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IIT2017-08-Hussain-StatLv

Pravastatin Intervention to Delay Hepatocellular Carcinoma Recurrence

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Funding Source: National Institute of Health (NIH)

Version: Protocol Version 5.0 dated 07/12/2019

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	α-fetoprotein
AUC	Area Under the Curve
BMI	Body Mass Index
CPK	Creatine Phosphokinase
CSMC	Cedars Sinai Medical Center
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
DSMB	Data Safety Monitoring Board
EU	Emory University
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HR	Hazard Ratio
LI-RADS	Liver Imaging Reporting and Data System
LRTs	Locoregional Therapies
LT	Liver Transplantation
MELD	Model for End Stage Liver Disease
MRE	Magnetic Resonance Elastography
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MRI-PDFF	Proton Density Fat Fraction
NASH	Nonalcoholic Steatohepatitis
NWU	Northwestern Memorial Hospital
ORA	Office of Regulatory Affairs
OPTN	Organ Procurement and Transplantation Network
OS	Overall survival
PT/INR	Prothrombin Time
QMC	Quality management core
RCT	Randomized Control Trial
RFA	Radiofrequency Ablation
RFS	Recurrence-Free Survival
SAE	Serious Adverse Event
sCD163/14	Soluble Cluster Differentiation 163/14
SOC	System Organ Class
sTNFR I/II	Soluble Tumor Necrosis Factor Receptor I/II
TAC	Treatment Assignment Code
TACE	Transarterial Chemoembolization
TGFβ1	Transforming Growth Factor-β1
TTR	Time to Recurrence
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
UNOS	Milan/United Network for Organ Sharing

STUDY SCHEMA

Patients with compensated liver cirrhosis with early stage hepatocellular carcinoma (HCC)
Tumor burden within Milan Criteria or OPTN tumor downstaging criteria at staging scan (CT or MRI)
Initial locoregional therapy with verification of adequate response

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Pre-Screen Chart Review – Initial determination of eligibility (N=162; 33 at CSMC, 32 at UCLA, 32 at NWU, 32 at UCSF, and 32 at EU)

Medical charts of patients with HCC reviewed for cirrhosis diagnosis, prior or current statin use, prohibited concomitant medications, medical contraindications, laboratory results, size and number of tumors from staging scan (confirm meeting Milan Criteria or OPTN tumor downstaging criteria), first liver directed therapy followed by an MRI or CT to verify HCC response. A study information packet that includes an introductory letter, leaflet, consent and HIPAA forms will be mailed to potentially eligible patients. Study coordinator will call all potentially eligible patients to introduce the study and answer questions.

▼

Screening Visit – Consent and Final determination of eligibility (N=144; 29 at CSMC, 28 at UCLA, 28 at NWU, 28 at UCSF, and 28 at EU)

Patients who are eligible based on pre-screen chart review will be consented into the trial before any research procedures are initiated. Study physician will thoroughly review the patient's medical history and medications and evaluate all inclusion/exclusion criteria. Patients will undergo blood tests to confirm eligibility and safety of statin initiation; urine pregnancy test for women able to become pregnant. *Patients with a MELD score ≥30 or, AST/ALT >5x ULN; and women who are pregnant will be excluded.*

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Eligible, consented patients with HCC randomized to pravastatin or placebo (N=130; 26 per site)

Pravastatin 40 mg, daily for 12 months (N=65)	Placebo identical in color, consistency, and appearance to pravastatin 40 mg, daily for 12 months (N=65)

▼ ▼

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

Review medical history, medications, and laboratory test results; symptom assessment; ECOG performance status; blood draw; MRE with fat fraction or FibroScan for liver stiffness testing review inclusion/exclusion criteria; interviewer-administered questionnaire; dispense study drug and diary

▼

Study Visit 2 (30 days ± 5 days after initiation of intervention)

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

▼

Study Visit 3 (3 months ± 15 days following initiation of intervention)

Review medical history, medications, and laboratory test results; symptom assessment; ECOG performance status; blood draw; MRI or CT for HCC surveillance; collect study drug and diary; assess compliance (pill count); review study diary; assess adverse events; review inclusion/exclusion criteria; dispense study drug and diary

▼

Study Visit 4 & 5 (6 and 9 months ± 15 days following initiation of intervention, respectively)

Review medical history, medications, and laboratory test results; symptom assessment; ECOG performance status; blood draw; MRI or CT for HCC surveillance; collect study drug and diary; assess compliance (pill count); review study diary; assess adverse events; review inclusion/exclusion criteria; interviewer-administered questionnaire (Visits 4 and 6 only); dispense study drug and diary

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Study Visit 6 (12 months ± 15 days following initiation of intervention, N=47 in each group)

Review medical history, medications, and laboratory test results; symptom assessment; ECOG performance status; blood draw; MRI or CT for HCC surveillance; MRE with fat fraction or FibroScan for liver stiffness testing collect study drug and diary; assess compliance (pill count); interviewer-administered questionnaire; assess adverse events; review study diary

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Endpoints – Evaluate the effect of pravastatin versus placebo after 12 months of treatment on:

1) Time to recurrence
2) Recurrence-free survival
3) Overall survival

4) Waitlist drop-off
5) Change in liver stiffness
6) Change in liver fat fraction
7) Change in serum biomarkers of monocyte/macrophage and stellate cell activation
8) Levels of liver tissue markers related to HCC

*Blue box = standard of care clinical visit

STUDY SUMMARY

Title	Pravastatin Intervention to Delay Hepatocellular Carcinoma Recurrence
Protocol Number	IIT2017-Hussain-StatLv
Phase	Phase II
Methodology	Randomized, double-blinded, placebo-controlled, Phase II trial of statin to increase time to recurrence in patients with liver cirrhosis and initial hepatocellular carcinoma
Study Duration	5 years
Study Center(s)	Cedars-Sinai Medical Center (CSMC), Ronald Reagan UCLA Medical Center (UCLA), Northwestern Memorial Hospital (NWU), UCSF Medical Center (UCSF), Emory University Woodruff Health Sciences Center (EU)
Objectives	Primary Objective: To evaluate the effect of a pravastatin intervention versus placebo on the change in time to recurrence (TTR) from baseline to 12 months following treatment initiation. Secondary Objective: To evaluate the effect of a pravastatin intervention versus placebo at 12 months from baseline on: 1) Recurrence-free survival 2) Overall survival 3) Waitlist drop-off 4) Change in liver stiffness 5) Change in liver fat fraction 6) Change in serum biomarkers of monocyte/macrophage and stellate cell activation 7) Levels of liver tissue markers related to HCC
Number of Subjects	130
Diagnosis and Main Inclusion Criteria	Patients with a confirmed diagnosis of liver cirrhosis (Child-Pugh A or B); current Model for End-Stage Liver Disease (MELD) < 30; Minimum 18 years of age; HCCs must fall within the Milan Criteria or OPTN tumor downstaging criteria; receipt of LRT with verification of adequate response; and patients whose lab results meet the inclusion criteria after the Screening visit blood tests.
Study Product(s), Dose, Route, Regimen	Pravastatin 40 mg and placebo identical in color, consistency, and appearance to pravastatin; oral administration daily (N=65 in each group)
Duration of administration	12 months
Statistical Methodology	Statistical analyses for the primary objective will be conducted on participants who complete the 12 month MRI or CT and blood specimen collection. The distribution of the clinical and demographical covariates, including but not limited to; age, race, smoking status, BMI, and comorbid conditions, will be summarized and compared between the intervention and control groups to assess the adequacy of the randomization. Chance differences between groups will be adjusted for using multiple regression modeling.

1.0 BACKGROUND AND RATIONALE

1.1 Study Disease

Hepatocellular carcinoma (HCC) is a highly lethal cancer with rising incidence and mortality rates. Approximately 33,000 HCC diagnoses were expected in 2016, 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). 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, 3). 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 patients with cirrhosis 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.

1.2 Study Agent

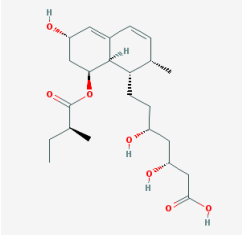

Figure 1. Molecular structure of pravastatin

Pravastatin (see Figure 1) is a lipid-lowering agent pravastatin is a derivative of ML236B (compactin), which was identified in a fungus called Penicillium citrinum in the 1970s. It 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 pravastatin is $C_{23}H_{36}O_7$ and its molecular weight is 424.534 g/mol. Pravastatin sodium tablets, USP are available for oral administration as 10 mg, 20 mg, 40 mg, and 80 mg tablets. Inactive ingredients include: croscarmellose sodium, lactose monohydrate, magnesium oxide, magnesium stearate, microcrystalline cellulose and povidone. The 10 mg tablet also contains ferric oxide red, the 20 mg and 80 mg tablets also contain ferric oxide yellow, and the 40 mg tablet also contains D & C yellow No. 10 aluminum lake & FD & C blue No. l aluminum lake.

