, you will be required to sign this consent form before you have any tests or procedures that are done only for this study. Most of the tests and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and procedures that you will need to have if you take part in this study, including review of your medical history and medications, blood tests, non-invasive scans and images of your liver,

completion of questionnaires, and pregnancy tests (only for women who are able to become pregnant). These extra tests and procedures are described in further detail below.

There are 3 main parts to this study: *Screening, Intervention*, and *Follow-up after Completion of Study Intervention*.

Screening
Screening is a period during which tests and procedures will be done to determine if you are eligible to participate in the study. After you sign the consent form, the following will be done to determine if you are eligible for the study:

- Your study doctor will review your medical history, medications, and laboratory test results, and evaluate the study inclusion and exclusion criteria as they apply to you
- A physical assessment including your vital signs and measurement of your weight
- Review of your symptoms and current activity level and limitations
- Blood tests (approximately 15 mL of your blood will be collected, which is about the same as 3 teaspoons) to check for a low blood count or clotting problems and to check your organ function
- Pregnancy test (for women who are able to become pregnant)

If the clinical laboratory results within the past 30 days are available in your medical record and are within the eligibility requirements for the study, and indicate that your organ function is acceptable, you may not need to have the blood tests during screening. If you are pregnant or if your blood tests show you have advanced liver disease, you will not be eligible for the study.

Intervention (Study Visits 1, 2, 3, and 4)
If the Screening exams and tests show that you can take part in the study, and you choose to, then you will be enrolled in the study and you will be randomized to a study group. During the *Intervention* portion of this study, you will be asked to take the study drug every day for 6 months and participate in 4 study visits. *Research staff will contact you approximately every four weeks by phone* to check on your progress and answer any questions regarding the study. You will also be asked questions about potential side effects of the study drug. These phone calls will last approximately 10 minutes.

Reminders to take your study drug: You will have the option of receiving email or text messages from research staff to remind you to take the study drug during the first week of the intervention period. We encourage you to respond to indicate if the dose has been taken. If you are having trouble remembering, these reminders can be extended beyond the first week. It is important that you stay on the study drug until the last study visit 6 months after you start intervention with the study drug. You will receive a phone call from research staff to remind you to stay on the study drug during the last week of the study intervention, as it is very important that you not miss any dose during this week so that we are able to fully use all data collected. Reminder messages to take the study drug will also be sent to you.

- *Study Visit 1*
  The first study visit will take place 0-30 days after the Screening tests. The following procedures will be done during this visit:
  - Review of your medical history, medications, and laboratory test results

- A vital signs assessment including your blood pressure, heart rate, and temperature, and measurement of your height and weight
- Review of your symptoms and current activity level and limitations
- Collection of a blood sample (approximately 30 mL will be collected, which is about the same as 6 teaspoons) for blood tests to check your organ function, for research measurements of molecular markers in the blood that are related to liver function, and for use in future research studies
- A FibroScan examination of your liver. You will be asked to refrain from eating for 3 hours before the FibroScan examination.
- Completion of a questionnaire that asks about your background (race, education, marital status), health habits, tobacco and alcohol use, and quality of life. The questionnaire will be administered by a research staff person, who will ask you the questions and record the answers.
- Completion of a diet questionnaire that asks about the types and quantities of food you eat. This is a self-administered electronic questionnaire that you will complete online using a computer or tablet.

This study visit will last approximately 3 hours. The blood sample is required in order for you to take part in this study because the research on the samples is an important part of the study.

The FibroScan is a non-invasive, pain-free examination of your liver. It is a scan similar to an ultrasound used during pregnancy. During the exam, you will be asked to lie on your back with your right arm raised and tucked behind your head. You may wish to wear a loose-fitting shirt as the skin covering your right rib cage area will need to be exposed in order to complete the exam. A staff member will place a probe, similar to an ultrasound probe, on your side near where your liver is. The probe sends a painless vibration through your body and into your liver, and measures how fast it takes the vibration to travel through the liver. The examination takes about 10 minutes.

The study drug (either simvastatin or placebo) will be provided to you at this visit or shipped to your home. Study staff will review instructions for how and when to take the study drug. You will be given a study diary to fill out and record each dose of study drug that you take. You should mark any missed or skipped doses in this diary, as well as any side effects that you are experiencing.

- *Study Visit 2*

The second study visit will take place 1 month after you start taking the study drug. The following procedures will be done during this visit:

- Review of your medical history, medications, and laboratory test results
- A vital signs assessment including your blood pressure, heart rate, temperature, and measurement of your weight
- Review of your symptoms and current activity level and limitations
- Collection of a blood sample (approximately 10 mL will be collected, which is about the same as 2 teaspoons) for blood tests to monitor you for side effects of the study drug

This study visit will last about 1 hour. You will receive a phone call the day before the visit to remind you to bring your study diary and any leftover study drugs to the visit. The bottle of study drug pills will be given back to you at this visit after we confirm that there are enough pills to last until your next study visit.

- *Study Visit 3*

  The third study visit will take place 3 months after you start taking the study drug. The following procedures will be done during this visit:
  - Review of your medical history, medications, and laboratory test results
  - A vital signs assessment including your blood pressure, heart rate, and temperature, and measurement of your weight
  - Review of your symptoms and current activity level and limitations
  - Collection of a blood sample (approximately 10 mL will be collected, which is about the same as 2 teaspoons) for blood tests to monitor you for side effects of the study drug

  This study visit will last about 1 hour. You will receive a phone call the day before the visit to remind you to bring your study diary and any leftover study drugs to the visit. You will be given another bottle of the study drug at this visit.

- *Study Visit 4*

  The final study visit will take place 6 months after you start taking the study drug. The following procedures will be done during this visit:
  - Review of your medical history, medications, and laboratory test results
  - A physical assessment including your vital signs and measurement of your weight
  - Review of your symptoms and current activity level and limitations
  - Collection of a blood sample (approximately 35 mL will be collected, which is about the same as 7 teaspoons) for blood tests to check your organ function, for research measurements of molecular markers in the blood that are related to liver function, and for use in future research studies
  - A FibroScan examination of your liver. This is the same test performed during Study Visit 1. You will be asked to refrain from eating for 3 hours before the FibroScan examination.
  - An imaging scan of your abdominal area. The procedure used may be ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

  This study visit will last approximately 3 hours. You will receive a phone call the day before the visit to remind you to bring your study diary and any leftover study drugs to the visit.

  An abdominal ultrasound is a safe and painless procedure that uses sound waves to create pictures of the organs and other structures in your upper belly. During the procedure, you will lie flat on your back on a padded exam table. The technologist will spread warm gel to the skin of your abdomen to help the sound waves work best. A transducer, a small, microphone-like device, will be pressed over various locations on your abdomen. Sound

waves will bounce off organs and tissue in your body, which creates echoes. The echoes are sent to the transducer, which converts them to electronic signals. A computer processes the signals into images and shows them on a screen. The ultrasound procedure usually takes 30 to 45 minutes.

An abdominal CT scan is an imaging method that uses x-rays to create cross-sectional pictures of the belly area. You will be given a special dye, called contrast, which helps certain areas show up better on the x-rays. Contrast can be given through a vein in your hand or forearm. Sometimes you may have to drink the contrast before the exam, and in other cases it may be placed by using an enema. During the procedure, you will lie on your back on a narrow exam table with your arms raised above your head. The table will slide into the center of the CT scanner. The scanner is open at the back and the front, allowing you to see out. The technologist will always be able to see and hear you during your exam. Once you are inside the scanner, the machine's x-ray beam rotates around you and a computer creates separate images of the belly area. You will be asked to hold very still during the exam because movement causes blurred images. You may be told to hold your breath for short periods of time. The CT procedure usually takes 15 and 30 minutes.

An abdominal MRI is a non-invasive procedure that uses a magnetic field and pulses of radio wave energy to create detailed images of organs and other internal body structures. The MRI does not use radiation (x-rays). You may be asked to wear a hospital gown or clothing without metal zippers or snaps (such as sweatpants and a t-shirt) because certain types of metal can cause blurry images. In some cases, a contrast agent (dye) may be injected into a vein in your hand or arm to improve the quality of the images. During the procedure, you will lie on the scanning table headfirst with arms at your side. Coils (special devices to improve image quality) may be placed on or around your abdomen. The table slides into a large tube-shaped magnet. As pictures are taken you must hold very still, and in some cases, you must hold your breath up to 25 seconds. Moving too much can blur MRI images and cause errors. During the MRI, the technologist who operates the machine monitors you from another room and will always be able to see and hear you during your exam. The MRI procedure usually takes 45 to 60 minutes.

