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Statin Therapy Operates to Prevent (STOP) Heart Disease in Breast Cancer Survivors Trial

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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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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

2-D echo	2-dimensional echocardiography
AC	Anthracycline and cyclophosphamide
AC-T	Anthracycline and cyclophosphamide followed by taxane
AC-TH	Anthracycline and cyclophosphamide followed by taxane and Herceptin (trastuzumab)
ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
BB	β-blocker; beta blocker
BNP	Brain natriuretic peptide; B-type natriuretic peptide
BRCA	Gene mutation that elevates the risk of breast cancer
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBDF	Complete Blood Count and Automated Differential
CHF	Congestive heart failure
CMPL	Comprehensive Metabolic Panel
CMRI	Cardiac magnetic resonance imaging
CO	Cardiac output
CPK	Creatine phosphokinase; creatine kinase
CrCl	Creatinine clearance
CRO	Clinical Research Office
CSd	Diastole rate
CSs	Systole rate
CSMC	Cedars-Sinai Medical Center
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen receptor
FDA	Food and Drug Administration

Gad	Gadolinium
GCS	Global circumferential strain
GTPase	Guanosine triphosphatase
HDAC	Histone deacetylase
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme a
Hs-CRP	High sensitivity C-reactive protein
Hs-TnT	High sensitivity troponin
IAB	Internal Advisory Board
ICF	Informed Consent Form
IL-6	Interleukin 6
IRB	Institutional Review Board
IV	Intravenous
LV	Left ventricular
LVEDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end systolic volume
LVOT	Left ventricular outflow tract
MOLLI	Modified Look-Looker Inversion Recovery
MRS	Magnetic resonance spectroscopy
NADPH	Nicotinamide adenine dinucleotide phosphate
PFR	Peak filling rate
PR	Progesterone receptor
Rac1	Ras-related C3 botulinum toxin substrate 1
ROS	Reactive oxygen species
RCT	Randomized controlled trial
SAE	Serious adverse event
SOCCI	Samuel Oschin Comprehensive Cancer Institute
SSFP	Steady-state-free-precession
SV	Systolic volume
TCH	Taxotere (docetaxel), carboplatin, and Herceptin (trastuzumab)
TCHP	Taxotere (docetaxel), carboplatin, Herceptin (trastuzumab), and pertuzumab
tPFR	Time to peak filling rate
UTR	Peak rate of basal to apical untwisting
WISE	Women's Ischemia Syndrome Evaluation

STUDY SCHEMA
Statin Therapy Operates to Prevent (STOP) Heart Disease in Breast Cancer Survivors Trial

Female patients with newly diagnosed stage 1-3 breast cancer

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Pre-Screen Medical Chart Review and Initial Determination of Eligibility

Clinical research staff reviews medical charts of patients diagnosed with breast cancer and completes pre-screen eligibility checklist: age, HER2/ER/PR status, lab results, medical contraindications, prohibited medications, prior or current statin use

↓

Recruitment and Consent

Oncologist introduces study to potentially eligible breast cancer patients recommended for trastuzumab treatment, with or without anthracycline. Patients receive study information packet; clinical research staff reviews study details with patient and contacts patient a few days later to answer questions. Patients who want to participate will be consented into the trial by one of the study physicians before any research procedures are initiated.

↓

Pre-Study Evaluations*

Physical exam; symptom assessment; ECOG performance status; blood tests to confirm eligibility and safety of statin initiation; urine pregnancy test for women able to become pregnant; 2D-echocardiogram. *Patients with an abnormal 2D-echocardiogram, AST/ALT > 3x ULN, creatinine > 1.8 mg/dL, or who are pregnant will be excluded.*

↓

Final Determination of Eligibility

Research staff completes full eligibility checklist for consented patients, retrieves support documents from medical charts. Oncologist, study cardiologist, or other physician-investigator reviews patient's checklist, medical history, and supporting documentation. Clinical Research Office designee conducts final eligibility check prior to registration and randomization.

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Eligible, consented patients with breast cancer registered and randomized to atorvastatin or placebo (N=60)

Atorvastatin 20 mg, daily for 12 months (N=30)	Placebo identical in color, consistency, and appearance to atorvastatin 20 mg, daily for 12 months (N=30)

↓

Visit 1^ – Baseline measurements and Initiation of the Statin Intervention (from 2 weeks before the patient starts systemic breast cancer treatment (trastuzumab with or without anthracycline) up to 3 weeks after starting treatment)

Review medical history, medications, and laboratory test results; vital signs assessment; ECOG performance status; blood draw; urine pregnancy test for women able to become pregnant; cardiac magnetic resonance imaging (CMRI); interviewer-administered questionnaire; self-administered QLQ-C30 and QLQ-BR23 quality of life questionnaire; review eligibility criteria; dispense study drug and diary

↓

Visit 2* (1 month ± 2 weeks after initiation of the statin intervention)

Review medical history, medications, and laboratory test results; physical exam; symptom assessment; ECOG performance status; clinical labs for CBDF and CMPL; collect study drug and diary; assess compliance and adverse events; review study diary; review eligibility criteria; dispense study drug and diary

↓

Visit 3* (3 months ± 2 weeks after initiation of the statin intervention)

Same procedures as Visit 2 and follow-up 2D-echocardiogram

↓

Visit 4^ (6 months ± 2 weeks after initiation of the statin intervention)

Same procedures as Visit 1 and: collect study drug and diary; assess compliance and adverse events; review study diary

↓

Visit 5* (9 months ± 2 weeks after initiation of the statin intervention)

Same procedures as Visit 3

↓

Visit 6^ (12 months ± 2 weeks after initiation of the statin intervention)

Same procedures as Visit 4 except no study drug dispense; collect study drug and diary

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Follow-up phone calls (day 30, 60, 90 ± 7 after completion of the statin intervention) to assess symptoms/adverse events

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Endpoints – Evaluate the effect of atorvastatin use versus placebo after 12 months of intervention on changes in:

1) Global circumferential strain (GCS), a sensitive measure of myocardial dysfunction, measured by cardiac magnetic resonance imaging (CMRI)
2) Other strain-related measures, myocardial diastolic function, and cardiac morphology, measured by cine CMRI and tissue tagging
3) Myocardial fibrosis and tissue viability, edema, and inflammation measured by CMRI T1 and T2 mapping values

**Pre-Study Evaluations and Visits 2, 3, and 5 are standard of care visits.*

^Visits 1, 4, and 6 are research visits to collect endpoint data and will coincide with standard of care visits when possible.