Pravastatin a commonly prescribed HMG-CoA reductase inhibitor, which has a widely accepted tolerability profile with few serious side effects (21-23). 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 (21-23). Historically, there has been reluctance to prescribe statins to patients with preexisting liver disease due to concerns regarding additional liver injury and diabetes (24) . However, in recent years, the benefits of statin use have proven to substantially outweigh the minimal potential for adverse events in patients with liver disease: statins delay liver disease progression, improve survival, reverse non-alcoholic steatohepatitis, and ameliorate metabolic syndrome (25-28).

Despite the overall excellent hepatic safety profile of statins, underlying liver disease is a label-defined contraindication. The hepatic safety of high dose pravastatin among 326 hyperlipidemic adults with well-compensated chronic liver disease was evaluated using a randomized, double-blind, placebo-controlled, trial (29). Patients were randomized to daily pravastatin (80 mg) or placebo for 36 weeks. The primary safety endpoint was doubling of baseline alanine aminotransferase (ALT) values during 36 weeks of therapy. Overall, 8% of patients in the pravastatin group and 13% of patients in the placebo group experienced doubling of baseline ALT values during 36 weeks of therapy (P>0.05). These results have lessened the concern over an increased potential for statin-induced hepatotoxicity in patients with chronic liver disease. Furthermore, recommendations from National Lipid Association Statin Safety Task Force state that chronic disease and compensated cirrhosis are not contraindications for statin therapy (30) .

Also, throughout the protocol, where we mention evaluation of medical contraindications to pravastatin we have included a clause “with the exception of active liver disease”.

Lastly, with regards to liver function monitoring, we will test liver function 30 days after the initiation of therapy, then again after 60 days, and then once every 3-months for the duration of the trial. Based on data from the RCT in patients with compensated cirrhosis who were on high-dose pravastatin for 36 weeks, the frequency of our monitoring is adequate (29). Therapy will be stopped in any patient whose AST or ALT exceeds 5 times the institutional upper limit of normal (ULN).

Pravastatin is prescribed for primary and secondary prevention of cardiovascular disease and thus is indicated for long-term use. We will administer pravastatin 40 mg daily for 12 months in this trial.

1.3 Rationale

Cirrhosis affects nearly 633,000 Americans, and HCC is a leading cause of death in non-symptomatic patients with cirrhosis (5, 31, 32). Less than 5% of patients with cirrhosis and HCC are candidates for liver resection due to the high degree of underlying liver dysfunction, which makes liver transplantation (LT) the definitive and curative treatment of choice. In 2015, 15,000 person-years were spent awaiting LT in the U.S, and only 6,600 patients received LT, underscoring the major competition among patients with cirrhosis for LT. Although patients with HCC receive priority listing for LT if they meet Milan/United Network for Organ Sharing (UNOS) T_2 criteria, the wait time often exceeds 1 year. Exacerbating the problem for patients with HCC, very recent changes to the national liver allocation policy (October, 2015) delay the assignment of Model for End Stage Liver Disease (MELD) exception points for 6 months after listing, and reduce the maximum value of exception points to 34 for those with HCC. MELD is a clinical score that is a validated predictor of survival among patients with advanced liver disease used to prioritize patients for LT, and exception points increase a patients MELD score and therefore chances for LT. These changes were intended to create a better balance in transplant opportunities between those with and without HCC, and allow observation of tumor behavior to avoid transplanting aggressive tumors too quickly. However, for patients with HCC, these policy changes translate to longer wait times and growing concern that the tumor biology may shift from less to more aggressive over time. “Bridging” locoregional therapies (LRTs) are utilized while a patient is on the waitlist for LT, however drop-out from the waitlist remains a problem largely due to tumor progression or recurrence to beyond accepted radiological criteria. For example, the cumulative recurrence rate 2–3 years after radiofrequency ablation (RFA), the most common LRT in patients with cirrhosis eligible for transplant, has been reported at 72%–80%. Novel therapeutics offered in conjunction with LRT that could achieve lower rates or delay time to recurrence, could maintain transplant candidacy for sufficient time to achieve treatment with LT.

Hypothesis:

1.) Participants randomized to pravastatin will experience an increase from baseline to 12 months in time to recurrence (TTR) compared to placebo group.
2.) Compared to placebo group, participants randomized to pravastatin will have:
    a. increase in recurrence-free survival
    b. increase in overall survival
    c. decrease in waitlist drop-off
    d. decrease in liver stiffness
    e. decrease in liver fat fraction
    f. greater modulation (increase or decrease, depending on the marker) of circulating biomarkers
    g. decrease in liver tissue markers related to HCC

2.0 STUDY OBJECTIVES

The objective of this randomized double-blinded, placebo-controlled Phase II trial is to examine the effects of pravastatin use versus placebo after 12 months of treatment on hepatocellular cancer (HCC) recurrence in 130 patients with liver cirrhosis, HCC meeting Milan Criteria or OPTN tumor downstaging criteria for tumor burden, and initial locoregional therapy (LRT) with adequate response.

2.1 Primary Objectives

To evaluate the effect of a pravastatin intervention versus placebo on the change in time to recurrence (TTR) from baseline to 12 months following treatment initiation.

2.2 Secondary Objectives

To evaluate the effect of a pravastatin intervention versus placebo at 12 months from baseline on:
1) Recurrence-free survival
2) Overall survival

3) Waitlist drop-off
4) Change in liver stiffness
5) Change in liver fat fraction
6) Change in serum biomarkers of monocyte/macrophage and stellate cell activation
7) Levels of liver tissue markers related to HCC

2.3 Endpoints

The overall objective of this trial is to examine the effects of pravastatin use versus placebo at 12 months from baseline (Study Visit 1) on TTR in high-risk patients with liver cirrhosis. Participants will be on the study drug from Study Visit 1 until the last study visit (Study Visit 6 at 12 months). Primary and secondary endpoints are measured radiographically and in biological samples.

- ***Primary Efficacy Endpoint***
  Following the American Association for the Study of Liver Diseases-Journal of the National Cancer Institute guidelines for trial design in HCC, we have set our primary endpoint as TTR, according to the recommendation for Phase II studies that assess adjuvant therapies secondary to liver directed therapy (33) . TTR will be defined as the time from randomization to the first occurrence of a documented HCC recurrence or HCC death, within the 12-month intervention and assessment period. Participants who experience death attributed to their underlying liver cirrhosis, or other cause, will be censored at death date. For participants who do not recur or die and are lost to follow-up prior to the 12-month study visit, analysis of TTR will be censored at their last date of evaluable scan before drop-out.

  In this study, we will rely heavily on the mRECIST outcome guidelines and the Liver Imaging Reporting and Data System (LI-RADS) diagnostic algorithm for defining hepatic recurrence (34, 35), and central expert independent radiographic review by MedQIA.

  Pathological Definition: Participants who receive a transplant will become ineligible at the time of transplantation. Recurrent HCCs may also be identified at time of transplantation during the examination of the explant by a pathologist. These “incidental” HCCs represent a sizable proportion, amounting to 22% of HCCs among those receiving a liver transplant. Thus, if transplantation occurs and a pathologically confirmed HCC is detected, we will examine these pathologically defined tumors as a **secondary** definition of recurrence.

- ***Secondary Efficacy Endpoints***
  Secondary endpoints include recurrence-free survival (RFS), overall survival (OS), waitlist survival, liver stiffness, liver fat fraction, circulating biomarkers, and liver tissue biomarkers. Differences in secondary endpoints will be compared in the pravastatin and placebo groups.

  1) RFS: We will assess the effect of pravastatin on RFS. RFS will be defined as the time from randomization to the first occurrence of a documented HCC recurrence, within the 12-month intervention and assessment period.

  2) OS: We will examine the effect of pravastatin on OS (defined as the time from randomization to death from any cause).

  3) Waitlist drop-off: We will evaluate the effect of pravastatin on reducing waitlist dropout due to any of the following causes: 1) HCC progression outside of Milan/T2 criteria, 2) cirrhosis progression (too sick to transplant), or 3) death.

Participants who are delisted for other reasons (such as positive alcohol test) will be censored at date of delisting.

4) Change in liver stiffness: We will evaluate the effect of pravastatin on within-person change in liver stiffness, as measured by magnetic resonance elastography (MRE) or FibroScan, between Study Visit 1 (0 month) and Visit 6 (12 month). Within-patient consistency is required between Study Visits 1 and 6 with regards to liver stiffness testing modality (MRE or FibroScan).

5) Change in liver fat fraction: We will evaluate the effect of pravastatin on within-person change in liver fat fraction, as measured by MRI-proton density fat fraction (PDFF), between Study Visit 1 (0 month) and Visit 6 (12 month).