Follow-up after Completion of Study Intervention
We will continue to follow your condition for 3 months after you stop taking the study drug. Research staff will contact you by phone to check on potential symptoms and side effects you may be experiencing, and to answer any questions you may have. These phone calls will last approximately 10 minutes. You will be contacted approximately 30 days, 60 days, and 90 days after you complete the study.

What possible risks can I expect from taking part in this study?
Your involvement in this study may involve the following risks:

Risks Associated with Simvastatin
The study drug simvastatin may affect how different parts of your body work, such as your liver and kidneys. You will have blood tests before and during the study to monitor your organ function. Your study doctor will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may be serious and may even result in death

Here are important points about how you and your study doctor can make side effects less of a problem:

- Tell your study doctor if you notice or feel anything different so they can see if you are having a side effect.
- Your study doctor may be able to treat some side effects.

The table below shows the most common side effects that we know about simvastatin, some of which may be serious. There might be other side effects that we do not yet know about. If important new side effects are found, your study doctor will discuss these with you. You will be asked to record any side effects and symptoms you may be experiencing in your study diary.

OCCASIONAL, SOME MAY BE SERIOUS (Out of every 100 people receiving simvastatin, 4 to 20 may experience)
• Upper respiratory infections (stuffy or runny nose, sneezing, sore throat, or cough) • Headache • Pain in the belly • Constipation • Nausea

RARE, SOME MAY BE SERIOUS (Out of every 100 people receiving simvastatin, 3 or fewer may experience)
• Diarrhea • Indigestion, heartburn • Gas in the belly, burping, passing gas • Feeling weak and having no energy • Muscle aches, pain, or weakness. <u>If you develop these symptoms, notify your study doctor immediately</u>. Rhabdomyolysis can develop which is when too many damaged muscle cells get into the bloodstream and can cause kidney failure. This is more common with higher doses of simvastatin. • Confusion, forgetfulness, or memory problems that go away when simvastatin is stopped • Abnormally high laboratory test results of liver function, which may be a sign of liver damage. Symptoms of liver failure are extreme tiredness, loss of appetite, belly pain, yellow skin or eyes, or dark urine. • Abnormally high blood sugar laboratory result • Allergic reactions which, if severe, can be deadly: hives, severe skin rash with blisters,

swelling and redness of the skin, face, eyes, or mouth, wheezing and difficulty breathing
- Damage to the body by the body's own immune system: irritation in blood vessels, arthritis, fever, chills, flushing, decreased white blood cells (cells that help fight infections), decrease in blood platelets (cells that stop bleeding) causing increased bruising or bleeding, death of tissue in muscles or skin

POSSIBLE, SOME MAY BE SERIOUS

The frequency of some individual side effects of simvastatin has not yet been determined:

- Dry skin, mouth, or eyes
- Skin color changes
- Bumps on the skin
- Hair or nail changes, hair loss
- Feeling dizzy or lightheaded
- Loss of feeling or feeling "pins and needles" in arms and legs
- Depressed mood, sadness
- Abnormal sexual function
- Vomiting
- Anemia (low blood) which may cause tiredness, or may require blood transfusion

Food and Medication Interactions

Grapefruit and grapefruit juice may interact with simvastatin and lead to potentially dangerous effects. Do not consume grapefruit products (grapefruit, grapefruit juice, grapefruit seed extract, or dietary supplements containing grapefruit) during the intervention portion of this study.

Simvastatin interacts with many other medications in ways that can increase or decrease the amount of medication in your blood. The interactions could result in increased levels that can be dangerous, or decreased levels so that drugs don't work. Please refer to the attached list of drugs that must be avoided while you are participating in this study.

Alcohol consumption

Simvastatin should be used with caution in patients who consume more than 5 drinks per day of alcohol as simvastatin may cause liver injury. We will monitor your liver function closely.

Reproductive Risks

Women who are pregnant or may become pregnant should not use simvastatin. When taken during pregnancy, simvastatin may cause harm to a developing baby. Women should not breastfeed a baby while using simvastatin. Women who are pregnant, attempting to become pregnant, or who are breastfeeding may not participate in the study. Women who are able to become pregnant will be required to have a pregnancy test before the study, and must agree to use adequate birth control (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Let your study doctor know immediately if you believe you might be pregnant.

Blood Collection

There may be pain, swelling, or bruising around the vein where your blood is collected. You may feel faint. There is a small risk of infection at the place on your body from which the blood is collected. The blood will be drawn by a person trained to collect blood using sterile (clean) equipment, and a very small needle will be used for drawing your blood to minimize discomfort.

Questionnaires
You may feel uncomfortable answering some of the questions you will be asked. If you feel uncomfortable answering any question, you can choose not to answer it.

Scans and Imaging Procedures

FibroScan
There are no known risks associated with a FibroScan examination.

Abdominal ultrasound
There are no known risks from having an abdominal ultrasound.

Abdominal computed tomography (CT)
An abdominal CT is a relatively safe procedure, but there are risks. CT scans expose you to more ionizing radiation than regular x-rays. CT scans have not been shown to cause long-term harm, although many x-rays or CT scans over time may increase your risk for cancer. However, the risk from any one scan is extremely small. If you have contrast through a vein (IV), you may have a warm, flushed sensation during the injection of the contrast materials and a metallic taste in your mouth that lasts for a few minutes. These feelings are normal and go away within a few seconds. Although rare, the contrast dye can cause medical problems or allergic reactions. Most reactions are mild and result in a rash or itchiness. In rare instances, an allergic reaction can be serious, even life-threatening. Tell your doctor about any allergies you may have, and tell the scanner operator right away if you have any trouble breathing during the procedure. Scanners come with an intercom and speakers, so the operator can hear you at all times.

Abdominal magnetic resonance imaging (MRI)
An abdominal MRI exam causes no pain. No side effects from the magnetic fields and radio waves have been reported. You may experience some discomfort as you will be asked to remain relatively motionless for a long period of time (about 1 hour). You may feel anxiety from the confinement in a tight space (claustrophobia). If you become anxious, you can stop the procedure at any time. At times, you may hear very loud noises as the MRI machine is taking pictures of your body. During the scan, earplugs will be provided to help mask the noise (intermittent humming, thumping, clicking, and knocking). You will be able to communicate with the technologist during the MRI and you may ask to stop the procedure at any time. The presence of metal in your body may be a safety hazard or affect a portion of the MRI image. Before receiving an MRI, tell the technologist if you have any metal or electronic devices in your body. The contrast agent used for MRIs is less likely to cause an allergic reaction than the contrast material used for CT scans.

What possible benefits can I expect from taking part in this study?
You should not expect to benefit from taking part in this research study. The results from this study will provide information that will help scientists to learn whether simvastatin will improve liver function in individuals with liver cirrhosis. This knowledge could help prevent liver cancer in the future.

Can I stop taking part in this study?
Your participation in this research study is voluntary so you may decline to participate or to stop being in this study at any time. If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely. If you choose not to participate in this study or decide to stop participating, you will not suffer any loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not negatively affect the care you receive or any present or future medical treatment.

You will be told about any new information or changes in the study that could affect your health or your willingness to continue in the study.

Your participation in this study may be ended without your consent by the Principal Investigator or your study doctor for the following reasons:

- If you develop a dangerous side effect;
- If you become pregnant;
- If your health changes;
- If the study is no longer in your best interest;
- If you do not follow the study rules;
- If the study is stopped early for any reason by the sponsor (NCI), the NCI Central IRB (CIRB), or FDA.

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study.

If you want to speak with someone who is not directly involved in this research, or have questions about your rights as a research subject, please contact the *(Insert institution name and Institutional Review Board or other site specific entity)*. You can call them at *(insert phone number)* or contact them by email at *(insert email address)*. The *(site specific entity)* has been established to protect the rights and welfare of research participants. You may also contact the *(site specific entity)* if you want to offer input or obtain information regarding the study.

What are the costs of taking part in this study?
The simvastatin and placebo will be supplied at no charge while you take part in this study. The cost of study-specific exams, tests, and any other procedures performed for research purposes will be paid for by the study.

The study may include some tests and procedures that may be considered part of your standard of care (routine medical care), and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer. Before you decide to be in the study, you should check with your health plan or insurance company to find out what they will pay for.

Will I receive payment for taking part in this study?
You will receive $50 after completing Screening and $100 at the completion of each study visit to reimburse you for your time, transportation, parking, and other expenses related to the study, as summarized in the table below. The total amount you will receive after you complete the entire study – Screening and all four study visits – is $450. If you do not complete the entire research study, you will only be reimbursed for those visits you do complete.