STUDY SUMMARY

Title	Statin Therapy Operates to Prevent (STOP) Heart Disease in Breast Cancer Survivors Trial
Protocol Number	IIT2015-12-Goodman-STOP
Phase	Phase II
Methodology	Randomized, double-blinded, placebo-controlled, Phase II trial of statin therapy to ameliorate or prevent cardiac damage in women with newly diagnosed stage 1-3 breast cancer
Study Duration	3.5 years
Study Center(s)	Cedars-Sinai Medical Center
Objectives	Primary Objective: To evaluate the effect of atorvastatin intervention versus placebo on a 1 year change from baseline on myocardial dysfunction in breast cancer patients who have undergone trastuzumab treatment, with or without anthracycline. The primary outcome is global circumferential strain (GCS), a sensitive measure of myocardial dysfunction, which is predictive of future cardiac events. Cardiac magnetic resonance imaging (CMRI) will be used to measure GCS. Secondary Objectives: To evaluate the effect of atorvastatin intervention versus placebo on a 1 year change from baseline on: 1) other strain-related measures, myocardial diastolic function, and cardiac morphology, measured by cine CMRI and tissue tagging; and 2) myocardial fibrosis, edema, and inflammation measured by T1 and T2 mapping values during the CMRI.
Number of Subjects	60
Diagnosis and Main Inclusion Criteria	Newly diagnosed stage 1-3 breast cancer; histologically confirmed HER2, ER, and PR status; minimum 18 years of age; recommended to undergo trastuzumab treatment, with or without anthracycline. Patients will be eligible for up to 3 weeks after starting treatment.
Study Product(s), Dose, Route, Regimen	Atorvastatin 20 mg and placebo identical in color, consistency, and appearance to atorvastatin; oral administration daily
Duration of Administration	12 months
Statistical Methodology	Analyses will be conducted on an intention-to-treat basis on all patients who complete the 12-month CMRI. The non-parametric Wilcoxon-Mann-Whitney test will be used to test the equality of statin treatment (atorvastatin) to placebo in reducing or preventing LV dysfunction through comparison of change in GCS values (Δ length / original length, expressed as %) measured from 2 weeks prior to start of systemic breast cancer treatment to 1 year post-initiation of the statin intervention. The distribution of the covariates, including age, race, dose of trastuzumab treatment (and anthracycline if applicable), laterality, radiation dose, smoking status, BMI, baseline measures of fibrosis, hormone use, 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

Breast cancer is a devastating disease for women in the U.S., but death rates due to breast cancer are declining and there are now more than 3.1 million breast cancer survivors [1]. While aggressive screening and targeted, advanced treatment for breast cancer have had a measurable impact on survival, treatment has significant acute and chronic cardiotoxicity [2-4]. The risk of cardiovascular-related death is eight-fold higher for long-term cancer survivors than for the remaining population [5]. Clearly, the question of prevention and mitigation of iatrogenic cardiotoxicity among women with breast cancer assumes greater importance now that long-term disease-free survival has been achieved. An urgent need exists to intervene early in women with breast cancer using a cardioprotective agent to reduce therapy-related cardiotoxicity.

1.2 Study Agent

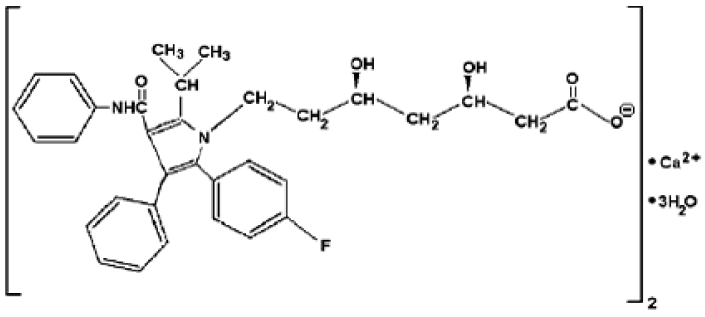


Figure 1. Molecular Structure of Atorvastatin Calcium

Atorvastatin calcium [Figure 1], a synthetic lipid-lowering agent, 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 cholesterol biosynthesis. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose, NF; lactose monohydrate; magnesium stearate; microcrystalline cellulose; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80; and simethicone emulsion.

Atorvastatin has a widely accepted tolerability profile with few serious side effects [6]. In the atorvastatin calcium tablets placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin calcium tablets vs. 7,311 placebo) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium tablets and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium tablets were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%) [7]. Potential, but uncommon side effects include muscle, liver, and kidney problems. Elevated levels of creatine kinase and rhabdomyolysis occur in < 1% of consumers.

Atorvastatin calcium is prescribed for primary and secondary prevention of cardiovascular disease and thus is indicated for long-term use. Among several lipophilic statins in the market, atorvastatin is considered to have the most potent effect on cardiometabolic measures [8]. We propose to administer atorvastatin 20 mg daily for 12 months in this trial.

1.3 Rationale

In spite of the substantial scientific literature that breast cancer treatment may be deleterious to the heart with long-term consequences to quality of life, there are few published results from randomized controlled trials (RCTs) using cardioprotective agents to attenuate the cardiomyopathy associated with cancer therapeutics. The *STOP Heart Disease in Breast Cancer Survivors Trial* is designed to evaluate the effectiveness of statins to reduce or prevent trastuzumab-induced left ventricular (LV) dysfunction. Trastuzumab, a monoclonal antibody to

the human epidermal growth factor receptor-2 (HER2/ErbB2), has become a potential cause of heart failure and cardiomyopathy among women treated for breast cancer, especially when given with anthracyclines [9].