6) Change in serum biomarkers of monocyte/macrophage and stellate cell activation: We will examine the effect of pravastatin on change in serum biomarkers including cytokines, chemokines, soluble receptors, and proteins (specifically, IL6, TNFα, sTNFRII, IL18BP, sCD163, IL10, IL17, IL-8, CCL17, TGFβ).

7) Levels of liver tissue markers related to HCC: We will examine the effect of pravastatin on levels of liver tissue markers related to HCC including those in the Wnt/β-catenin pathway (specifically, β-catenin and glutamine synthetase).

3.0 STUDY DESIGN SUMMARY

This is a Phase II randomized, double-blinded, placebo-controlled clinical trial including 130 patients with cirrhosis diagnosed with HCC recruited from Cedars-Sinai Medical Center (CSMC), Ronald Reagan UCLA Medical Center (UCLA), Northwestern Memorial Hospital (NWU), UCSF Medical Center (UCSF), or Emory University Woodruff Health Sciences Center (EU). We will randomize study participants 1:1 to daily pravastatin 40 mg or placebo, created to be identical in color, consistency, and appearance to pravastatin, for an intervention period of 12 months. We expect to have a final sample of 47 study participants on pravastatin and 47 on placebo after accounting for the competing risk of transplantation or death due to cirrhosis (Figure 3). Evaluations will be taken at baseline and at study visits 1-6. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study.

The following treatment regimens will be used:

- Experimental treatment: 40 mg pravastatin (N=65).
- Placebo: (N=65).

Total duration of active participation will be 12 months. Total duration of the study is expected to be 5 years.

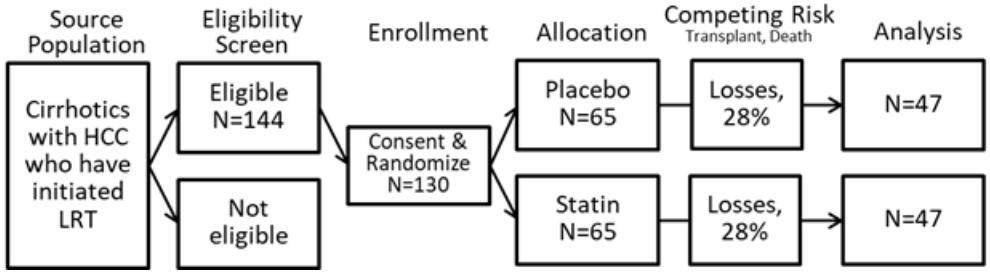

Figure 3. Study profile for the primary endpoint of time to HCC recurrence

3.1 Study Measurements.

Following is a brief description of study measurements.

3.1.1 Non-laboratory Measurements

Imaging review. Review of medical record by research coordinator to identify imaging required for eligibility purposes (see section 4.1.3 and 4.1.4) or all imaging studies conducted since eligibility or since the last study visit. Images will be sent to MedQIA (see 3.1.3) for central imaging review.

Medical history. Detailed medical history, including past medical/surgical interventions, disease history, and relevant laboratory results, obtained via patient interview and/or review of medical records by a study physician or research coordinator.

Concomitant medications review. Review of all current concomitant medications, including start and stop dates, dose, frequency, route, and indication (if available/applicable), obtained via review of the medical record or by patient self-report by a study physician or research coordinator.

Medication 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.

Physical assessment. Physician-directed physical assessment. Each assessment will include an interval symptom history; ECOG performance status assessment; vital signs, including blood pressure, heart rate, respiratory rate, and temperature; weight; and assessment of liver disease sequelae (varices, ascites and encephalopathy).

Health assessment. RN-directed assessment, consisting of ECOG performance status assessment and vital signs (including blood pressure, heart rate, temperature; and weight)

Baseline symptom assessment. Assessment of symptoms presenting prior to start of study intervention (Study Visit 1), obtained via review of the medical record or by patient self-report, by a study physician or research coordinator. NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) term, start and stop dates, grade, and treatment will be recorded on the Baseline Symptom Log. Grade should be determined by a study physician. Symptom assessment includes:

- Upper respiratory infection
- Headache
- Abdominal pain
- Constipation
- Nausea
- Vomiting
- Mild muscle aches
- Any other symptoms

Symptom/adverse event assessment. Assessment of symptoms presenting after the start of study intervention (Study visit 1), obtained via review of the medical record or by patient self-report, by a study physician or research coordinator. CTCAE v5.0 term, start and stop dates, grade, treatment, attribution, action taken, outcome, and expectedness will be recorded on the Adverse Event Log. Grade, attribution, and expectedness should be determined by a study physician. Symptom assessment includes:

- Upper respiratory infection
- Headache
- Abdominal pain

- Constipation
- Nausea
- Vomiting
- Mild muscle aches
- Any other symptoms

Baseline risk factor questionnaire. A structured questionnaire will be administered by the research coordinator via patient interview of approximately 45 minutes' duration. The interview will elicit information on detailed race/ethnicity; acculturation, quality of life; medical and medications history; alcohol and tobacco use; and anthropometry including weight at different decades of life.

Follow-up risk factor questionnaire. A shorter questionnaire will be administered by the research coordinator via patient interview to assess changes in exposures and behaviors between visits. The interview will elicit information on quality of life, medical and medications history, and alcohol and tobacco use.

3.1.2 Laboratory Measurements

MELD-Na score. MELD-Na score is calculated using a patient's laboratory 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-Na = 1.32 x (137 – sodium [mEq/L]) – [0.033 x MELD x (137 – sodium [mEq/L])]

If the patient has undergone dialysis at least twice within the last seven 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.

MELD-Na score may be computed using the following online calculator:
https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/

Physiological Model for End-Stage Liver Disease (MELD) must be less than 30 at the time of screening. After enrollment, if a patient's MELD increases to 30 or greater, they can still be eligible.

Research blood specimen. A blood specimen of approximately 20 mL will be collected from each participant for research purposes for measurement of protocol-specific biomarkers and biobanking. See *Laboratory Manual* for research blood collection and processing details.

Eligibility blood specimen. A blood specimen of approximately 15 mL will be collected from each participant at the Screening eligibility visit to confirm eligibility, including AFP, a blood chemistry and prothrombin time (PT/INR). If a patient's lab results are current (within the past 30 days) in the medical record and within eligibility range, labs will not be re-tested at the Screening visit. See section 6.5 for lab details.

Clinical blood specimen. A blood specimen of approximately 10-15 mL will be collected from each participant for blood tests to establish baseline levels and monitor for potential adverse effects of the intervention. Clinical labs include blood chemistry, lipid panel, hemoglobin A1C, creatine phosphokinase (CPK), and prothrombin time. If a patient's lab

results are current (within the past 30 days) in the medical record, labs will not be re-tested. See section 6.5 for clinical lab details.

Pregnancy test. 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. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately. 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.

Liver stiffness. MRE will be utilized to measure liver stiffness. If the subject has a contraindication to MRE, a FibroScan can be used instead. Subject must use the same modality of either MRE or FibroScan throughout their participation in the study in order to assess intra-individual change using the same procedure.

Liver fat fraction. MRI-PDFF will be utilized to measure fat fraction.

Transplant tissue specimen. For all patients who enter the trial and receive a liver transplant before the end of this study, we will collect explant tissue (from the native liver), that would otherwise be discarded, to examine biomarkers in liver tissue that are putatively related to HCC risk, progression, or statin intervention. See *Laboratory Manual* for tissue collection and processing details.

3.1.3 Central Imaging Review (MedQIA)

Imaging will be conducted throughout the duration of the study as standard clinical care for HCC surveillance (recurrence or metastasis) and will be no cost to the study. All standard of care imaging scans (MRIs, CTs, or ultrasounds) will be sent to the central imaging core laboratory (MedQIA) and reviewed per the *Imaging Charter.* Assessment of eligibility and HCC recurrence will be made by an independent team of reviewers outside of the patient's care team, coordinated by our imaging core laboratory (MedQIA), per the *Imaging Charter*. Image procedures, acquisition, and transfer guidelines will be harmonized across the clinical sites by MedQIA and the study team. MedQIA uses proprietary computer-aided technologies for image analysis to maximize accuracy and reproducibility and reduce adjudication rates. Tumor measurements will be computed from radiologist-approved volumetric contours, providing data on diameter, volume, density, and heterogeneity. MedQIA was chosen for this study given their past performance, including serving as the imaging core for oncology clinical trial submissions to the FDA with imaging as the primary endpoint.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

4.1.1 Age ≥ 18 years

4.1.2 Confirmed diagnosis of liver cirrhosis (Child-Pugh A or B) assessed by the presence of clinical signs, symptoms, body imaging, or liver biopsy

4.1.3 Diagnosis of HCC falling within <u>one</u> of the following criteria prior to LRT.

a. One lesion ≤ 5 cm or two to three lesions, each ≤ 3 cm.

b. One lesion > 5 cm and ≤ 8 cm.

c. Two or three lesions, of which at least one is > 3 cm and all are ≤ 5 cm each. The sum of all diameters must be ≤ 8 cm.

d. Four or five lesions, each < 3 cm. The sum of all diameters must be ≤ 8 cm.