Research Visit	**Covered by the study** (done for research purposes at no cost to you)	**Not covered by the study** (routine medical care, billed to you or your insurance)	**Reimbursement to you when you finish the visit**
Screening	Medical history, medications, and laboratory test results review, vital signs and symptom assessment, blood tests, pregnancy test (for women who are able to become pregnant)	Physical assessment	$50
Study Visit 1	Medical history, medications, and laboratory test results review, vital signs and symptom assessment, blood tests, FibroScan exam, questionnaires		$100
Study Visit 2	Medical history, medications, and laboratory test results review, vital signs and symptom assessment, blood tests		$100
Study Visit 3	Medical history, medications, and laboratory test results review, vital signs and symptom assessment, blood tests		$100
Study Visit 4	Medical history, medications, and laboratory test results review, vital signs and symptom assessment, blood tests, FibroScan exam	Physical assessment; imaging scan of your abdominal area (ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI))	$100

(If W-9 information is not applicable to your institution then please remove the below paragraph)
You may be required to complete a W-9 Form in order to receive payment. The W-9 Form will be maintained by the accounting department at *(Insert institution name)*. Although any amount of payment may be reportable (check with a tax professional if you have questions about your obligations), if total payment by *(Insert institution name)* is $600 or more in a calendar year, a 1099 Form will be filed with the IRS in accordance with federal tax law. If you are a *(Insert institution name)* employee, you should provide your employee identification number to the

research team so that your payment can be appropriately processed through Payroll. For your own protection and to comply with tax laws, your payment for participation will be reported to the IRS together with other compensation you receive from *(Insert institution name)*.

What happens if I am injured or hurt because I took part in this study?
It is possible a research injury or illness may result from participating in this study. Any expenses incurred as a result of research related injury will be the responsibility of the study participant and/or their insurance carrier. If you feel you have been injured or hurt as a result of taking part in the study, it is important that you contact your study doctor immediately: *(Insert site specific investigator's name and contact number)*. If it is a medical emergency, call 911 or go to an emergency room. You will get medical treatment if you are injured or hurt as a result of taking part in this research study.

Who will see my medical information?
Your privacy is very important to us and we will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and information about your specimens, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor, the National Cancer Institute (NCI)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the US.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.

Where can I get more information?
You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Who can answer my questions about this study?
You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *(insert name of site-specific study doctor(s)* at *(insert telephone number)*.

This section is about optional studies you can choose to take part in.

Optional Sample Collections for Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples from your biopsies, blood, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

The researchers, *insert names of site specific investigators,* would like to ask your permission to store left over samples and health information obtained during your participation in this study for future medical research. Storing samples for future studies is called biobanking. The Biobank is being run by Cedars-Sinai Medical Center and supported by the National Cancer Institute.

The research that may be done is unknown at this time. Future research may include: 1) studies to identify genes and/or biomarkers and proteins that influence a risk of cancer in people with liver disease; 2) studies to identify specific pathways and mechanisms that promote cancer. A biomarker is a biological molecule found in blood, other body fluids, or tissues that may be a sign of a condition or disease.

What is involved?
If you agree to take part, your samples and related information will be stored at Cedars-Sinai Medical Center until the end of the study, when they may be transferred to the NCI Biobank, along with samples and information from other people who take part. These are not additional samples that will be collected, but will consist of any material (blood samples) that remains after the tests described for this study have been conducted.

Qualified researchers can submit a request to use the materials stored in the NCI Biobank. A research committee will review each request. There will also be an ethics review to ensure that the request is necessary and proper. You will not be notified if/when research is conducted using your samples.

What are the possible risks?

1) There is a risk that an unauthorized person could obtain the personal information in your medical records or other information we have stored about you.
2) There is a potential risk someone could trace the genetic information about you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

How will information about me be kept private?
Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name or birth date) will be sent. Samples will be identified by a unique study code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any NCI Biobank and Cedars-Sinai Medical Center staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom Cedars-Sinai Medical Center sends your samples and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) The results from research on your samples will not be put in your medical record.
6) If research results are published, your name and other personal information will not be used.

What are the possible benefits?
You will not benefit from taking part. We hope that studying your samples and data may, in the future, help to decrease or prevent liver cancer in people who have liver disease.

Are there any costs or payments?
There will be no cost to you or your insurance company for storage of your samples. Your blood samples will be used only for research and will not be sold. You will not be paid for allowing your leftover samples to be used in research. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call Dr. Marc T. Goodman at (310) 423-6188, who will let the researchers know. Then, any samples that remain in the bank will be destroyed. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?
If you have questions about the use of your samples for research, contact the Principal Investigator, Dr. Marc T. Goodman, at (310) 423-6188.

Samples for future research studies
Please circle your answer to show whether or not you would like to take part in each option.

My blood samples and related information may be kept in the NCI Biobank for use in future health research. These are blood samples left over from the main study.

Please circle one: YES NO

I agree that the researchers, *insert names of site specific investigators,* or their representative, *insert names of site specific research staff,* may contact me or my physician to see if I wish to participate in other research in the future.

Please circle one: YES NO

Access to unused samples
The researchers, *insert names of site specific investigators,* would like your permission to access unused samples collected for clinical purposes as part of your usual care, such as leftover tissue from biopsies, pathology slides, and tissue blocks. These unused samples would be tissue samples routinely collected as part of your clinical care including surgical procedures, endoscopy procedures, and outpatient procedures. The samples would be obtained from the pathology laboratory and routine doctor's visits. Please circle your answer to show whether or not you give permission.

I agree that the researchers, or their representative, may have to access to my unused samples.

Please circle one: YES NO

Medical records access and future contact
There may be other important questions about you that have not been answered during the course of this research study. In order to answer these questions, we may need to contact you or review your medical records in the future. We request access to your medical records for 10 years.

Please circle your answer to show whether or not you give permission for each of the following.

I agree that the researchers, *insert names of site specific investigators,* or their representative, *insert names of site specific research staff,* may review my medical records in the future.

Please circle one: YES NO

I agree that the researchers, *insert names of site specific investigators,* or their representative, *insert names of site specific research staff,* may contact me in the future if they have additional questions.

Please circle one: YES NO

I agree that the researchers, *insert names of site specific investigators,* or their representative, *insert names of site specific research staff,* may contact me in the future to see if I wish to learn about results from the study.

Please circle one: YES NO

This is the end of the section about optional studies.

Consent Summary
I have read this consent form and the research study has been explained to me. I have been given time to ask questions, and have been told whom to contact if I have more questions. I agree to be in the research study described above. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Name (printed) and Signature of Research Participant	Date of Signature
Name (printed) and Signature of Person Obtaining Consent	Date of Signature

APPENDIX A
PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Karnofsky Performance Scale

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B
LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha Fetoprotein
AFP-L3	Alpha Fetoprotein glycoform (third electrophoretic form of lentil lectin-reactive AFP)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CBDF	Complete Blood Count and Automated Differential
CIRB	NCI Central IRB
CMPL	Comprehensive Metabolic Panel
CPK	Creatine Phosphokinase / Creatine Kinase
CSMC	Cedars-Sinai Medical Center
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCA	Deoxycholic acid
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
GCA	Glycocholic acid
GCDCA	Glycochenodeoxycholic acid
GDCA	Glycodeoxycholic acid
GU	Georgetown University/MedStar Georgetown University Hospital
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme A
ICF	Informed Consent Form
IL-6	Interleukin 6
IRB	Institutional Review Board
kPa	Kilopascal
LCA	Lithocholic acid
MELD	Model for End-Stage Liver Disease
MRI	Magnetic Resonance Imaging
NASH	Nonalcoholic steatohepatitis
NF-kB	Nuclear factor-kappaB
NWU	Northwestern University
PT	Prothrombin Time
RCT	Randomized controlled trial
ROS	Reactive Oxygen Species
TCDCA	Taurochenodeoxycholic acid
UPR	The University of Puerto Rico

APPENDIX C
STUDY DIARY
Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer

Please bring your completed diary and your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Protocol Number: NWU2015-06-03 **Site: _____**

Participant Study ID: _____ **Participant Name: _____**

Date Study Drug Dispensed: _____ **Participant Signature: _____**

Reminder: Do not consume any grapefruit products, including grapefruit, grapefruit juice, grapefruit seed extract, or dietary supplements containing grapefruit, while you are participating in the study.

Instructions

Complete one line in the table for each day you take the study drug.
Please contact the study coordinator at <<Study number>> if you have any questions.