Statins and Cardioprotection. The prophylactic and therapeutic use of cardioprotective agents, including statins, angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), and β-blockers (BB), have been reported to ameliorate cancer treatment cardiotoxicity, although evidence from RCTs in breast cancer patients have been limited. A recent review and meta-analysis of cardioprotective therapy to reduce adverse cardiac outcomes in cancer chemotherapy patients found that statins showed a similar efficacy compared to other cardioprotective agents [3]. Statins decrease CVD-related morbidity and mortality and are widely used for cardiovascular disease prevention [10]. In addition to cholesterol lowering anti-atherosclerotic effects, statins also exert pleiotropic effects that are anti-oxidative and may be cardioprotective, and therefore relevant to trastuzumab-induced cardiotoxicity [11]. While observational studies suggest that statins may attenuate chemotherapy-induced cardiac toxicity, this outcome has not been rigorously tested in a clinical trial. We hypothesize that the diverse and beneficial effects of statins will help protect the heart during trastuzumab treatment. Our multi-disciplinary research team will randomize newly diagnosed stage 1-3 breast cancer patients to prophylactic statin versus placebo and evaluate longitudinal structural and functional changes to the myocardium using CMRI. Our RCT with a longitudinal approach to studying detailed imaging changes of the myocardium from baseline through 12 months of treatment will elucidate pathophysiological pathways of myocardial damage and could lead to a new cardioprotection strategy in breast cancer treatment.

Hypotheses. We anticipate that trastuzumab treatment, with or without anthracycline treatment, will impair global circumferential strain (GCS) and diastolic function, and increase markers of fibrosis, edema, and/or inflammation. We hypothesize that after 12 months of intervention, participants randomized to atorvastatin will experience:

1) Less GCS impairment compared to the placebo group;
2) Less diastolic dysfunction compared to the placebo group; and
3) Less myocardial fibrosis, edema, and inflammation compared to the placebo group.

Chemotherapy-Induced Cardiotoxicity. Adverse cardiac events, including heart failure, myocardial ischemia, venous thromboembolism, and bradycardia may result from common breast cancer treatments [12]. The focus of our RCT is on the subacute cardiotoxic effect of trastuzumab therapy that has long-term consequences, especially diastolic LV dysfunction and subsequent risk of heart failure [5]. Cardiac risk is particularly elevated in breast cancer patients treated with a combination of anthracycline and trastuzumab. Early clinical trials showed that the addition of trastuzumab to anthracycline treatment for breast cancer led to a synergistic increase in cardiac symptoms from 13% to 27% compared to 2-8% of patients receiving trastuzumab or anthracyclines alone [13]. A recent analysis of a population-based cohort study of 12,500 women with invasive breast cancer demonstrated hazard ratios for heart failure and cardiomyopathy during treatment of 1.4 (1.1-1.8) in patients on anthracycline alone, 4.1 (2.3-7.4) in patients treated with trastuzumab alone, and 7.2 (5.0-10.4) in patients treated with both agents as compared to patients who received no chemotherapy [14].

Trastuzumab. Trastuzumab (Herceptin) targets the HER2/neu receptor which is overexpressed in 25% of breast cancer [15]. This receptor is also expressed at low levels in the heart and can be upregulated under stress [16]. Inhibition of the HER2 receptor contributes to cardiac injury in patients receiving trastuzumab, although mechanisms are still unclear. HER2 signaling is fundamental to cardiomyocyte development and survival [17]. HER2-knock out mice develop dilated cardiomyopathy progressing to systolic dysfunction, suggesting an important role for HER2 expression in maintaining cardiac function [18]. Trastuzumab is capable of inhibiting autophagy in human cardiomyocytes, leading to increased production of reactive oxygen species [19]. Trastuzumab down-regulation of the HER2 pathway has been linked to asymptomatic cardiac dysfunction and symptomatic congestive heart failure (CHF) [20]. A recent meta-analysis of five RCTs, found a RR of 5.8 (3.6-9.3) for the association of trastuzumab and all-grade CHF with a number needed to harm of 9 (for every 9 patients treated with trastuzumab one additional case of CHF will occur compared to placebo) [21]. While trastuzumab-related cardiac dysfunction was initially thought to be reversible with no frank ultra-structural changes, advanced CMRI data shows myocyte damage with fibrosis and scarring [22]. In spite of the increased cardiac monitoring

included to ensure patient safety in HER2-positive breast cancer patients, LV dysfunction occurs in up to 23% of patients receiving trastuzumab alone [15,20]; and in a joint analysis of two large clinical trials, 4.1% of patients receiving trastuzumab experienced CHF or cardiac death [15]. In a recent trial, 7% of women with HER2-positive breast cancer had a decrease in LV ejection fraction (LVEF) >10% at 2 years, with CHF in 0.8% of patients [23]. A meta-analysis of three RCTs found a RR of 6.7 (4.9-9.2) for the association of trastuzumab with high grade decreased left ventricular ejection fraction (number needed to do harm was 3) [21]. These sequelae were amplified by the fact that cardiotoxicity was the leading cause of trastuzumab interruption: 5% of clinical trial participants in year 1 and 9% of participants in year 2 discontinued trastuzumab treatment, which has serious consequences for control of HER2-positive breast cancer [15]. Moreover, the cardiotoxic effects of trastuzumab will likely be greater in the community setting where the presence of comorbidities is higher than in carefully selected clinical trial patients. Indeed, a Medicare-based study found that the incidences of cardiomyopathy and heart failure were increased by >10% among elderly patients treated with trastuzumab compared to non-trastuzumab / non-anthracycline based therapy [24]. In another Medicare study [25], the 41% of patients who discontinued trastuzumab early - usually due to cardiovascular complications - were at higher risk of heart failure / cardiomyopathy, atrial fibrillation, and other cardiovascular events than were women who were able to tolerate the full course of trastuzumab.