Criteria fulfillment will be confirmed by the *Imaging Charter* and MedQIA.

4.1.4 Initiation of LRT (according to clinical judgement) within 24 months prior to Screening Visit, with adequate response as determined by *Imaging Charter* and MedQIA.

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

4.1.6 AST (SGOT) & ALT (SGPT) ≤ 5x institutional ULN

4.1.7 AFP < 400 ng/mL

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

4.1.9 Agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation; for women who are able to become pregnant.

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

4.2 Exclusion Criteria

4.2.1 Current use of statin medication or statin use within 12 months of Screening visit.

4.2.2 Current systemic use of medications known to interact with statins and potentially increase toxicity, including (e.g., gemfibrozil, cyclosporine, clarithromycin, colchicine, niacin and fibrates).

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

4.2.4 Current use of any other investigational agents

4.2.5 Women who are pregnant. Women who are able to become pregnant must have a confirmed negative pregnancy test prior to enrollment.

4.2.6 Women who are breastfeeding. It is not known whether pravastatin 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 pravastatin, breastfeeding should be discontinued if the mother is treated with pravastatin.

4.2.7 Prior liver transplant

4.2.8 MELD score ≥ 30.

4.2.9 History of chronic myopathy

4.2.10 Active malignancy within the past 5 years (excluding HCC, basal/squamous cell skin cancer, or prostate cancer with a Gleason score 6 or less)

4.2.11 Known HIV infection

4.2.12 Hemophilia

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

4.2.14 Concurrent 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 ethnicity groups are eligible for this trial.

4.4 Source Population

Participants will be recruited from all eligible patients who have liver cirrhosis and a first HCC meeting Milan criteria or OPTN tumor downstaging criteria (described in eligibility). We will recruit patients from liver transplant hepatology clinics and will target patients who are currently waitlisted, or under evaluation, for a liver transplant. Patients who are inactive on the waitlist, or ineligible for a transplant (for reason other than HCC) may still be recruited if they meet all eligibility criteria.

4.5 Recruitment and Feasibility

Recruitment will occur over 3 years. We will identify patients via the physician's upcoming appointments and reviewing their medical records for eligibility. The research staff will notify the study physician that a patient is potentially eligible for the trial based on the pre-screen evaluation. The physician will review the eligibility information and notify research staff whether the patient may be considered for participation. A study information packet may be mailed to potential participants. Clinical research staff will call all potentially eligible patients before their scheduled standard of care clinical 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 by a study physician.

For potentially eligible patients who may not be mailed a recruitment packet in advance of the regular clinic visit (e.g., new patients who do not already have an established relationship with the physician or patients added to the clinical schedule late), a study physician will introduce the study to the patient during the standard of care clinic visit. The patient will 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 come to the clinic to sign informed consent documents with the study physician. 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. Patients who do not speak English may be consented according to the policies at their local institutions. In an effort to minimize participant burden and increase the likelihood of enrollment and follow-up, we will coordinate study visits with usual care appointments and tests to the extent practical.

There will be six study visits. Study Visit 1 (baseline measurements and initiation of the intervention) will occur 0-30 days after the Screening eligibility visit. Follow-up visits will be scheduled at 1 month (± 15 days), 3 months (± 15 days), 6 months (± 15 days), 9 months (± 15 days), and 12 months (± 15 days) after initiation of the intervention to avoid protocol deviations. Participants will receive $75 when they complete Study Visits 1, 2, 3, and 5 (which do not coincide with usual care visits or require significant time/burden in addition to the usual care visit) and $25 when they complete Screening, Study Visits 4 and 6 for their time, transportation, parking, and other expenses related to the study. Participants who complete the entire study will receive $375.

Compensation schedule

Screening Visit	Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4	Study Visit 5	Study Visit 6
$25	$75	$75	$75	$25	$75	$25

The participant will be contacted prior to the scheduled study visit to confirm or reschedule his/her visit, for example a telephone call 5-7 days prior to the scheduled study visit. If a study participant misses his/her study visit, s/he will be called promptly to reschedule. Study visits will be rescheduled for up to 2 months, at which point the participant is considered lost to follow-up.

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

Patients who were identified as a potential participant will be 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, HCC diagnosis, HCC treatment history, prior liver transplant, prior statin use, prohibited concomitant medications, previous malignancies, medical contraindications, laboratory results, and HCC characteristics (size and number of tumors).

4.7 Consent and Eligibility

The study physician will review the consent document with the patient and will answer any questions regarding the trial. After the patient's questions have been answered, the study physician will obtain signatures on the consent documents from patients who wish to volunteer for the study. The patient will review and sign the study consent form and HIPAA authorization. Copies of each document will be given to patients who agree and consent into the study, the original signed consent will be placed in the research binder, and copies will be distributed/maintained per local institutional policy. Written consent will be obtained before any research related procedures are initiated. After consent has been obtained, the screening visit and procedures will be completed. Final determination of eligibility will be conducted using an eligibility checklist that requires double signoff (by

the study physician and study team member) and also central eligibility verification by the Quality management core (QMC) at Cedars-Sinai.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

One hundred and thirty participants with liver cirrhosis and an initial HCC diagnosis will be randomized into one of 2 groups: 65 participants will be randomized to receive 40 mg pravastatin per day and 65 participants will be randomized to receive a placebo identical in color, consistency, and appearance to pravastatin 40 mg. Pravastatin and placebo will be provided as over-encapsulated tablets. Dosing will extend for 12 months

- Agent(s): Pravastatin and placebo
- Daily dose(s) and regimen(s) for each agent: One capsule per day
- Duration for each agent: Daily treatment for 12 months

The usual recommended dose of pravastatin is 10-40 mg/day, and the toxicity and tolerability are comparable for 20 mg and 40 mg (21-23). In a prior published trial of patients with chronic hepatitis or cirrhosis and HCC, pravastatin dosing began at 20 mg and was titrated up to 40 mg, and no serious side effects or discontinuation of therapy were noted (37). Thus, we feel that a 40 mg dose will be well-tolerated by the participants in this trial.

Patients will self-administer the 40 mg capsule of pravastatin 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 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), Study Visit 4 (Month 6), and Study Visit 5 (Month 9).

5.2 Method of Assigning Subjects to Treatment Groups

A designee of the QMC at Cedars-Sinai will conduct a final eligibility check prior to registration. Randomization will be carried out by the Research Pharmacy at each site among consented subjects who meet all eligibility criteria after the eligibility evaluations.

5.3 Blinding/Unblinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or subjects. The following study procedures will be in place to ensure double-blind administration of study treatments.

- The study biostatisticians will set up randomization blocks.
- After registration, participants will be randomized to treatment with the study agent or placebo
- Investigators and participants will be blinded as to the result of randomization. The following people will be unblinded: the study biostatisticians at Cedars-Sinai and the investigational pharmacists at each participating site.
- The investigational pharmacist will manage the study agent and placebo.
- Unblinding will only occur when it is deemed medically necessary.

5.3.1 Emergency Unblinding

- Emergency unblindings are left up to the discretion of the accrual site clinical PI.

- Prior to unblinding, the accrual site should attempt to notify the protocol PI that an unblinding will occur, and why.
- The accrual site should work with their pharmacy in the event of an emergency that requires an immediate unblinding.
- In case of medical emergency, the participant may discontinue the study agent under the advice of a doctor, and if unblinding is deemed medically necessary by the accrual site clinical investigator, this can be addressed during the next business hours.

5.3.2 Non-Emergency Unblinding

- The pharmacy may unblind in a non-emergency only upon approval of the protocol PI.
- In the event of a non-emergency unblinding, the pharmacy will receive an Unblinding Request Note to File indicating:
  - The PID(s) to be unblinded
  - The reason for unblinding
  - Study staff responsible for unblinding
  - Signed or emailed approval by the protocol PI
- Upon receipt, the pharmacy will compose a Pharmacy Note to File based on their dispensing records, indicating:
  - The requested PID(s)
  - The corresponding unblinded treatment assignments
  - A pharmacist signature
- The Pharmacy Note to File should be sent to the accrual site clinical investigator.

- Once a participant is unblinded, they will be taken off treatment but may remain on study as long as no off study criteria are met.

5.4 Toxicities and Dosing Delays/Dose Modifications

Toxicities

All participants will be evaluable for toxicity from the time of their first dose of pravastatin.