- Take your study drug once per day at bedtime or with an evening meal. Take the capsule at the same time every day. Please swallow the capsule whole and do not chew, crush, or open it.
- Record the date and time of day you took the study drug.
- If you notice any side effects such as headache, abdominal pain, constipation, nausea or vomiting, respiratory infection, or mild skin rash, or if you have any other symptoms or comments, please record them in the Side Effects/Comments column and report them to the study staff when they call you.
- If you miss a dose of the study drug, take it as soon as you remember. Do not take the drug if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of the study drug at the same time. Please write the reason for missing a dose in the Side Effects/Comments column.
- For telehealth visits we will ask you to remotely review your pill diary and photograph unused pills

Day	Date	Time Study Drug Taken	Side Effects/Comments (Please include reason for missed dose)
1		____:____ ☐ a.m. / ☐ p.m.	
2		____:____ ☐ a.m. / ☐ p.m.	
3		____:____ ☐ a.m. / ☐ p.m.	
4		____:____ ☐ a.m. / ☐ p.m.	
5		____:____ ☐ a.m. / ☐ p.m.	
6		____:____ ☐ a.m. / ☐ p.m.	
7		____:____ ☐ a.m. / ☐ p.m.	
8		____:____ ☐ a.m. / ☐ p.m.	
9		____:____ ☐ a.m. / ☐ p.m.	
10		____:____ ☐ a.m. / ☐ p.m.	
11		____:____ ☐ a.m. / ☐ p.m.	
12		____:____ ☐ a.m. / ☐ p.m.	
13		____:____ ☐ a.m. / ☐ p.m.	
14		____:____ ☐ a.m. / ☐ p.m.	
15		____:____ ☐ a.m. / ☐ p.m.	
16		____:____ ☐ a.m. / ☐ p.m.	

Day	Date	Time Study Drug Taken	Side Effects/Comments (Please include reason for missed dose)
17		____:____ ☐ a.m. / ☐ p.m.	
18		____:____ ☐ a.m. / ☐ p.m.	
19		____:____ ☐ a.m. / ☐ p.m.	
20		____:____ ☐ a.m. / ☐ p.m.	
21		____:____ ☐ a.m. / ☐ p.m.	
22		____:____ ☐ a.m. / ☐ p.m.	
23		____:____ ☐ a.m. / ☐ p.m.	
24		____:____ ☐ a.m. / ☐ p.m.	
25		____:____ ☐ a.m. / ☐ p.m.	
26		____:____ ☐ a.m. / ☐ p.m.	
27		____:____ ☐ a.m. / ☐ p.m.	
28		____:____ ☐ a.m. / ☐ p.m.	
29		____:____ ☐ a.m. / ☐ p.m.	
30		____:____ ☐ a.m. / ☐ p.m.	
31		____:____ ☐ a.m. / ☐ p.m.	
32		____:____ ☐ a.m. / ☐ p.m.	
33		____:____ ☐ a.m. / ☐ p.m.	
34		____:____ ☐ a.m. / ☐ p.m.	
35		____:____ ☐ a.m. / ☐ p.m.	
36		____:____ ☐ a.m. / ☐ p.m.	
37		____:____ ☐ a.m. / ☐ p.m.	
38		____:____ ☐ a.m. / ☐ p.m.	
39		____:____ ☐ a.m. / ☐ p.m.	
40		____:____ ☐ a.m. / ☐ p.m.	
41		____:____ ☐ a.m. / ☐ p.m.	
42		____:____ ☐ a.m. / ☐ p.m.	
43		____:____ ☐ a.m. / ☐ p.m.	
44		____:____ ☐ a.m. / ☐ p.m.	
45		____:____ ☐ a.m. / ☐ p.m.	
46		____:____ ☐ a.m. / ☐ p.m.	
47		____:____ ☐ a.m. / ☐ p.m.	
48		____:____ ☐ a.m. / ☐ p.m.	
49		____:____ ☐ a.m. / ☐ p.m.	
50		____:____ ☐ a.m. / ☐ p.m.	
51		____:____ ☐ a.m. / ☐ p.m.	

Day	Date	Time Study Drug Taken	Side Effects/Comments (Please include reason for missed dose)
52		____:____ ☐ a.m. / ☐ p.m.	
53		____:____ ☐ a.m. / ☐ p.m.	
54		____:____ ☐ a.m. / ☐ p.m.	
55		____:____ ☐ a.m. / ☐ p.m.	
56		____:____ ☐ a.m. / ☐ p.m.	
57		____:____ ☐ a.m. / ☐ p.m.	
58		____:____ ☐ a.m. / ☐ p.m.	
59		____:____ ☐ a.m. / ☐ p.m.	
60		____:____ ☐ a.m. / ☐ p.m.	
61		____:____ ☐ a.m. / ☐ p.m.	
62		____:____ ☐ a.m. / ☐ p.m.	
63		____:____ ☐ a.m. / ☐ p.m.	
64		____:____ ☐ a.m. / ☐ p.m.	
65		____:____ ☐ a.m. / ☐ p.m.	
66		____:____ ☐ a.m. / ☐ p.m.	
67		____:____ ☐ a.m. / ☐ p.m.	
68		____:____ ☐ a.m. / ☐ p.m.	
69		____:____ ☐ a.m. / ☐ p.m.	
70		____:____ ☐ a.m. / ☐ p.m.	
71		____:____ ☐ a.m. / ☐ p.m.	
72		____:____ ☐ a.m. / ☐ p.m.	
73		____:____ ☐ a.m. / ☐ p.m.	
74		____:____ ☐ a.m. / ☐ p.m.	
75		____:____ ☐ a.m. / ☐ p.m.	
76		____:____ ☐ a.m. / ☐ p.m.	
77		____:____ ☐ a.m. / ☐ p.m.	
78		____:____ ☐ a.m. / ☐ p.m.	
79		____:____ ☐ a.m. / ☐ p.m.	
80		____:____ ☐ a.m. / ☐ p.m.	
81		____:____ ☐ a.m. / ☐ p.m.	
82		____:____ ☐ a.m. / ☐ p.m.	
83		____:____ ☐ a.m. / ☐ p.m.	
84		____:____ ☐ a.m. / ☐ p.m.	
85		____:____ ☐ a.m. / ☐ p.m.	

Day	Date	Time Study Drug Taken	Side Effects/Comments (Please include reason for missed dose)
86		____:____ ☐ a.m. / ☐ p.m.	
87		____:____ ☐ a.m. / ☐ p.m.	
88		____:____ ☐ a.m. / ☐ p.m.	
89		____:____ ☐ a.m. / ☐ p.m.	
90		____:____ ☐ a.m. / ☐ p.m.	
91		____:____ ☐ a.m. / ☐ p.m.	
92		____:____ ☐ a.m. / ☐ p.m.	
93		____:____ ☐ a.m. / ☐ p.m.	
94		____:____ ☐ a.m. / ☐ p.m.	
95		____:____ ☐ a.m. / ☐ p.m.	
96		____:____ ☐ a.m. / ☐ p.m.	
97		____:____ ☐ a.m. / ☐ p.m.	
98		____:____ ☐ a.m. / ☐ p.m.	
99		____:____ ☐ a.m. / ☐ p.m.	
100		____:____ ☐ a.m. / ☐ p.m.	
101		____:____ ☐ a.m. / ☐ p.m.	
102		____:____ ☐ a.m. / ☐ p.m.	
103		____:____ ☐ a.m. / ☐ p.m.	
104		____:____ ☐ a.m. / ☐ p.m.	
105		____:____ ☐ a.m. / ☐ p.m.	
106		____:____ ☐ a.m. / ☐ p.m.	
107		____:____ ☐ a.m. / ☐ p.m.	
108		____:____ ☐ a.m. / ☐ p.m.	
109		____:____ ☐ a.m. / ☐ p.m.	
110		____:____ ☐ a.m. / ☐ p.m.	
111		____:____ ☐ a.m. / ☐ p.m.	
112		____:____ ☐ a.m. / ☐ p.m.	
113		____:____ ☐ a.m. / ☐ p.m.	
114		____:____ ☐ a.m. / ☐ p.m.	
115		____:____ ☐ a.m. / ☐ p.m.	
116		____:____ ☐ a.m. / ☐ p.m.	
117		____:____ ☐ a.m. / ☐ p.m.	
118		____:____ ☐ a.m. / ☐ p.m.	
119		____:____ ☐ a.m. / ☐ p.m.	
120		____:____ ☐ a.m. / ☐ p.m.	