Anthracyclines. Anthracyclines cause dose-dependent irreversible LV dysfunction likely resulting from oxidative stress and mitochondrial damage associated with myofibrillar disarray and necrosis [26]. Irreversible cardiotoxicity may progress to heart failure and death in breast cancer survivors [27]. It is thought that the acute decline in cardiac contractility caused by anthracyclines is dose-dependent, and that onset cardiomyopathy may occur in up to 5% of patients in the year following anthracycline therapy. The cardiotoxic effects of anthracycline (doxorubicin) treatment are dose-responsive, with heart failure noted in 26% of patients given the maximum lifetime cumulative dose of 550 mg / m^2 [12]. The BCIRG-006 trial compared doxorubicin plus cyclophosphamide followed by docetaxel (AC-T); AC-T plus one year trastuzumab (AC-TH); and a non-anthracycline-containing arm, docetaxel, carboplatin, and one year trastuzumab (TCH) among 3,222 HER2-positive women with early breast cancer [28]. While the 10-year follow-up results suggested no difference in overall survival for the AC-TH compared with the TCH patients, the AC-TH patients experienced 5-fold more cardiac deaths and CHF events (p=0.0005) in the AC-TH arm (21 events) compared with the TCH arm (4 events) [9]. We are especially interested in the subgroup of women treated with both trastuzumab and anthracycline.

Mechanisms for Treatment-Associated Cardiotoxicity. Mechanisms for trastuzumab-induced cardiotoxicity are still being clarified, but it is thought that trastuzumab leads to heart failure by blocking the physiological actions of HER2 in the heart [29,30]. HER2 is essential for normal fetal cardiac development and cardiac-specific deletion of HER2 leads to cardiomyopathy in mice [20,31]. HER2 is present in cardiomyocytes and, in the presence of the ligand neuregulin-1, HER2 upregulates phosphoinositide-3-kinase (PI3K) signaling, AKT activation, and the extracellular signal-regulated kinase (ERK1/2) mitogen-activated pathway; and HER2 suppresses apoptotic signaling. In the absence of HER2 signaling, cardiac dysfunction develops, characterized by mitochondrial dysfunction, excessive production of reactive oxygen species (ROS), opening of the mitochondrial permeability transition pore, and cell death [32,33]. Anthracyclines likely cause myofibrillar loss and cellular necrosis through direct injury and oxidative stress [34]. Anthracyclines target cellular topoisomerase-2α and DNA to form a cleavage complex that triggers apoptosis in tumor cells [35]. The inhibition of topoisomerase-2β by anthracycline causes double-stranded breaks and death of cardiomyocytes. Topoisomerase-2β inhibition also reduces p53 activation of the apoptotic pathway, and decreases expression of uncoupling proteins that regulate NADPH oxidase-mediated mitochondrial ROS production [4]. NADPH oxidase, an important cause of cardiovascular disease, consists of several protein components, including Rac1, a Rho guanosine triphosphatase (GTPase). Inhibition of Rac1 was found to protect mice from doxorubicin-induced myocardial dysfunction, while Rac1 overexpression led to decreased activity of histone deacetylases (HDAC), mimicking the effects of doxorubicin on p53-mediated apoptosis [36].

Radiation-Induced Cardiotoxicity. Cardiovascular toxicity resulting from radiotherapy for mostly left-sided breast cancer has been well-documented, especially among women receiving whole heart doses of ≥ 5 gray, as was common in the past [37]. Radiation-related injury may include structural damage to the heart, such as fibrosis, pericardial adhesions, microvascular damage and valvular stenosis, as well as damage to the coronary

arteries [38]. Despite this, radiation to left-sided breast tumor was not found to be associated with congestive heart failure in a national population of elderly women with breast cancer [39]. The radiation dose to the heart has decreased substantially during the past decade, driven by medical advances such as accelerated partial breast irradiation [40]. Although tangential radiation treatment for left-sided breast cancer is now computed tomography (CT)-guided, delivering the lowest dose of radiation for the shortest duration, coronary arteries in the field can be affected [41]. The degree to which improved radiotherapeutic technologies have ameliorated long-term risk of heart failure in breast cancer patients is unknown. We expect that randomization of patients to statin and placebo will balance the frequency of left-sided breast cancer and the relative radiation exposure to the heart. If by chance the radiation dose to the heart is imbalanced between the two groups, we will conduct a sensitivity analysis following our primary intention-to-treat analysis to investigate if variations in radiation dose affected the results of statin.

Statins (3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)) Inhibitors and Breast Cancer. Statins, used primarily to reduce LDL-cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, are well-tolerated with few serious side effects [6]. Statin use reduces the incidence of major vascular events, such as myocardial infarction, stroke and coronary revascularization, as well as overall mortality [10]; and this risk reduction extends to healthy individuals at low baseline risk of cardiovascular disease. Emerging evidence implicates an imbalance of angiogenic and antiangiogenic factors in hypertension and coronary artery disease [42,43] that can be normalized by statin treatment [44]. A key mechanism whereby statins can inhibit cardiotoxicity includes the reduced production of isoprenoid (e.g., farnesyl pyrophosphate, geranyl pyrophosphate), a necessary post-translational modifier of the RAS superfamily of GTPase proteins, including Rac. Rac is an important activator of the NADPH oxidase [45]. When prenylated, Rac tethers co-activator p67 to the membrane and induces a conformational change leading to the assembly of NADPH oxidase complex and production of O^2 [46]. By inhibiting the prenylation of Rac1, statins have been shown to decrease ROS production, attenuating cardiac hypertrophy [47]. Statins also promote mitochondrial turnover, attenuating ROS production and accumulation of mtDNA mutations [48,49]. Statins may alter the expression of vascular growth factors, thereby improving the capillary network and reversing the anti-angiogenic effects of trastuzumab in the heart [50]. Taken together, these studies provide compelling evidence that statins regulate, either directly or indirectly, several signaling pathways implicated in cardiomyocyte damage. We hypothesize that the diverse and beneficial effects of statins will help protect the heart during cancer chemotherapy.