Dosing Delays/Dose Modifications

No dose modifications are planned. The study agent will be temporarily 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 pravastatin below 40 mg (*e.g.* cyclosporine).

5.5 Concomitant Medications/Treatments

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, 2) dose, 3) frequency, 4) route of administration, and 5) indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included.

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

The combined use of pravastatin with systemic formulations of gemfibrozil, cyclosporine, clarithromycin, erythromycin, azithromycin, colchicine, fibrates, and niacins contraindicated due to an increased risk for myopathy. Additionally, other drug-drug interactions exist with pravastatin such as; boceprevir, cimetidine, cholestyramine, colestipol, darunavir, digoxin, diltiazem, fluconazole, itraconazole, probucol, ritonavir, verapamil, and warfarin. These medications should be avoided if possible or used with caution per investigator discretion.

Pravastatin must be administered either 1 hour or more before or at least 4 hours after bile acid resins (e.g., cholestyramine, colestipol). Patients will be screened for contraindications to pravastatin 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.

5.6 Adherence/Compliance

Compliance will be measured by pill counts and patient diaries. Compliance is defined as 85% of the total dose of the study agent. A participant diary will be used to monitor daily compliance. 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 2-6. Compliance will be reinforced throughout the study with regular telephone calls and text/email messages as detailed in Section 6.2.1.

Patients will return the unused capsules to the study coordinator at Visits 3 through 6. Study agent should be received and accounted for according to local institutional policy. See Pharmacy Manual for further details on study agent accountability and compliance.

All participants that receive a study agent for any period of time will be evaluable for toxicity.

5.7 Stopping Rules

Continuous assessment of the 40 mg dose of pravastatin 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.

5.8 Duration of Therapy

Participants will be on study agent pravastatin or placebo for a duration of 12 months.

5.9 Duration of Follow Up

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 6 to assess symptoms and adverse events. For all patients who enter the trial and receive a liver transplant before the end of this 5-year study (within or beyond the 12-month intervention period), we will obtain specimens at the time of transplantation.

5.10 Removal of Patients from Protocol

Patients will be removed from the study when any of the criteria listed in Section 6.7 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol (Section 6.3).

5.11 Subject Replacement

Subjects who withdraw from the study treatment will not be replaced.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. 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 may be done at the Screening visit. The study coordinator will collect a urine sample to test for pregnancy (for women of child bearing potential, defined in 3.1.2), and blood tests will be conducted for confirmation of eligibility (see section 4.0 for details). MedQIA will review the patient's scans to confirm eligibility per the *Imaging Charter* (see 4.1.3 and 4.1.4).

All screening procedures must be performed within 60 days prior to registration with the exception of imaging. Historical (standard of care) images taken greater than 30 days prior to registration will be required to verify eligibility per the *Imaging Charter*. The screening procedures are detailed below.

6.1.1 Screening Visit- Consent, Final determination of eligibility, registration, and randomization

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

For definition of any procedures, please see section 3.1 Study Measurements. The following procedures will be performed during the Screening Visit:

- Physical assessment
- Pregnancy test
- Imaging review
- Eligibility blood specimen
  - AFP
  - Blood chemistry
  - PT/INR
- Review Subject Eligibility Criteria
  - All inclusion and exclusion criteria will be evaluated for the patient
- Registration and randomization
  - Eligible participants will be registered and randomized to pravastatin or placebo

6.2 Procedures During Treatment

There will be six study visits along with telephone calls during treatment. A packet of material, including an appointment letter, a map, and parking instructions will be sent to the study participant prior to each scheduled study visit. For definition of any items please see section 3.1 Study Measurements.

6.2.1 Telephone Calls and Email/Text Messages.

Study participants will be followed during the intervention via telephone calls once a month (± 3 days) by the clinical research staff to assess compliance and adverse events. 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.

The following information with be collected during the telephone calls:

- Medication compliance review
- Concomitant medications review
- Symptom/adverse event assessment

6.2.2 Study Visit 1- Baseline Testing and Initiation of the Intervention

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

- Medical history
- Concomitant medication review
- Health assessment
- Clinical blood specimen
  - Blood chemistry
  - Lipid
  - HbA1C
  - CPK
- Research blood specimen
- Liver stiffness
- Liver fat fraction
- Baseline risk factor questionnaire

- Baseline symptom assessment
- Study agent
    - Dispense the study agent (one bottle of 120 capsules) and review instructions for how to take it
    - Dispense and review the study diary

6.2.3 Study Visit 2

Study Visit 2 will occur 1 month (± 15 days) after initiation of the Intervention. The following procedures will be performed during this visit:

- Symptom/adverse events assessment
- Medical history
- Concomitant medications review
- Health assessment
- Clinical blood specimen
    - Blood chemistry
    - Lipid
- Imaging review
- Study agent
    - Collect study agent and diary
    - Assess compliance (pill count)
    - Review study diary
    - Dispense study agent (same bottle that was brought to the visit/collected for pill count)

6.2.4 Study Visit 3

Study Visit 3 will occur 3 months (± 15 days) after initiation of the intervention (study drug initiation).
The following procedures will be performed during this visit:

- Symptom/adverse events assessment
- Medical history
- Concomitant medications review
- Health assessment
- Imaging review
- Study agent
    - Collect study agent and diary
    - Assess compliance (pill count)
    - Review study diary
    - Dispense study agent (one new bottle of 120 capsules) and diary

6.2.5 Study Visit 4

Study Visit 4 will occur 6 months (± 15 days) after initiation of the Intervention (study drug initiation). The following procedures will be performed during this visit:

- Symptom/adverse events assessment
- Medical history
- Concomitant medications review
- Physical assessment
- Clinical blood specimen
    - Blood chemistry
    - Hba1c
    - AFP
- Research blood specimen
- Follow-up risk factor questionnaire

- Imaging review
- Study agent
    - Collect study agent and diary
    - Assess compliance (pill count)
    - Review study diary
    - Dispense study agent (one bottle of 120 capsules) and diary

6.2.6 Study Visit 5

Study Visit 5 will occur 9 months (± 15 days) after initiation of the intervention (study drug initiation). The following procedures will be performed during this visit:

- Symptom/adverse events assessment
- Medical history
- Concomitant medications review
- Health assessment
- Imaging review
- Study Agent
    - Collect study agent and diary
    - Assess compliance (pill count)
    - Review study diary
    - Dispense study agent (one new bottle of 120 capsules) and diary

6.2.7 Study Visit 6

Study Visit 6 will occur 12 months (± 15 days) after initiation of the intervention (study drug initiation). The following procedures will be performed during this visit:

- Symptom/adverse events assessment
- Medical history
- Concomitant medication review
- Physical assessment
- Clinical blood specimen
    - Blood Chemistry
    - Lipid
    - Hba1c
    - PT/INR
    - AFP
- Research blood specimen
- Imaging review
- Liver stiffness
- Liver fat fraction
- Follow-up risk factor questionnaire
- Study agent
    - Collect study agent and diary
    - Assess compliance (pill count)
    - Review study diary

6.2.8 Unscheduled Visit (Transplant Specimen Collection). For all patients who enter the trial and receive a liver transplant before the end of this study, we will obtain specimens at the time of transplantation. The research blood specimen will be collected prior to transplant (while the patient is being prepped for surgery).

- Research blood specimen
- Transplant tissue specimen

6.3 Follow-up telephone contact

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 6 (or earlier if study agent discontinued prior to completion) to assess symptoms and adverse events.

6.4 Schedule of Events Table

Study Activity/Measurement	Screen 1	Month 0 Study Visit 1	Month 1 Study Visit 2	Month 3 Study Visit 3	Month 6 Study Visit 4	Month 9 Study Visit 5	Month 12 Study Visit 6	30, 60, 90 days Follow-up Calls[^]	Unscheduled Liver Transplant[%]
Review subject eligibility criteria	X								
Obtain informed consent and HIPPA authorization	X								
Pregnancy test	X								
Imaging review	X		X	X	X	X	X		
Registration/randomization	X								
Medical history		X	X	X	X	X	X		
Concomitant medication review		X	X	X	X	X	X		
Physical assessment	X				X		X		
Health assessment		X	X	X		X			
Baseline symptom assessment		X							
Blood chemistry	X	X	X		X		X		
Prothrombin time	X						X		
Creatine kinase		X							
Hemoglobin A1c (glycated hemoglobin)		X			X		X		
Lipid panel		X	X				X		
Serum AFP test	X				X		X		
Liver stiffness		X					X		
Liver fat fraction		X					X		
Research blood specimen		X			X		X		X
Baseline risk factor questionnaire		X							
Follow-up risk factor questionnaire					X		X		
Dispense study drug and diary with instructions		X	X	X	X	X			
Symptom/adverse event assessment			X	X	X	X	X	X	
Collection and review agent and diary, assess medication compliance			X	X	X	X	X		
Telephone contact[#]	X	Once a Month						X	X
Transplant tissue specimen									X

[+] Abdominal imaging results will be reviewed during pre-screen medical chart review to determine initial eligibility. At study visits 3-6, all standard of care images occurring since screening or the last study visit will be reviewed.