FOR STUDY TEAM USE ONLY	Staff Initials:
Date study drug dispensed:	Date study drug returned:
Number of pills/capsules dispensed:	Number of pills/capsules returned:
Number of pills/capsules that should have been taken:	
Discrepancy/notes:	

APPENDIX D

Food and Medications to Avoid During Your Participation in the Study

Do not consume grapefruit products (grapefruit, grapefruit juice, grapefruit seed extract, or dietary supplements containing grapefruit) while you are participating in the study. You should not use oral formulations (i.e., tablets or capsules) of any of the following medications while you are participating in the study. Topical formulations, including creams, shampoos, foams, and gels applied to the skin, are acceptable. Tell your study doctor immediately if you use any of these medications, or if any of these medications or any new medications are prescribed for you during the study.

Generic name	Brand name(s)
amiodarone	Pacerone, Cordarone
amlodipine	Lotrel, Norvasc
bosentan	Tracleer
boceprevir	Victrelis
carbamazepine	Tegretol
clarithromycin	Biaxin, Prevpac
cobicistat-containing medications	Evotaz, Genvoya, Prezcobix, Stribild
colchicine	Colcrys
cyclosporine	Gengraf, Neoral, Sandimmune
danazol	Danocrine
diltiazem	Cardizem, Dilacor, Taztia, Tiazac
dronedarone	Multaq
efavirenz	Sustiva, Stocrin
etravirine	Intelence
erythromycin	EES, Erythrocin, Ery-Tab, E-Mycin
gemfibrozil	Lopid
itraconazole	Onmel, Sporanox
ketoconazole	Nizoral
lomitapide	Juxtapid
modafinil	Provigil
nafcillin	Nallpen, Unipen
nefazodone	Serzone
phenytoin	Dilantin
posaconazole	Noxafil, Posanol
ranolazine	Ranexa
red yeast rice	Over-the-counter supplement, various brands
rifampin	Rifadin
St. John's wort *(Hypericum perforatum)*	Over-the-counter herbal remedy, various brands
telaprevir	Incivek
telithromycin	Ketek
verapamil	Calan, Covera, Isoptin, Verelan
voriconazole	Vfend

HIV protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)	Aptivus, Crixivan, Invirase, Kaletra, Lexiva, Norvir, Prezista, Reyataz, Viracept

APPENDIX E

Clinical Laboratory Minimum Test Requirements

Clinical labs will be done at Screen 1 to confirm eligibility for the trial; and at Study Visits 1, 2, 3, and 4 to monitor for potential adverse effects of the intervention. Labs must include at least the following tests. It is acceptable to do additional tests if they are included in the blood panels at your institution.

Blood Hematology: Complete Blood Count and Differential	**Blood Chemistry: Comprehensive Metabolic Panel**	**Lipid Panel ***	**Other Blood Tests**
Hemoglobin Platelet count Leukocytes (White blood cell count, total) Neutrophil count, absolute	Alanine aminotransferase (ALT (SGPT)) Aspartate aminotransferase (AST (SGOT)) Alkaline phosphatase (ALP) Bilirubin, total Creatinine Sodium Glucose Potassium Total Protein	Total cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglycerides	Hemoglobin A1C (HbA1C) * Prothrombin Time (PT/INR) † Creatine phosphokinase (CPK) §

* Lipid panel and hemoglobin A1C will be done at Study Visits 1, 3, and 4.

† Prothrombin Time will be done at Screen 1 and Study Visit 4 to calculate the MELD score.

§ Creatine phosphokinase (CPK) will be measured at Study Visit 1 to establish a patient-specific reference for this indicator of muscle toxicity. If the patient reports unexplained muscle pain or weakness during the trial, CPK will be tested again to check for elevation.

APPENDIX F

Participant ID: _____

Date: _____

Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer

Risk Questionnaire

We appreciate the time you are taking to complete this interview. We will be asking you questions about factors and behaviors that we believe may be related to the development of liver cancer. Please try to answer each question as completely as you can, even if you are unsure about the answer. All answers will be kept confidential.

DEMOGRAPHICS

The next questions ask about your personal background.

1. Were you born in the United States? [1] ☐ Yes → *If YES skip to question # 2* [0] ☐ No
   <<IF NO>> a. Where were you born? *(Show list of Countries and U.S. territories)* _____
   b. Do you currently live in the United States? [1] ☐ Yes [0] ☐ No
   <<IF YES>> c. In what year did you begin residence in the U.S.? _____

2. Where was your biological mother born?
   [1] ☐ In the United States [2] ☐ Outside of the United States [9] ☐ Don't know
   <<IF Outside of the United States >> a. Where was she born? *(Show list of Countries)* _____

3. Where was your biological father born?
   [1] ☐ In the United States [2] ☐ Outside of the United States [9] ☐ Don't know
   <<IF Outside of the United States >> a. Where was he born? *(Show list of Countries)* _____

4. What is your racial background? *Check all boxes that apply.*
   [1] ☐ White or Caucasian
   [2] ☐ African-American or Black
   [3] ☐ Chinese or Taiwanese
   [4] ☐ Filipino
   [5] ☐ Japanese or Okinawan
   [6] ☐ Korean
   [7] ☐ Vietnamese
   [8] ☐ Asian Indian
   [9] ☐ Other Asian _____
   [10] ☐ American Indian or Alaska Native
   [11] ☐ Native Hawaiian
   [12] ☐ Samoan
   [13] ☐ Other Pacific Islander _____
   [14] ☐ Iranian
   [15] ☐ Armenian
   [16] ☐ Israeli
   [17] ☐ Egyptian
   [18] ☐ Other race (please specify) _____

5. Are you of Hispanic or Latino/a ancestry?
   [1] ☐ Yes, Mexican, Mexican American, Chicano [2] ☐ Yes, Puerto Rican [3] ☐ Yes, Cuban
   [4] ☐ Yes, Other Hispanic _____ [0] ☐ No → *If NO skip to question # 6 (education)*

   <<IF YES, administer SASH – validated questionnaire for Hispanic acculturation, English or Spanish>>

   a. In general, what language(s) do you read and speak?

Only English	English better than Spanish	Both equally	Spanish better than English	Only Spanish
[5] ☐	[4] ☐	[3] ☐	[2] ☐	[1] ☐

   b. What language do you usually speak at home?

Only English	More English than Spanish	Both equally	More Spanish than English	Only Spanish
[5] ☐	[4] ☐	[3] ☐	[2] ☐	[1] ☐

   c. In what language do you usually think?

Only English	More English than Spanish	Both equally	More Spanish than English	Only Spanish
[5] ☐	[4] ☐	[3] ☐	[2] ☐	[1] ☐

   d. What language do you usually speak with your friends?

Only English	More English than Spanish	Both equally	More Spanish than English	Only Spanish
[5] ☐	[4] ☐	[3] ☐	[2] ☐	[1] ☐

6. What is the **highest** grade or level of schooling you have completed? *Check one box only.*

1 ☐ No formal education	5 ☐ Technical or vocational school
2 ☐ 8th grade or less	6 ☐ Associate degree or some college
3 ☐ Some high school (9th -11th grade)	7 ☐ Bachelor's degree
4 ☐ High school graduate or GED	8 ☐ Advanced degree (Master's or Doctoral degree)

7. Are you currently employed (including self-employed)?

1 ☐ Yes 0 ☐ No

a. On average, how many hours do you work each week? *Check one box only.*

1 ☐ 1-29 hours 2 ☐ 30-44 hours 3 ☐ 45-54 hours 4 ☐ 55+ hours

8. What is your current marital status? *Check one box only.*

1 ☐ Single (never married) 2 ☐ Married 3 ☐ Living with partner
4 ☐ Separated 5 ☐ Divorced 6 ☐ Widowed

9. With whom do you currently live? *Check all boxes that apply.*

1 ☐ Spouse/partner 2 ☐ Children 3 ☐ Parent(s) 4 ☐ Parent(s)-in-law 5 ☐ Other relative(s)
6 ☐ Friend(s) 7 ☐ I live alone 8 ☐ Other (please describe) _____

10. **Excluding you**, how many people live in your home who are age… *If none enter 0.*

over 18 years old	between 12–18 years old	between 6–11 years old	under 6 years old
_____	_____	_____	_____

11. Are you covered by health insurance or a health care plan?

1 ☐ Yes 0 ☐ No → *If NO skip to next section – SLEEP*

a. What type of health insurance or health care plan are you enrolled in? *Check all boxes that apply.*

1 ☐ Employer group insurance through my job or my partner's job	2 ☐ Self-employed health plan
3 ☐ Medicaid/Medi-Cal or other government program	4 ☐ Medicare
5 ☐ Private health insurance that I pay for myself	6 ☐ Military health care
7 ☐ I have health insurance, but I don't know what type	
8 ☐ Other health insurance plan (please describe) _____	

SLEEP

<< SLEEP-50 Questionnaire (selected subscales) >>

The following questions ask about your sleep habits.