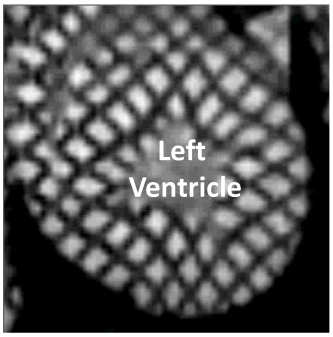
Not all statins are expected to have a specific local effect on cardiomyocytes, as they vary in hepatoselectivity. *Hydrophilic statins*, such as rosuvastatin, accumulate in the liver, as they are taken into liver cells by carrier-mediated transporters that are expressed in hepatocytes. *Lipophilic statins* such as atorvastatin enter cells in the hepatic and extrahepatic tissue via passive diffusion and do not accumulate in the liver, thus making it more available to other organs [51]. Congruent with this property, lipophilic statins were found to be associated with reduced recurrence of cancer in a large cohort of Danish women with stage I-III breast cancer, while hydrophilic statins did not have any impact on outcome [52]. Given these observations, we decided to select a lipophilic statin for our intervention. Among several lipophilic statins on the market, including atorvastatin, simvastatin, fluvastatin, and lovastatin, we have chosen atorvastatin not strictly for its greater lipid-lowering efficacy when compared to simvastatin [8], but also because of its anti-inflammatory and anti-apoptotic properties [53,54].

Global Circumferential Strain (GCS). Global circumferential strain (GCS) is a composite measure of the strain and relaxation of the heart during the systole and diastole. In a prospective follow-up of 84 women with HER2-positive breast cancer treated with anthracyclines, taxanes and trastuzumab, both peak systolic longitudinal myocardial strain < 19% and ultrasensitive troponin I measured at the completion of therapy were the most predictive of subsequent cardiotoxicity, as defined by Cardiac Review and Evaluation Committee criteria [55]. In support of this finding, results from a study of 81 women undergoing trastuzumab and anthracycline treatment showed that a ≥ 11% reduction in global strain measured by echocardiography was strongly predictive of later reductions in ejection fraction [56]. The clinical relevance of myocardial strain in predicting long-term cardiac left ventricular (LV) dysfunction is further underscored by the significant 7.7% reduction in global strain observed up to 6 years following cessation of anthracycline therapy in 75 asymptomatic breast cancer survivors [57]. The global circumferential strain was also reported to be an independent predictor of future heart failure and cardiac death in patients with a previous episode of heart failure [58]. A meta-analysis of 1,500 cancer patients

undergoing chemotherapy showed that early changes in myocardial strain precede significant change in left ventricular ejection fraction and that global strain measures can predict clinically diagnosed cardiotoxicity [27]. Furthermore, in patients with a history of heart failure, each % increase in GCS was associated with a 15% increase in the risk of future cardiac event, and GCS was a better predictor of future cardiac events than left ventricular ejection fraction [58].

Cardiac Magnetic Resonance Imaging (CMRI). Evidenced-based guidelines for monitoring cardiotoxicity following breast cancer treatment are presently lacking [37]. Reliance on 2-dimensional echocardiography (2-D echo) for the identification of cardiac damage is limited as it lacks the requisite sensitivity to detect subtle changes in LV function. Newer sophisticated echocardiographic imaging techniques, including myocardial strain imaging by 2D-speckle tracking, can identify early pre-clinical LV systolic dysfunction pre- and post-treatment [59]. While speckle tracking echocardiography may be helpful, the quality is sonographer-dependent, limited by patient body habitus, and not available in all echocardiography labs. CMRI is considered the gold standard imaging technique for accurate quantification of LV morphology and function, and mitigates many of the limitations of echo. The addition of tissue tagging helps determine specific myocardial structural changes related to twist and torsion of the left ventricle during systole and diastole. CMRI can also detect fibrosis with late gadolinium enhancement and T1 mapping. MR tissue tagging utilizes selective radiofrequency pulses to generate a pattern of lines or a 'grid' through the tissue [Figure 2]. Because myocardial tags are formed by modification of the tissue magnetization itself, the 'tagged' tissue moves with the myocardium throughout the cardiac cycle allowing for highly accurate, regional quantification of tissue deformation (i.e. strain). Circumferential deformation mechanics provide a sensitive predictor and identification of heart failure and mortality than global LV parameters. Results from the Multi-Ethnic Study on Atherosclerosis (MESA) of an asymptomatic population showed that reductions in the shortening and lengthening of the LV circumference, known as circumferential strain, are associated with myocardial fibrosis and decreased systolic function [60]. Similar alterations in circumferential strain assist in the prediction of heart failure and all-cause mortality, independent of preserved global ejection function [58,61]. Furthermore, circumferential strain has been demonstrated to be a sensitive detector of early cardiomyopathy in young muscular dystrophy patients who suffer from myocardial fibrosis [62], and is closely associated with mortality, hospital readmission, and sudden cardiac death in heart failure patients [58,63,64]. The combination of CMRI and 2D echocardiography provides an excellent opportunity to gain important mechanistic insight (i.e. tissue characterization by T1 mapping) and gold-standard verification (tissue tagging strain imaging) balanced by clinical feasibility and population health (2D echo). The use of CMRI to study the impact of a statin intervention on detailed structural and functional changes that occur as a result of breast cancer treatment is exciting, and findings can be directly translated to inform clinical care. This project has promise to provide mechanistic and immediately translatable strategies in the care of breast cancer survivors.

Figure 2. MR tissue tagging



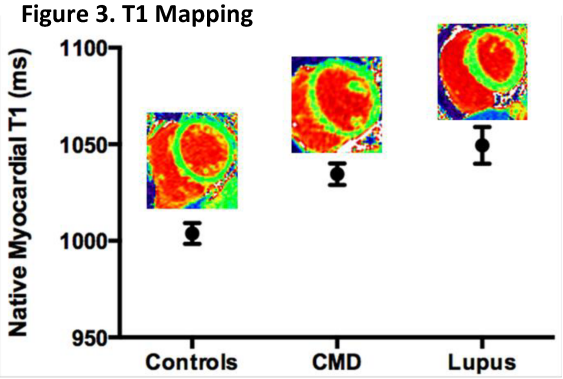
Supporting Preliminary Data. The Barbra Streisand Women's Heart Center (The Heart Center) at Cedars-Sinai Medical Center (CSMC) focuses on the identification of female-pattern heart disease, developing new diagnostic tools, and advancing specialized care for women. The Heart Center is designed to help women reduce their chances of heart disease through prevention, including state-of-the-art screening and testing. The Cardio-Oncology Program provides specialized clinical services dedicated to the heart health of cancer patients and survivors, including comprehensive cardiac risk assessment and stratification. These activities require close collaboration between oncologists and cardiologists and are strongly supported by the Cancer Institute and Heart Center. During the past few years, we have gained substantial experience in cardiac imaging, positioning ourselves for the successful implementation of the *STOP Heart Disease in Breast Cancer Survivors Trial*.