[#]Telephone contact once a month (± 3 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 6 to assess adverse events.

[%] Unscheduled liver transplant may occur at any time post-intervention depending on the date of the transplant.

6.5 Clinical Laboratory Minimum Test Requirements

Blood Chemistry	Lipid Panel	Other Blood Tests
Alanine aminotransferase (ALT (SGPT)) Aspartate aminotransferase (AST (SGOT)) Alkaline phosphatase (ALP) Bilirubin, total Creatinine Glucose Sodium	Total cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglycerides	Hemoglobin A1C (HbA1C) Creatine phosphokinase (CPK) Prothrombin Time (PT/INR) Alpha-fetoprotein (AFP)

6.6 Off Agent Criteria

Participants may stop taking study agent for the following reasons:

- Completed the protocol-prescribed intervention
- Adverse event or serious adverse event
- Inadequate agent supply
- Noncompliance/refusal due to non-medical reasons
- Concomitant medications
- Medical contraindication
- Receive a liver transplant prior to completion of the intervention

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 6.3, clinical research staff will follow participants by telephone 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, laboratory test results, concomitant medications, HCC surveillance data) will continue to be collected via review of the participant's electronic medical record at the time points specified in the Schedule of Time and Events.

6.7 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient demonstrates recurrence of HCC (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);
- Patient experiences toxicity that makes continuation in the protocol unsafe;

- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second primary malignancy (basal/squamous cell skin cancer, or prostate cancer with a Gleason score 6 or less) that requires treatment, which would interfere with this study;
- Lost to follow-up. *If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.*

7.0 ADVERSE EVENTS

7.1 Risks of participation

The most common reported adverse events (incidence ≥4.0%) associated with pravastatin are upper respiratory infection (stuffy or runny nose, sneezing, sore throat, or cough), diarrhea, and musculoskeletal pain (aching or stiffness of the body, twitching muscles, etc.). Other adverse events reported in clinical trials (<4%) were angina pectoris, rash, nausea, muscle myalgia, pharyngitis, rhinitis, fatigue, headache, dyspepsia, flatulence, confusion, abdominal distension, influenza, dizziness, allergic reaction, liver failure, and rhabdomyolysis.

Persistent increases in serum transaminases (to more than 3× the ULN) have occurred in approximately 1% of patients who received pravastatin 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.

Pravastatin 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. Pravastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs which inhibit this metabolic pathway can raise the plasma levels of pravastatin and may increase the risk of myopathy. These include gemfibrozil, cyclosporine, clarithromycin, erythromycin, azithromycin, colchicine, fibrates, niacin, or grapefruit-containing products. Combination of these drugs with pravastatin is contraindicated. If short-term treatment with strong CYP3A4 inhibitors is unavoidable, therapy with pravastatin 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 pravastatin.

7.2 Adverse Event Monitoring

Adverse events will be reported in a routine manner at scheduled times during the trial using CTCAE Version 5.0. Certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- The adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline
- Any abnormal laboratory values have returned to baseline
- There is a satisfactory explanation other than the study drug for the changes observed
- Death

7.3 DEFINITIONS

7.3.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.3.2 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.3.2.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.3.2.2 Is life-threatening.

The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

7.3.2.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.3.2.4 Results in persistent or significant disability or incapacity.

7.3.2.5 Is a congenital anomaly/birth defect

7.3.2.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event”.
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.3.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was originally anticipated.

7.4 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.5 Procedures for Recording AEs, SAEs, and Ups

The PI is ultimately responsible for the required reporting of all adverse events.
All AEs that occur after the informed consent is signed and baseline measurements (Visit 1) are completed must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) 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

7.6 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely related – The AE is *doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
- The current known adverse events listed in the Agent Information Section of this protocol
- The drug package insert
- The current Investigator's Brochure

7.7 Reporting Requirements for Adverse Events

7.7.1 Expedited Reporting

- The site PI, CSMC protocol PI (Dr. Shehnaz Hussain, CSMC) and medical monitor must be notified by phone within 24 hours of learning of any fatal or serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug. Include the following information when calling:
    - Date and Time of SAE
    - Date and time of the SAE report
    - Name of reporter
    - Call back phone number
    - Affiliation/Institution conducting study
    - Protocol Number
    - Title of Protocol
    - Description of the SAE, including attribution
- A Serious Adverse Event deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression), must be reported to the DSMC within 24 hours for medical monitor ad hoc review between meetings to determine if immediate action is required. Reports may be emailed to the DSMC Admin at GroupSOCCICCTODSMCAdmin@cshs.org.
- Within 48 hours, research study staff must document the SAE using the NCI DCP Serious Adverse Event Form (https://prevention.cancer.gov/clinical-

trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia) and email the following people:

- Site PI
- Protocol PI
  Shehnaz Hussain, PhD.
  Phone: (310) 423-6401
  Email: Shehnaz.hussain@cshs.org
- Medical Monitor
  BJ Rimel, MD
  Phone: 310-423-1126
  Email: bobbie.rimel@cshs.org

An unanticipated problem is considered reportable to the Reviewing (CSMC) Institutional Review Board (IRB) and possibly local IRB depending on the institutional/local IRB policies. Research study staff must notify the Site PI, Protocol PI, and the Medical Monitor within 48 hours of learning of any unanticipated problems. Reviewing Institutional Review Board will be notified as soon as possible but no later than 10 calendar days after the Protocol PI becomes aware of any internal or external reportable event. Prompt follow-up reports of the clinical outcome will be sent to the Site PI, Protocol PI, and Medical Monitor.

7.7.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation are to be reported annually as part of regular data submission.

8.0 SPECIMEN MANAGEMENT

- Clinical lab testing for blood chemistry, prothrombin time, a lipid panel, hemoglobin A1C, creatine phosphokinase, and AFP will be conducted or coordinated by the clinical laboratories at each institution.
- Research blood specimens and transplant tissue specimens will be collected, processed, and tested as described in the *Laboratory Manual*.

9.0 STATISTICAL CONSIDERATIONS

This is a randomized double-blinded, placebo-controlled Phase II trial of statin to evaluate the impact of statin treatment on HCC progression in 130 patients. The primary objective of this study will be to demonstrate that statins will increase TTR. Secondary outcomes will include RFS, overall survival, waitlist drop-off, liver stiffness, liver fat fraction, serum biomarkers, and liver tissue biomarkers.

9.1 Randomization/Stratification

Patients will be randomized by the Research Pharmacy at each site. Randomization will be carried out among consented patients meeting the Screening Visit eligibility criteria at each site with a 1:1 ratio for pravastatin and placebo assignment, by blocks based on clinical site and initial HCC treatment type.

9.2 Sample Size and Randomization

Sample size: Intervention = 130 (65 statin: 65 placebo) randomized sample; Analytic sample = 94 (47:47) after 28% drop-out. The expected accrual rate is 5 participants per month across three sites (1.6 participants per site), and the planned recruitment duration

is 3 years. We anticipate that all evaluable participants will have completed all study procedures within 4 years. Power and precision arguments are provided below.

9.3 Study Endpoints

We have set our primary endpoint as TTR. Secondary endpoints include RFS, OS, waitlist survival, liver stiffness, and circulating biomarkers. Differences in secondary endpoints from baseline to 12-month follow-up will be compared in the pravastatin and placebo groups using a similar approach to the main endpoint.