Please respond to what extent each of the following statements has been applicable to you **during the past 4 weeks**.

During the **past 4 weeks:**	Not at all	Somewhat	Rather much	Very much
1. I am told that I snore.	1 ☐	2 ☐	3 ☐	4 ☐
2. I sweat during the night.	1 ☐	2 ☐	3 ☐	4 ☐
3. I am told that I hold my breath when sleeping.	1 ☐	2 ☐	3 ☐	4 ☐
4. I am told that I wake up gasping for air.	1 ☐	2 ☐	3 ☐	4 ☐
5. I wake up with a dry mouth.	1 ☐	2 ☐	3 ☐	4 ☐
6. I wake up during the night while coughing or being short of breath.	1 ☐	2 ☐	3 ☐	4 ☐
7. I wake up with a sour taste in my mouth.	1 ☐	2 ☐	3 ☐	4 ☐
8. I wake up with a headache.	1 ☐	2 ☐	3 ☐	4 ☐
9. I would rather go to bed at a different time.	1 ☐	2 ☐	3 ☐	4 ☐
10. I go to bed at very different times (more than 2-hour difference).	1 ☐	2 ☐	3 ☐	4 ☐
11. I do shift work.	1 ☐	2 ☐	3 ☐	4 ☐
12. I feel tired at getting up.	1 ☐	2 ☐	3 ☐	4 ☐
13. I feel sleepy during the day and struggle to remain alert.	1 ☐	2 ☐	3 ☐	4 ☐
14. I would like to have more energy during the day.	1 ☐	2 ☐	3 ☐	4 ☐
15. I am told that I am easily irritated.	1 ☐	2 ☐	3 ☐	4 ☐
16. I have difficulty in concentrating at work or school.	1 ☐	2 ☐	3 ☐	4 ☐
17. I worry whether I sleep enough.	1 ☐	2 ☐	3 ☐	4 ☐
18. Generally, I sleep badly.	1 ☐	2 ☐	3 ☐	4 ☐

19. On a scale of 1 to 10 where 1 is **very bad** and 10 is **very good**, how would you rate your sleep?

Very Bad									Very good
1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

20. I sleep _____ hours, mostly from *(times of day or night)* _____ to _____.

DISEASE SPECIFIC QUALITY OF LIFE
CHRONIC LIVER DISEASE QUESTIONNAIRE (CLDQ)

These questions are designed to find out how you have been feeling **during the last two weeks**. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. *Please select only one response for each question.*

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
2. How much of the time have you been tired or fatigued during the last two weeks?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
3. How much of the time during the last two weeks have you experienced bodily pain?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
4. How often during the last two weeks have you felt sleepy during the day?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
5. How much of the time during the last two weeks have you experienced abdominal pain?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
6. How much of the time during the last two weeks has shortness of breath been a problem for you in your daily activities?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
7. How much of the time during the last two weeks have you not been able to eat as much as you would like?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
8. How much of the time in the last two weeks have you been bothered by having decreased strength?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
9. How often during the last two weeks have you had trouble lifting or carrying heavy objects?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
10. How often during the last two weeks have you felt anxious?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
11. How often during the last two weeks have you felt a decreased level of energy?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
12. How much of the time during the last two weeks have you felt unhappy?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
13. How often during the last two weeks have you felt drowsy?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
15. How often during the last two weeks have you been irritable?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
16. How much of the time during the last two weeks have you had difficulty sleeping at night?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
19. How much of the time during the last two weeks have you had mood swings?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
20. How much of the time during the last two weeks have you been unable to fall asleep at night?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
21. How often during the last two weeks have you had muscle cramps?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
22. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
23. How much of the time during the last two weeks have you had a dry mouth?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
24. How much of the time during the last two weeks have you felt depressed?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
25. How much of the time during the last two weeks have you been worried about your condition getting worse?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
26. How much of the time during the last two weeks have you had problems concentrating?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
27. How much of the time have you been troubled by itching during the last two weeks?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
28. How much of the time during the last two weeks have you been worried about never feeling any better?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
29. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

PHYSICAL HEALTH & COMORBIDITY

<< Components of FRAIL AAH Questionnaire >>

1. How much of the time during the **past 4 weeks** did you feel tired? Please select one answer only.
   [1] ☐ All of the time [2] ☐ Most of the time [3] ☐ Some of the time [4] ☐ A little of the time [5] ☐ None of the time

2. By yourself and not using aids, do you have any difficulty **walking up 10 steps without resting**?
   [1] ☐ Yes [0] ☐ No

3. By yourself and not using aids, do you have any difficulty **walking several hundred yards**?
   [1] ☐ Yes [0] ☐ No

MEDICATIONS AND MEDICAL CONDITIONS

The next questions ask about your medication use and medical history. Please answer the best you can.

Antibiotics

1. Have you taken antibiotics in the **past 12 months**?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 2*
   a. How many courses of antibiotics have you taken during the **past 12 months**? A course usually lasts about one week, and does not count refills. _____ courses

   <<Ask i, ii, and iii for each course of antibiotics taken; use continuation sheet if needed>>

   i. What was your reason for taking this course of antibiotics?
      [1] ☐ Prevent an infection [2] ☐ Treat an infection
   ii. When did you **start** this course of antibiotics? _____/_____ (Month/Year)
   iii. When did you **stop** this course of antibiotics? _____/_____ (Month/Year)

Aspirin, NSAIDS, Statins, Beta Blockers

2. Have you ever taken **aspirin** *(examples: Bayer, Bufferin, Excedrin, Anacin, Ecotrin)* at least **4 days per week** for **3 months** or longer?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 3*
   a. How old were you when you **started** taking **aspirin** at least **4 days per week**? _____ years old
   b. Was it a baby or low-dose aspirin (162 mg or less)? [1] ☐ Yes [0] ☐ No [9] ☐ Don't know
   c. Do you take **aspirin** at least **4 days per week** now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> d. When did you **stop** taking **aspirin** at least **4 days per week**? _____ years old

3. Have you ever taken **ibuprofen** *(examples: Motrin, Advil, Nuprin, Mediprin)* at least **4 days per week** for **3 months** or longer?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 4*
   a. How old were you when you **started** taking **ibuprofen** at least **4 days per week**? _____ years old
   b. Do you take **ibuprofen** at least **4 days per week** now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> c. When did you **stop** taking **ibuprofen** at least **4 days per week**? _____ years old

4. Have you ever taken **acetaminophen** *(example: Tylenol)* at least **4 days per week** for **3 months** or longer?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 5*
   a. How old were you when you **started** taking **acetaminophen** at least **4 days per week**? _____ years old
   b. Do you take **acetaminophen** at least **4 days per week** now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> c. When did you **stop** taking **acetaminophen** at least **4 days per week**? _____ years old

5. Have you ever taken **Celebrex** at least **4 days per week** for **3 months** or longer?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 6*
   a. How old were you when you **started** taking **Celebrex** at least **4 days per week**? _____ years old
   b. Do you take **Celebrex** at least **4 days per week** now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> c. When did you **stop** taking **Celebrex** at least **4 days per week**? _____ years old

6. Have you ever taken **other anti-inflammatory pain relievers** *(examples: Aleve, naproxen, mobic, nabumetone, meloxicam, diclofenac, indomethacin)* at least **4 days per week** for **3 months** or longer?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 7*
   a. How old were you when you **started** taking **other anti-inflammatory pain relievers** at least **4 days per week**? _____ years old
   b. Do you take **other anti-inflammatory pain relievers** at least **4 days per week** now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> c. When did you **stop** taking **other anti-inflammatory pain relievers** at least **4 days per week**? _____ years old

7. Have you ever taken **beta blockers** *(examples: Sectral, Tenormin, Zebeta, Lopressor, Corgard, Bystolic, Inderal LA, InnoPran XL)* at least **4 days per week** for **3 months** or longer?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 8*
   a. How old were you when you **started** taking **beta blockers** at least **4 days per week**? _____ years old
   b. Do you take **beta blockers** at least **4 days per week** now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> c. When did you **stop** taking **beta blockers** at least **4 days per week**? _____ years old

8. Current Medications *<< Review Current Medication list with participant to verify what has been extracted from the medical chart with respect to drug name, drug dosage, and age started. >>*

9. Has a doctor or health care provider ever told you that you had diabetes?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 10*
   a. How old were you when a doctor **first told** you that you had diabetes? _____ years old
   b. Did you do any of the following to monitor or treat your diabetes?