CMRI Experience. We are fortunate to have internationally-recognized expertise in advanced cardiac imaging at CSMC and are among the few centers in the country with a research-dedicated MR scanner. We have a track-record of successful collaboration with the imaging group in studies using CMRI to advance the field of non-invasive cardiac imaging in women [65-67]. CMRI does not involve ionizing radiation, and therefore does not contribute to risk of second malignancy in this patient population. CMRI is uniquely suited to be 'one-stop shop' for cardiac imaging and can accurately quantify cardiac morphology (atrial and ventricular size and volume,

valves, pericardium), function (both local and regional systolic and diastolic function), and tissue characteristics (diffuse myocardial fibrosis, focal scar, and myocardial edema). In addition to measures of diastolic function such as peak filling rate (PFR) and time to peak filling rate (tPFR) that provide information about left ventricular (LV) filling, the novel tissue tagging method provides additional information on myocardial twist and torsion. Through data collected in the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study on diastolic dysfunction detected by CMRI we have demonstrated a relationship between chronic ischemia and diastolic dysfunction in women [68].

Myocardial Fibrosis Imaging and Tissue Viability. CMRI late gadolinium enhancement imaging assesses fibrosis and scarring. However, late gadolinium enhancement cannot detect diffuse patterns of fibrosis, nor can it provide insight into changes in tissue viability. T1 mapping directly addresses these limitations. Whereas *native* T1 mapping (without contrast) provides quantitative information about the myocyte and interstitium, post-contrast T1 mapping can help to partition the myocardium into its cellular and interstitial components. T1 mapping has also been used to estimate the myocardial extracellular volume using Modified Look-Locker Inversion (MOLLI) recovery images to characterize diffuse myocardial fibrosis [69,70]. We have extensive experience with each of these measurements and have used native T1 mapping to distinguish patients with ischemic heart disease or systemic lupus erythematosus from healthy age-matched controls [Figure 3]. Our imaging group can perform CMRI acquisition with myocardial perfusion and T1 mapping for myocardial fibrosis in a single session [71]. These two unique capabilities make CMRI an ideal non-invasive tool for cardiotoxicity mechanistic pathway investigation.

Figure 3. T1 Mapping



T1 mapping using a standardized MOLLI sequence before contrast, demonstrating abnormal myocardium in women with coronary microvascular disease (CMD) and systemic lupus erythematosus (Lupus) compared to healthy reference controls (P = 0.011 and 0.001, respectively). Image inserts showing representative T1 map from a subject in each of the respective groups.

Subclinical LV Dysfunction with Anthracycline Therapy. Our group has extensive experience with CMRI tissue tagging and the measurement of LV strain and tissue deformation [68,72-76]. We found substantial subclinical LV dysfunction in a breast cancer patient treated with 4 cycles of anthracycline therapy [Figure 4]. Note that conventional metrics of LV morphology and function (ejection fraction, volumetric) are indistinguishable from baseline [Table 1]. However, MR tissue tagging shows marked increase in GCS (primary endpoint for the current trial) and decrease in LV twist mechanics (secondary endpoint for the current trial), that signal a reduced ability of the heart to contract.

Figure 4. Subclinical LV Dysfunction with Anthracycline

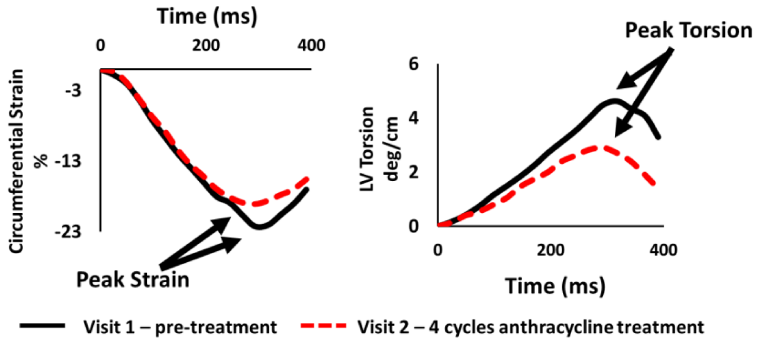


Table 1. LV Dysfunction with Anthracycline

	Baseline	Anthracycline
LV EDV, mL	117.7	130.0
LV ESV, mL	47.5	54.3
SV, mL	70.2	75.8
LV EF, %	60	58
CO, L/min	5.2	6.2
LV mass, g	83.1	82.2
LV Concentricity, g/mL	0.71	0.63

Importance of the Study. We now have ample evidence that women can have significant cardiac injury following chemotherapy and radiotherapy for breast cancer, yet we lack evidence-based guidelines for the prevention and management of pre-clinical and clinical cardiotoxicity [5]. Cardiac dysfunction secondary to treatment is an important morbidity and mortality concern among breast cancer survivors and will contribute to potentially avoidable health care costs. While monitoring LVEF measured by echocardiography is routine clinical practice, decreased LVEF is a late manifestation of myocardial injury. Early changes in cardiac function, myocardial injury, myocardial edema, and fibrosis are missed on echocardiography and there is concern that

delaying diagnosis and treatment by ≥ 6 months may reduce the benefit of heart failure treatment [3]. Presently, there is little evidence regarding risk reduction schema to reduce myocardial injury during cancer treatment despite the existence of effective cardiovascular disease preventive strategies [77]. A recent meta-analysis showed that several medications, including statin, had efficacy for reducing the risk of cardiac injury in cancer patients [3]. Statins are well-accepted and well-tolerated medications [6] and have demonstrated a reduction in mortality in primary and secondary prevention of cardiovascular diseases [10]. Our multi-disciplinary approach will allow us to integrate findings regarding structural changes to the myocardium with pre- and post-therapeutic functional and metabolic characteristics. We focus on women undergoing trastuzumab treatment (with or without anthracycline) for breast cancer because they will derive the greatest benefit from an early intervention to prevent cardiac injury. Our short-term follow-up will facilitate an examination of initial changes in cardiotoxicity among breast cancer survivors. Detailed imaging changes to the myocardium from baseline through one year of statin therapy will ultimately inform mechanistic pathways of treatment-induced myocardial damage.