9.3.1 Analysis of Primary Endpoint: TTR

The log-rank test will be carried out to compare the distributions of TTR between placebo and pravastatin groups and the Kaplan-Meier estimators will be presented graphically. Cox proportional hazards model will be fitted to the data where the explanatory variable of interest is the indicator of treatment allocation adjusting for clinical and demographic baseline covariates, including sex. Patients who did not experience HCC recurrence, or receive a liver transplant and are still alive at the end of the study will be right censored. Patients who are transplanted or die before HCC recurrence will be treated as a competing risk. A competing risk model for TTR will be used to estimate the cumulative incidence of TTR using time to transplant or death as a competing risk. The proportional hazards assumption will be tested graphically and analytically, and model diagnostics such as martingale and Schoenfeld residuals will be conducted to assess model adequacy. Violation of the proportional hazards assumption will be addressed by use of time-dependent covariates or extended Cox models. The possibility of collinearity among the explanatory variables will be reduced after careful assessment of the correlation matrix and condition index. Automatic variable selection methods in a multivariable Cox proportional hazards model such as stepwise, backward, and forward will be used as a guideline to identify sets of important predictors and a more rigorous approach based on a 4-step procedure outlined in Collett (2003) will be employed (55). **Power.** Preliminary data indicate that the 12-month RFS is between 57% and 78% in patients with: 1) Child Pugh A or B cirrhosis, 2) small HCCs (typically meeting Milan criteria) 3) liver directed therapy (typically RFA or resection), and 4) no other interventions (27, 56-59). Therefore, we will assume that the 12-month RFS in the control group is 65%. Assuming a common cumulative incidence of the competing risk events at 12 months of 20% (10% due to liver transplant and 10% due to death), a 42-month accrual time and 15-month follow up time, and 10% drop out, data from 47 patients per group achieve 80% power to detect a hazard ratio of 0.45 using a two-sided log-rank test with a 0.1 level of significance. This is equivalent to detecting a decrease in the 12-month cumulative incidence of disease recurrence from 35% in the control group to 18% in the treatment group, which is clinically meaningful. The choice of a type I error rate of 0.1 is appropriate for a randomized phase II trial since this can serve as a randomized screening design for a nondefinitive comparison of statin vs placebo (reference: Mandrekar and Sargent (2010)). We further assumed that TTR and time to death or transplant are independent and exponentially distributed. Statistical power was based on the formulas in Machin et al. (2008) and Pintilie (2006) and were carried out using PASS version 13 (60, 61).

Mandrekar SJ, Sargent DJ. Randomized Phase II Trials. Thorac Oncol. 2010 July ; 5(7): 932–934

9.3.2 Analysis of Secondary Endpoints

RFS and OS

For the secondary objective, comparison of overall survival and recurrence free survival between the pravastatin and placebo groups will be achieved by fitting a Cox proportional hazards model as described above for TTR. In this analysis, a competing risk model will

be fitted to the data using time to transplant only as a competing risk since overall survival includes death from any cause.

Waitlist drop-off. Fischer's exact test will be used to compare the proportions of patients on the waitlist who drop off between the pravastatin and placebo group. We expect about 35% of patients in the placebo group to drop off due to various causes such as death and HCC progression beyond Milan. Data from 47 patients per group achieve 80% power to detect a decrease in drop-off rates from 35% in the control group to 14% in the treatment group using a one-sided Fisher's exact test at the 0.1 level of significance.

Liver stiffness and Liver fat fraction. The two-sample t-test will be used to compare the change in liver stiffness/fat fraction from 3 to 12 months between pravastatin and placebo groups. If the distribution of the change in liver stiffness/fat fraction is highly skewed so that the sample mean based on 47 measurements is not approximately normally distributed, the Mann-Whitney test will be used instead. Measurements of liver stiffness vary between 1.5 and 75 kPa. Therefore, we conservatively estimate the standard deviation of liver stiffness at 3 months as (75-1.5)/4 = 18.4. If X and Y denote the random variables of liver stiffness at 3 and 12 months, respectively, the Var(Y-X) = Var(X)+Var(Y) -2ρ Var(X) Var(Y), where ρ is the correlation coefficient between X and Y. Assuming a non-negative correlation between the measurements at 3 and 12 months and the same variance at 12 months σ2, then a conservative estimate for the standard deviation of the change in liver stiffness is 1.4 σ. Therefore, data from 47 patients per group achieve 80% power to detect an effect size of 0.5 using a two-sided two-sample t-test with 0.1 level of significance. We therefore have enough patients to detect clinically meaningful differences in mean liver stiffness. Here, the effect size is the ratio of the difference in the mean change between the two groups relative to the baseline standard deviation σ assumed to be the same for the treatment and control groups. Linear regression analysis will be carried out to estimate the adjusted pravastatin effect if there is evidence of imbalance between the two groups with respect to one or more baseline clinical and demographic covariates.

Change in biomarkers. Two-sample t-test will be carried out to compare the change in biomarkers from baseline to each of the two follow-up time points, 6 and 12 months, between treatment and placebo groups. The Man-Whitney test will be used in the presence of highly skewed distributions and Fisher exact test will be used for dichotomous stratifications (high versus low). Assuming a common standard deviation of the change in biomarker from baseline to each time point between the two groups SD(diff), data from 47 patients per group achieve 80% power to detect an effect size of 0.72 using a two-sided two-sample t-test with a Bonferroni corrected 0.01 level of significance since we plan to test 10 biomarkers (0.1 / 10). Here, the effect size is the ratio between the difference in change of biomarkers between the two groups over SD(diff). Linear or logistic regression analysis will be carried out if there is evidence of imbalance between the two groups with respect to one or more baseline clinical and demographic covariates at each time point as in Aim 3.

9.3.3 Interim Analysis

There are no planned interim analyses.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Registration Procedures

All subjects that sign informed consent will be assigned a screening identification number by the study coordinator sequentially by their date of consent, please refer to MOP. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the site PI and CSMC protocol PI. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

The study team will track all subjects who sign consent on a subject screening/enrollment log using a unique screening ID. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered.

10.3.1 Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the QMC at Cedars-Sinai. The following documents will be completed and provided for review:

- Registration form (or equivalent)
- Copy of required MedQIA CRF
- Full Eligibility Checklist (signed by a consenting investigator) with source
- Signed patient consent form and Subject's Bill of Rights
- HIPAA authorization form

Please see MOP for Eligibility Verification details.

10.3.2 Randomization

After eligibility is verified, study coordinator assigns the participant ID (PID) and registration is completed as follows:

- The study coordinator at each site will send an email to the research pharmacist.
- Site investigational pharmacist enters patient data into RANDI3 software (housed on CSMC server) for randomization, and assigns patient to pravastatin or placebo, and emails the study coordinator that randomization has been completed.
- Study coordinator enters the patient in OnCore to complete registration

Only the research pharmacists and the study biostatistician are unblinded; all other study team members are blinded and should not have access to the subject's treatment arm. See Pharmacy Manual for more details.

Research pharmacists can only view subjects they have randomized at their site. The study biostatistician maintains the master randomization list and is responsible for the predetermined randomization scheme prior to the start of study. Of note, the inform and participant eligibility form must be completed prior to randomization

Oversight by the site PI and CSMC protocol PI are required throughout the entire registration process.

10.3.3 Registration

OnCore (https://eoncore.csmc.edu) is the clinical research management system that will be used for this study. Refer to the *OnCore Instructions for Patient Registration* for detailed instructions.

10.4 Data Management and Quality Control and Reporting

The data will be entered into a validated database. Data and/or completed case report forms must be uploaded to the study database within two weeks following the study visit.

A data system compliant with the Code of Federal Regulations (CFR) Title 21 and the Health Insurance Portability and Accountability Act (HIPAA) must be in place prior to enrollment of the first patent. The data system must be provided to each participating site and managed by the site research coordinator.

The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

10.5 Data and Safety Monitoring

10.5.1 Data Monitoring and Quality Assurance

Adherence to the protocol, recruitment and retention, participant accrual, safety of subjects, regulatory compliance, data management, Good Clinical Practices (GCP) and

institutional policy will be monitored by the Protocol PI and the Site PIs during the course of the study through routine study team meetings (Steering Committee or equivalent). In addition, the CSMC QMC and the UCLA CTSI Office of Regulatory Affairs (ORA) Services will conduct the following:

- Central Eligibility Pro00048985 Checklist Review and Eligibility Verification, for all subjects enrolled as described in the protocol
- Monitoring, 100 percent of data will be monitored for the first 5 subjects enrolled at each site. If there are no data quality issues, the monitoring of subjects will be reduced to every 3rd subject. Should the data quality continue to be acceptable after 20 enrolled subjects, the monitoring frequency will reduce to every 5 subjects. This reduction in monitoring frequency will be implemented on a per site basis.
- Auditing, is a review of historic performance of the research effort and is performed on case report forms, regulatory files and source documents to measure the quality of the research effort in a retrospective manner. During the audit, the auditor will review specific data related to the protocol and regulatory requirements. Source documents are used to independently verify study data. Source documents may include, but are not limited to, inpatient and outpatient medical records, study flow sheets and other research records that are signed and dated, protocol or study road maps, appointment books, enrollment tracking sheets, subject diaries/calendars, and Drug Accountability Record Forms (DARFs).

  The auditing visit consists of reviewing and evaluating (1) conformance to IRB and informed consent requirements, (2) individual patient records and (3) the pharmacy and use of DARFs. The first audit will occur within 2-3 months after the first subject is enrolled at each site and will include a thorough review of subject charts, subject drug accountability, pharmacy records, and regulatory files. Subsequent audits will occur annually and will include review of select subject cases (3 subjects or 10% of subjects enrolled since last audit), pharmacy records and regulatory documents. The Auditor has the authority to request more frequent reviews or closer data auditing if it is deemed appropriate for any reason.