Check Yes or No for each item.	Yes	No
a. Use a home glucose test to monitor your insulin level?	[1] ☐	[0] ☐
b. Change your diet?	[1] ☐	[0] ☐
c. Take medication by mouth?	[1] ☐	[0] ☐
d. Take insulin by injection?	[1] ☐	[0] ☐

10. Have you ever had surgery to remove your [*type of tissue*]? *Repeat for each type of tissue. If Yes, ask question about age when had surgery.*	Yes	No	How old were you when you had this surgery?
a. Appendix	[1] ☐	[0] ☐	_____
b. Gall Bladder	[1] ☐	[0] ☐	_____
c. Gall Stones	[1] ☐	[0] ☐	_____
d. Stomach or part of your stomach	[1] ☐	[0] ☐	_____
e. Colon or rectum	[1] ☐	[0] ☐	_____
WOMEN ONLY:			
f. Breast (mastectomy)	[1] ☐	[0] ☐	_____
g. Uterus (hysterectomy)	[1] ☐	[0] ☐	_____
h. Ovaries (oophorectomy)	[1] ☐	[0] ☐	_____

11. Have you ever had a transjugular intrahepatic portosystemic shunt (TIPS)? TIPS is a **non-surgical** procedure to create new connections between two blood vessels in your liver.

[1] ☐ Yes [0] ☐ No → *If NO skip to question # 12*

a. How old were you when you had this procedure? _____ years old

12. Have you ever had a distal splenorenal shunt (DSRS)? DSRS is a **surgical** procedure where the vein from the spleen (called the splenic vein) is detached from the portal vein (the vein that carries blood from the digestive organs to the liver) and reattached to the left kidney (renal) vein.

[1] ☐ Yes [0] ☐ No → *If NO skip to question # 13*

a. How old were you when you had this procedure? _____ years old

---

ANTHROPOMETRY

The following questions ask about your physical development.

1. What is your **current** height? _____ Feet _____ Inches

2. What was your **maximum height** as an adult? _____ Feet _____ Inches

<< The next 2 questions are Components of the FRAIL AAH Questionnaire >>

3. How much do you **currently** weigh with your clothes on but without shoes? _____ Pounds

4. **One year ago** in (___/____ Month/Year), how much did you weigh with your clothes on but without shoes? _____ Pounds

5. Compared with other [*insert boys/men or girls/women*] in the same age range, when you were [*age range*], were you considered: *(Check one box for each age range, and ask about average weight in age range.)*

	15-19 years old	20-29 years old	30-39 years old	40-49 years old	50-59 years old	60-69 years old	70+ years old
Very Thin	[1] ☐	[1] ☐	[1] ☐	[1] ☐	[1] ☐	[1] ☐	[1] ☐
Somewhat Thin	[2] ☐	[2] ☐	[2] ☐	[2] ☐	[2] ☐	[2] ☐	[2] ☐
Average Weight	[3] ☐	[3] ☐	[3] ☐	[3] ☐	[3] ☐	[3] ☐	[3] ☐
Somewhat Heavy	[4] ☐	[4] ☐	[4] ☐	[4] ☐	[4] ☐	[4] ☐	[4] ☐
Very Heavy	[5] ☐	[5] ☐	[5] ☐	[5] ☐	[5] ☐	[5] ☐	[5] ☐
Not Applicable	[8] ☐	[8] ☐	[8] ☐	[8] ☐	[8] ☐	[8] ☐	[8] ☐
What was your **average weight** in this age range?	_____ lbs.	_____ lbs.	_____ lbs.	_____ lbs.	_____ lbs.	_____ lbs.	_____ lbs.

TOBACCO

The next questions ask about your use of tobacco. Please answer to the best of your ability.

1. Have you ever smoked **at least one cigarette a day** for **6 months or longer**?
   [1] ☐ Yes [0] ☐ No → *If NO skip to next section – ALCOHOL*
2. How old were you when you first started smoking cigarettes **daily**? _____ years old
3. During the time you smoked, how many cigarettes did you usually smoke **each day**? ____ cigarettes per day
4. How many years have you (or did you use) smoke **at least one cigarette a day**? _____ years
5. Do you smoke cigarettes now? [1] ☐ Yes [0] ☐ No
   <<IF NO>> a. How old were you when you **quit smoking cigarettes**? _____ years old

---

ALCOHOL

<<Alcohol Use Disorders Identification Test for Alcohol Consumption (AUDIT-C)>>

The last questions ask about your use of alcohol. Your answers will remain confidential so please be honest.

*Now I am going to ask you some questions about your use of alcoholic beverages **during this past year**. One drink of alcohol is a 12-ounce bottle or can of beer, an 8-ounce bottle or can of malt liquor, a 12-ounce wine cooler, a 5-ounce glass of wine, a 1½ ounce shot of liquor, or a mixed drink containing 1½ ounces of liquor, such as gin, vodka, rum, or whisky.*

1. How often do you have a drink containing alcohol?
   [0] ☐ Never → ***If Never the interview is completed***
   [1] ☐ Monthly or less
   [2] ☐ 2 to 4 times a month
   [3] ☐ 2 to 3 times a week
   [4] ☐ 4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   [0] ☐ 1 or 2
   [1] ☐ 3 or 4
   [2] ☐ 5 or 6
   [3] ☐ 7, 8, or 9
   [4] ☐ 10 or more
3. How often do you have **six or more drinks** on one occasion?
   [0] ☐ Never
   [1] ☐ Less than monthly
   [2] ☐ Monthly
   [3] ☐ Weekly
   [4] ☐ Daily or almost daily

END OF INTERVIEWER-ADMINISTERED QUESTIONNAIRE

Thank you for taking the time to complete the interview. This information is vitally important to our study and we greatly appreciate your contributions.

INTERVIEWER'S REMARKS

1. Participant ID _____

2. Interviewer ___ ___ (Initials)

3. Participant's sex [1] ☐ Male [2] ☐ Female

4. Participant's date of birth Month _____ Day _____ Year _____ (*Current Age*: _____)

5. Date of Interview Month _____ Day _____ Year _____

6. Interview Start Time ___ ___ : ___ ___ (Hour: Minutes [24-hour time])

7. Interview End Time ___ ___ : ___ ___ (Hour: Minutes [24-hour time])

8. The interview included: *(Check all boxes that apply.)*
   [1] ☐ The participant only
   [2] ☐ A spouse or partner
   [3] ☐ Another family member
   [4] ☐ Another person (please specify) _____

9. The participant's cooperation was: *(Check one box only.)*
   [1] ☐ Excellent [2] ☐ Very Good [3] ☐ Good [4] ☐ Fair [5] ☐ Poor

10. The quality of the interview is: *(Check one box only.)*
    [1] ☐ Excellent [2] ☐ Generally reliable [3] ☐ Questionable [4] ☐ Unreliable

_____ _____
Signature of Clinical Research Staff who administered questionnaire Date

APPENDIX G

Medication Reminder to be sent via Text Message and Email

Text Message:

This is a reminder to take your medication for the Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer research study this evening. Please swallow the capsule whole, and please remember to fill out your study diary. Thank you!

Email:

This is just a friendly reminder to take your medication for the Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer research study at bedtime or with your evening meal. Please swallow the capsule whole and do not chew, crush, or open it. Please also remember to fill out your study diary, noting the date and time when you took the medication. Let us know if you have any questions or concerns. Thank you very much!

APPENDIX H

Patient Appointment Letter – No FibroScan

[Insert Clinical Site Logo or Name]

Date»

«Name»
«Address»
«City, state, zip code»

Dear «Name»

Thank you very much for participating in our research study, Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer. Your participation is vital to the success of this study.

Following are the date, time, and location of your research study visit. Please see the attached map. The visit appointment will take about one hour.

Date: _____

Time: _____

Place:

We look forward to meeting with you. This research could not be conducted without your participation, and we are grateful for your time and interest. If you have any questions or if you need to change the date or time of the appointment, please call me at «clinical research staff phone number».

Sincerely,

«Clinical research staff name»
«Clinical research staff job title»

[Insert directions to clinic and map on next page]

APPENDIX I
Patient Appointment Letter – FibroScan

[Insert Clinical Site Logo or Name]

«Date»

«Name»
«Address»
«City, state, zip code»

Dear «Name»

Thank you very much for participating in our research study, Statin Therapy to Reduce Disease Progression from Liver Cirrhosis to Cancer. Your participation is vital to the success of this study.