Our review of the literature and ClinicalTrials.gov identified no published RCT evaluating the benefit of early initiation of statin specifically in breast cancer patients. However, a number of past or ongoing studies (e.g., NCT 01022086, 00679874, 02306538, 02062983) have used CMRI to examine heart function in breast cancer patients treated with trastuzumab, supporting the utility of non-invasive imaging in the proposed RCT. Randomizing women planning to undergo breast cancer treatment to prophylactic therapy with statin, which is known to be inexpensive, well-tolerated, safe, effective and approved for prevention of cardiovascular disease, is a strength as it may make the trial more attractive to oncologists who are enrolling patients, as well as to potential subjects. Presently, no consensus-based guidelines exist for post-treatment cardiovascular disease monitoring of breast cancer survivors [77]. Subtle injury to cardiac muscle during breast cancer treatment that fails to heal following cessation of therapy is a critical health and quality of life concern among breast cancer survivors. This knowledge gap in the cardiovascular care of breast cancer patients is understandable in that these women are generally excluded from cardiac clinical trials. Evidence is needed regarding the benefit of implementing measures early to reduce or prevent cardiac injury among women with the most aggressive molecular subtypes of breast cancer. The management strategies being tested are logical and consistent with present clinical care of women at risk for cardiac disease, yet novel for the population. This short-term trial will document the feasibility of recruiting breast cancer patients to statin therapy, will evaluate efficacy and safety of this preventive strategy, and will inform the search for key biologic mechanisms and time course through which breast cancer treatment leads to myocardial dysfunction with future progression to ischemia and heart failure. Future studies will include longer follow-up to capture longer-term cardiotoxicity and larger numbers of breast cancer patients to optimize our cardioprotection strategies.

2.0 STUDY OBJECTIVES AND ENDPOINTS

The objective of the *Statin Therapy Operates to Prevent* (STOP) *Heart Disease in Breast Cancer Survivors Trial* is to examine the effect of statin use versus placebo on myocardial functional and structural changes in 60 women diagnosed with stage 1-3 breast cancer recommended to undergo trastuzumab treatment, with or without anthracycline. We will conduct a randomized, double-blinded, placebo-controlled, Phase II trial of atorvastatin to ameliorate or prevent cardiac damage in women with newly diagnosed breast cancer. Detailed imaging changes to the myocardium from baseline through 12 months of follow-up will ultimately inform mechanistic pathways of treatment-induced myocardial damage. Our ultimate goal is to develop strategies that will attenuate the long-term cardiotoxicity from trastuzumab treatment.

2.1 Primary Objectives

2.1.1 To evaluate the effect of atorvastatin intervention versus placebo on a 1 year change from baseline in myocardial dysfunction in breast cancer patients who have undergone trastuzumab treatment, with or without anthracycline. The primary outcome is global circumferential strain (GCS), a sensitive measure of myocardial dysfunction, which is predictive of future cardiac events. Cardiac magnetic resonance imaging (CMRI) will be used to measure GCS.

2.2 Secondary Objectives

2.2.1 To evaluate the effect of atorvastatin intervention versus placebo on a 1 year change from baseline in other strain-related measures, myocardial diastolic function, and cardiac morphology, measured by cine CMRI and tissue tagging;

2.2.2 To evaluate the effect of atorvastatin intervention versus placebo on a 1 year change from baseline in myocardial fibrosis, edema, and inflammation measured by T1 and T2 mapping values during the CMRI.

2.3 Primary Endpoint

The primary endpoint is change in global circumferential strain (GCS) measured by CMRI. GCS is a composite measure of myocardial deformation as the heart contracts and relaxes. The equality of atorvastatin intervention to placebo in reducing or preventing left ventricular (LV) dysfunction will be assessed through comparison of change in GCS values measured from baseline (from 2 weeks before the patient starts systemic breast cancer treatment (trastuzumab with or without anthracycline) up to 3 weeks after starting treatment) to 12 months post-initiation of the statin intervention.

2.4 Secondary Endpoints

Secondary outcomes include additional global measures of cardiac function, diastolic function, cardiac morphology, and tissue viability. Differences in secondary outcomes from baseline to 12 months follow-up will be compared in the atorvastatin and placebo groups using a similar approach to the main outcome.

2.4.1 Changes in other strain-related measures (global longitudinal strain (GLS), peak LV twist and torsion), myocardial diastolic function (LV untwisting rate, diastolic strain rate) and cardiac morphology (mass, wall thickness, internal dimensions)

2.4.2 Changes in myocardial fibrosis and tissue viability, edema, and inflammation

3.0 PARTICIPANT SELECTION

3.1 Inclusion Criteria

3.1.1 Female patients with newly diagnosed stage 1-3 breast cancer

3.1.2 Histologically confirmed HER2, ER, and PR status

3.1.3 Recommended to undergo trastuzumab treatment, with or without anthracycline. Patients will be eligible for up to 3 weeks after starting treatment.

3.1.4 Age minimum 18 years

3.1.5 Able and willing to read, understand, and sign an informed consent form (ICF) and medical release form

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

3.1.7 ECOG performance status 0-1 (Karnofsky ≥ 70%; see Appendix A)

3.2 Exclusion Criteria

3.2.1 Prior use of statin medication within the past year

3.2.2 Not using statin medication but is eligible for statin therapy based on the 2013 ACC/AHA guidelines (LDL cholesterol >190, or LDL <190 and ASCVD risk >7.5%; http://tools.acc.org/ASCVD-Risk-

Estimator/) and is > 50 years old; or is eligible for statin therapy based on the 2013 ACC/AHA guidelines and is 40-50 years old and wishes to be placed on statin therapy

3.2.3 History of adverse effects, intolerance, or allergic reactions attributed to statin medication

3.2.4 Current use of gemfibrozil, cyclosporine, clarithromycin, itraconazole, erythromycin, the hepatitis C protease inhibitor telaprevir, HIV protease inhibitors, colchicine, or red yeast rice

3.2.5 Current use of any other investigational agent

3.2.6 Pregnant or intention to get pregnant during the next 18 months. Pregnant women are excluded from this study because atorvastatin is a lipid-lowering agent with the potential for teratogenic or abortifacient effects, and MRI is contraindicated in pregnant women.