10.5.2 Safety Monitoring

A Data Safety Monitoring Committee (DSMC) will be convened and will meet at least once per year to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the SOCCI DSMC Charter. There will be interim reviews conducted by the DSMC for the purpose of monitoring study conduct and assessing subject safety. The interim reviews will include review of all monitoring and audit reports; serious adverse events (SAEs) that occur; and protocol deviations and exceptions. The DSMC findings and any concerns and recommendations will be reported in writing to the Principal Investigator. A summary report will be forwarded by the Principal Investigator or his/her designee to the IRB.

10.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file per institutional guidelines.

10.6.1 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and CSMC IRB, the study shall be conducted exactly as described in the approved protocol.

10.6.2 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator's awareness of the event.

10.6.3 Protocol Exceptions and Eligibility Waivers

An exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy*, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.*

A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

All exception requests, except logistical protocol deviations as defined below, must be reviewed by the SOCCI Medical Director and the Institutional Review Board prior to implementation. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents to the SOCCI Medical Director for review. Planned exceptions to the protocol that are more than logistical and/or have the potential to affect the subject's safety and/or study integrity may not be implemented without prior approval from the SOCCI Medical Director and IRB.

Study team should refer to the IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement guidelines to determine which deviations and exception requests require prior approval from the SOCCI CCTO Medical Director. Once approved, the deviation or exception request must be submitted to the IRB for review and approval prior to implementation.

Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be forwarded to the SOCCI CCTO Medical Director for assessment **prior** to submission to the IRB for approval.

The CCTO Medical Director will review the case and contact the investigator if additional information is needed or further discussion is warranted. The CCTO Medical Director will provide a written assessment/recommended course of action. The CCTO Medical Director's assessment must be uploaded into CS-IRB with the waiver request for IRB review and consideration. The CCTO Medical Director may recommend future protocol changes.

Eligibility Waiver Submission Process

The PI and/or treating physician should provide written request for waiver which includes case history and justification for prospective deviation from the study design to the SOCCI CCTO Medical Director. "IIT Monitoring – Eligibility Waivers and Exception

Requests (EW/ER) Form" must be completed, along with any applicable supporting documents, must be emailed to QMC (GroupSOCCICROQMC@cshs.org) to request an eligibility exception request from the CCTO Medical Director. This is only a requirement for studies with DSM classification of moderate or high. An assessment from the CCTO Medical Director or designee must be done prior to submission to the IRB for review.

10.6.4 Other Protocol Deviations/Violations

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI Clinical Research Office's Working Instruction 11: Deviation and Noncompliance Reporting. In this case, a Protocol Deviation report must be submitted to the IRB, per IRB policy, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

10.6.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the CSMC protocol PI. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

10.7 Obligations of Investigators

The Site PIs are responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The site PI is responsible for personally overseeing the treatment of all study patients. The site PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The site PI will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the site PI will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the site PI and will require his/her final signature to verify the accuracy of the data.

11.0 REFERENCES

1. Siegel R, Ma JM, Zou ZH, Jemal A. Cancer Statistics, 2014. Ca-a Cancer Journal for Clinicians 2014;64(1):9-29.
2. Setiawan VW, Hernandez BY, Lu SC, Stram DO, Wilkens LR, Marchand LL, et al. Diabetes and Racial/Ethnic Differences in Hepatocellular Carcinoma Risk: The Multiethnic Cohort. Journal of the National Cancer Institute 2014;106(12).
3. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing Hepatocellular Carcinoma Incidence and Liver Cancer Mortality Rates in the United States. American Journal of Gastroenterology 2014;109(4):542-553.
4. Yu J, Shen J, Sun TT, Zhang X, Wong N. Obesity, insulin resistance, NASH and hepatocellular carcinoma. Semin Cancer Biol 2013;23(6 Pt B):483-91.
5. El-Serag HB, Rudolph L. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology 2007;132(7):2557-2576.
6. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009;136(1):138-48.
7. Tong MJ, Hsien C, Song JJ, Kao JH, Sun H-E, Hsu L, et al. Factors Associated with Progression to Hepatocellular Carcinoma and to Death from Liver Complications in Patients with HBsAg-Positive Cirrhosis. Digestive Diseases and Sciences 2009;54(6):1337-1346.
8. Mair RD, Valenzuela A, Ha NB, Ayoub WS, Daugherty T, Lutchman GA, et al. Incidence of Hepatocellular Carcinoma Among US Patients With Cirrhosis of Viral or Nonviral Etiologies. Clinical Gastroenterology and Hepatology 2012;10(12):1412-1417.
9. Ascha MS, Hanouneh IA, Lopez R, Tamimi TAR, Feldstein AF, Zein NN. The Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis. Hepatology 2010;51(6):1972-1978.
10. El-Serag HB, Kanwal F. Obesity and Hepatocellular Carcinoma: Hype and Reality. Hepatology 2014;60(3):779-781.
11. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) Annual Data Report. Rockville: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012.
12. Agopian VG, Harlander-Locke M, Zarrinpar A, Kaldas FM, Farmer DG, Yersiz H, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. J Am Coll Surg 2015;220(4):416-27.
13. Welzel TM, Graubard BI, Quraishi S, Zeuzem S, Davila JA, El-Serag HB, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol 2013;108(8):1314-21.
14. Ogden CL, Carroll MD, Kit BK, Flegal KM. PRevalence of childhood and adult obesity in the united states, 2011-2012. JAMA 2014;311(8):806-814.
15. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among a Largely Middle-Aged Population Utilizing Ultrasound and Liver Biopsy: A Prospective Study. Gastroenterology 2011;140(1):124-131.
16. Beltran-Sanchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. J Am Coll Cardiol 2013;62(8):697-703.
17. Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002;123(1):134-40.
18. Quillin RC, Wilson GC, Sutton JM, Hanseman DJ, Paterno F, Cuffy MC, et al. Increasing prevalence of nonalcoholic steatohepatitis as an indication for liver transplantation. Surgery 2014;156(4):1049-1058.
19. Agopian VG, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, et al. Liver Transplantation for Nonalcoholic Steatohepatitis The New Epidemic. Annals of Surgery 2012;256(4):624-633.

20. Wong G, Chapman JR, Craig JC. Death from cancer: a sobering truth for patients with kidney transplants. Kidney International 2014;85(6):1262-1264.
21. Hu M, Tomlinson B. Evaluation of the pharmacokinetics and drug interactions of the two recently developed statins, rosuvastatin and pitavastatin. Expert Opinion on Drug Metabolism & Toxicology 2014;10(1):51-65.
22. Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation 2004;109(23 Suppl 1):III50-7.
23. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions. Expert Opin Drug Saf 2012;11(6):933-46.
24. Bell DSH, DiNicolantonio JJ, O'Keefe JH. Is statin-induced diabetes clinically relevant? A comprehensive review of the literature. Diabetes Obesity & Metabolism 2014;16(8):689-694.
25. Simon TG, King LY, Zheng H, Chung RT. Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. Journal of Hepatology 2015;62(1):18-23.
26. Kargiotis K, Athyros VG, Giouleme O, Katsiki N, Katsiki E, Anagnostis P, et al. Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome. World Journal of Gastroenterology 2015;21(25):7860-7868.
27. Kumar S, Grace ND, Qamar AA. Statin use in patients with cirrhosis: a retrospective cohort study. Dig Dis Sci 2014;59(8):1958-65.
28. Souk K, Al-Badri M, Azar ST. The Safety and Benefit of Statins in Liver Cirrhosis: a Review. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2015;123(10):577-80.
29. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology 2007;46(5):1453-63.
30. Bays H, Cohen DE, Chalasani N, Harrison SA, The National Lipid Association's Statin Safety Task F. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol 2014;8(3 Suppl):011.
31. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. J Clin Gastroenterol 2014;8:8.
32. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127(5 Suppl 1):S35-50.
33. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100(10):698-711.
34. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52-60.
35. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology 2015;61(3):1056-65.
36. Liver Transplant Program Report (2015), Cedars-Sinai Medical Center. In: Scientific Registry of Transplant Recipients. http://www.srtr.org/csr/current/Centers/centerdetail.aspx?facility=CACSTX1LI. Accessed on 9/26/2016.
37. Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer 2001;84(7):886-91.

12.0 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.

13.0 APPENDIX B

Pravastatin Intervention to Delay Hepatocellular Carcinoma Recurrence

STUDY DIARY

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: **Site:**
Participant Study ID: __ **Participant Name: _____**
Date Study Drug Dispensed: ___ **Participant Signature: _____**

Instructions

Complete one line in the table for each day you take the study drug.
Please contact the clinical research coordinator at <<phone 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, mild skin rash) or if you have any other symptoms or comments, please record them in the Side Effects/Comments column and tell 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 two doses of the study drug at the same time. Please write the reason for missing a dose in the Side Effects/Comments column.

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.	