Following are the date, time, and location of your research study visit. Please see the attached map. The visit appointment will take about three hours.

Date: _____

Time: _____

Place:

Please do not eat or snack during the 3 hours before your study appointment. Since your appointment is at _____, please do not eat any food or chew any gum after _____ on the day of your appointment. You may drink water and take medications with water according to your normal schedule.

We look forward to meeting with you. This research could not be conducted without your participation, and we are grateful for your time and interest. If you have any questions or if you need to change the date or time of the appointment, please call me at «clinical research staff phone number».

Sincerely,

«Clinical research staff name»
«Clinical research staff job title»

[Insert directions to clinic and map on next page]

APPENDIX J
VioScreen Instructions

Instructions to Complete the VioScreen Dietary Assessment

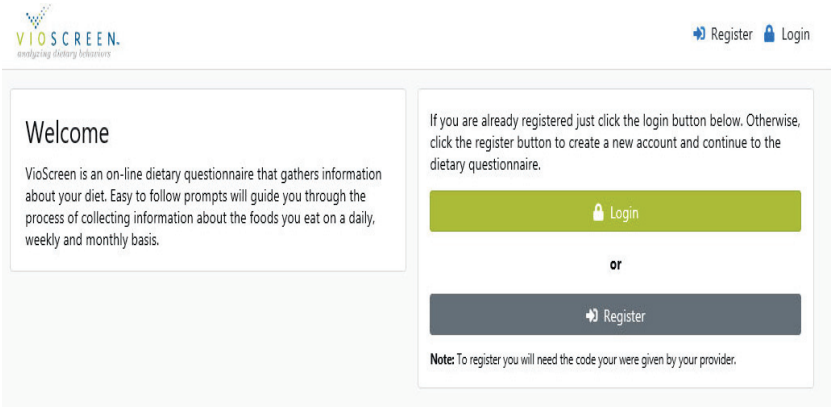
- ✓ For best results reserve 20 minutes of quiet time to complete the assessment.
- ✓ If for some reason you need to exit the questionnaire prior to completion your answers will be remembered and you may resume where you left off on next login.
- ✓ Take the assessment from a tablet or computer not a mobile phone.
- ✓ Use one of these browsers: IE, Fire Fox, Chrome, Opera, Safari
- ✓ The new password you create is important to keep, you will use it throughout the study.
- ✓ If you have questions or concerns please contact << Coordinator Name and Number>>

My Subject ID: _____

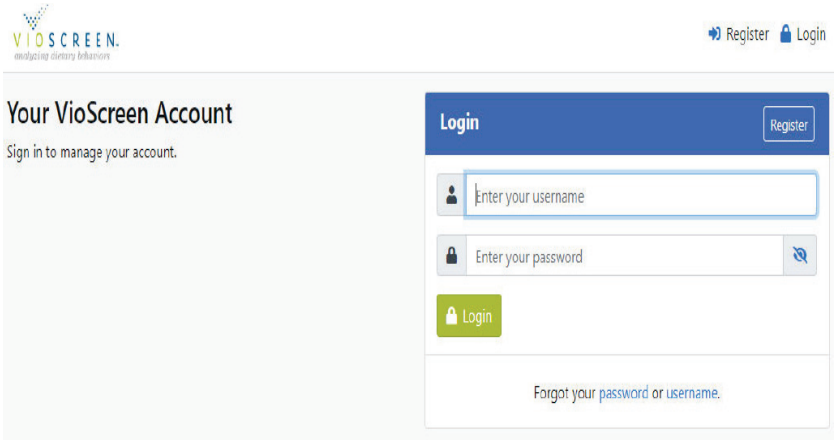
My Username: _____

Password: _____

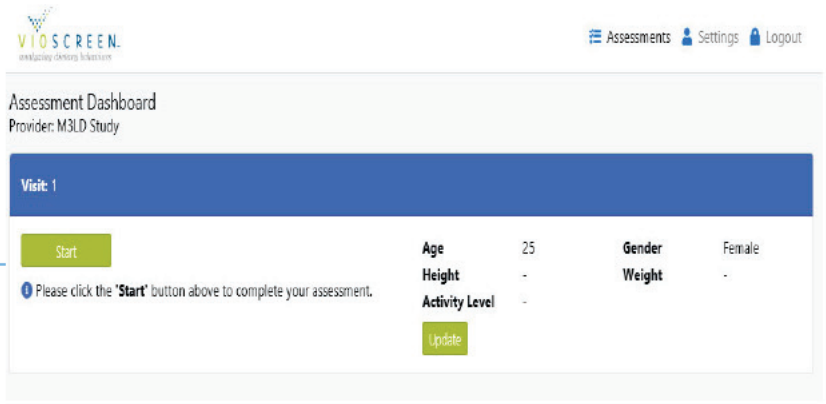
1. Go to https://vioscreen.com. Select the Login button.



2. Enter the username and password above to log in.



3. Select the *Start* button on the Assessment Dashboard to begin the Assessment.



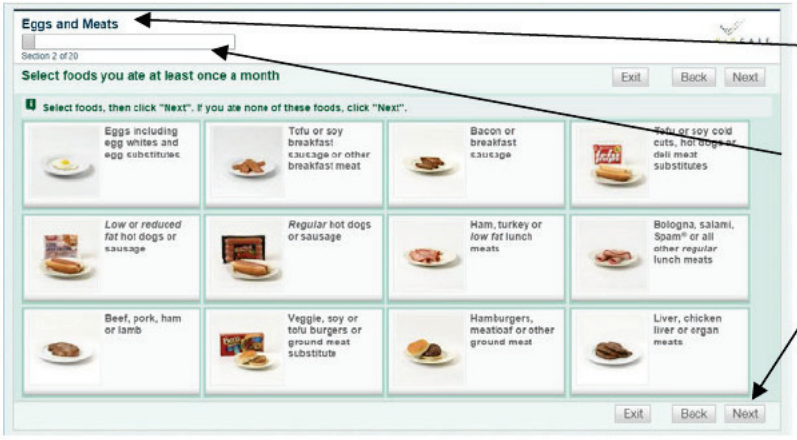
Click Start to begin →

4. Take the Assessment.

The Dietary Assessment will ask about the foods you usually ate over the last 3 months. You will be asked to provide the portion size and frequency for each food you select. To begin answering questions, click the Start button on the Welcome Page.

All screens include a number of tools to aid you in completing the questions. The tools include:

- Title Bar – Displays the food group in focus.
- Progress Meter –in the top left corner of the screens, indicates how much you have completed.
- Back and Next buttons – allow you to move forward or backward one screen at a time. ***Use these and NOT the browser's Forward and Backward buttons.*** The system requires that you make a selection on the current screen before it will allow movement to the next screen.

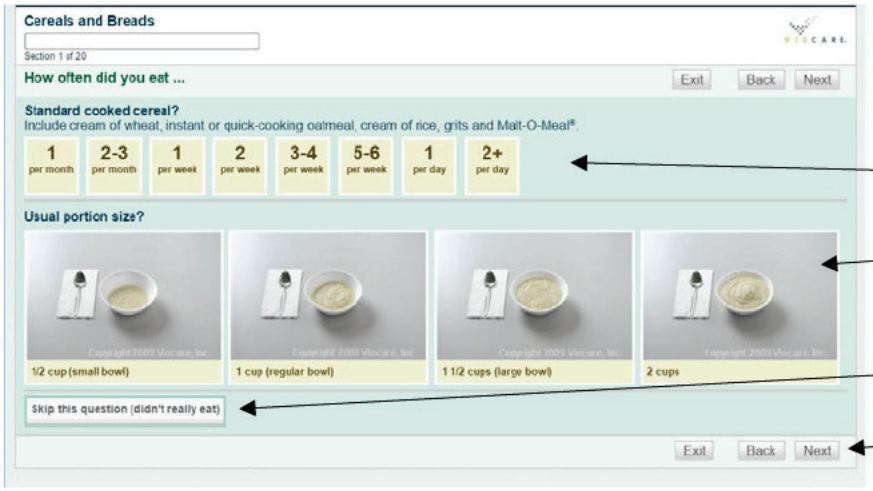


The *Title Bar* displays the questions group.

The *Progress Meter* displays position within the questions.

Use the ***Back*** and ***Next*** buttons to move between screen, one page at a time. Do not use your browser's buttons.

For each food you consume at least once a month, you will be prompted to provide your typical frequency and portion size. A *Skip* option is also provided in the event an error was made in selecting the food.



5. Great job! You have answered all the questions.

   - If you need to go back and change an answer select *Review*
   - If no changes are needed and you are done, click *Finish*