3.2.7 History of diabetes, severe lung disease, renal disease (creatinine > 1.8 mg/dL or CrCl ≤ 50 mL/min), or hepatic disease (AST and ALT > 3 times upper normal limits)

3.2.8 Abnormal baseline echocardiogram or cardiac MRI (detection of congenital heart disease; ischemic heart disease; moderate or severe valvular heart disease; cardiomyopathy; EF < 55%)

3.2.9 Previously known or diagnosed heart disease (e.g. congenital; valvular; coronary artery disease; history of myocardial infarction or acute coronary syndrome; cardiomyopathy, including infiltrative, hypertensive, hypertrophic, dilated, constrictive pericarditis, or other cardiomyopathy)

3.2.10 Left ventricular dysfunction (EF < 55%)

3.2.11 Prior non-cardiac illness with an estimated life expectancy < 4 years

3.2.12 Known active infection with HIV

3.2.13 Allergy or contraindication to MRI testing, including metallic parts in the body prohibiting MRI, prior gadolinium contrast reaction, or uncontrolled moderate hypertension (sitting blood pressure >160/95 mm Hg with measurements recorded on at least 2 occasions)

3.2.14 Has metallic breast expanders in place at the time of screening

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

3.3 Inclusion of Women and Minorities

Women and members of all races and ethnic groups are eligible for this trial. Men are excluded from the study because there are very few cases of male breast cancer.

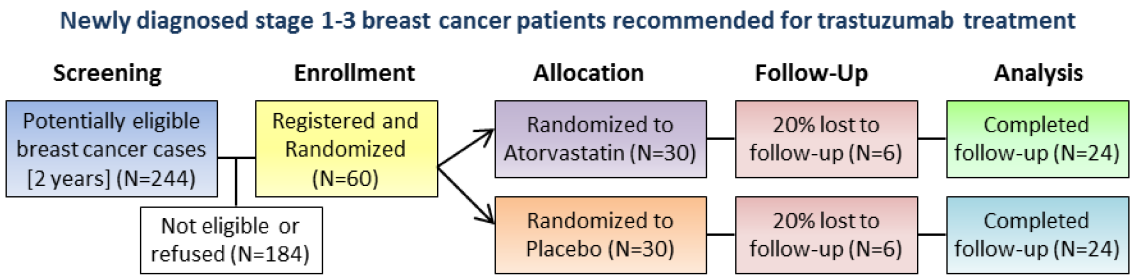
4.0 STUDY PLAN

4.1 Recruitment

Women with newly diagnosed stage 1-3 breast cancer will be recruited from the Brandman Breast Center at Cedars-Sinai Medical Center (CSMC), the Tower Hematology Oncology Medical Group, and the offices of CSMC affiliated oncologists. Between January and June 2016, 61 women with breast cancer were recommended to undergo trastuzumab treatment at Cedars-Sinai. The number of women who received trastuzumab treatment may be greater because data collection guidelines do not require the Cancer Registry to collect individual agent names, and chemotherapy and immunotherapy agents are coded as notes in text fields only. Based on this patient

population and the importance of our objectives to the breast cancer community, our recruitment goal of 60 women with newly diagnosed breast cancer [40 white (67%), 6 black (10%), 6 Asian (10%), 3 other race (5%), and 5 Hispanic (8%)] is feasible. This goal accounts for a ~25% participation rate among potentially eligible non-statin users, with a final analytic sample of 48 women after 20% lost to follow-up [Figure 5]. Recruitment will occur over 24 months with an expected accrual rate of 2-3 participants per month.

Figure 5. Trial Profile



Each of the investigators, the advocate, and members of the Internal Advisory Board, brings substantial experience with patient recruitment to the study and will insure that our recruitment goals are met. Dr. Mita (oncologist) and Ms. Travis-Teague (advocate) will work closely with our oncologists and surgeons in the recruitment effort. We will utilize physician education techniques such as physician mailings, presentations at CSMC conferences, and one-to-one referring physician-investigator interactions to enhance recruitment. An information leaflet that describes the study will be available in the clinic waiting rooms at the Brandman Breast Center, the Tower Hematology Oncology Medical Group, and the offices of CSMC affiliated oncologists. The leaflet will direct interested patients to speak with their treating oncologist for more information about the study.

In order to better ensure that only those patients who may be eligible to participate in the research are approached with information about the study, the clinical research staff will identify potential participants via a review of participating oncologist-investigator schedules to identify breast cancer cases that would be appropriate to screen via medical records. Medical records will be reviewed for age, breast cancer diagnosis (stage; HER2, ER, and PR status), medical contraindications, laboratory results, prior or current use of statin medication, and current use of prohibited concomitant medications. A protocol specific checklist will be used to identify basic inclusion and exclusion criteria. Research staff will indicate if the patient appears to meet the general criteria, i.e., yes or no response, and will not record specific test results or other detailed data points on the checklist. The names of the patients who appear to meet the study eligibility criteria will be recorded along with the name of their treating physician. Research staff will contact the oncologist-investigator and advise that the patient has been identified as a potential research participant, and the eligibility checklist will be forwarded to the oncologist for review.

The treating oncologist will introduce the study to potentially eligible breast cancer patients recommended for trastuzumab treatment (with or without anthracycline) during the treatment planning visit after standard care options have been presented. Patients will receive a study information packet to take home that includes the study information leaflet, the IRB approved study informed consent form and HIPAA authorization, and the *Learning More about Research Opportunities* brochure to advise them of the voluntary nature of participation. Clinical research staff will be present at the clinic during this visit and will be available to review the study information packet with the patient. 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 she receives, and that she can withdraw from the study at any time. The study coordinator will follow up with the patient a few days later by phone to address any additional questions.

Patients who are interested and want to volunteer for the trial will be consented to participate in the study by the treating oncologist at their next standard of care visit, or by one of the study physician-investigators present during the patient's baseline pre-study standard of care echocardiogram appointment. Copies of the signed consent documents will be given to the patient and placed in the medical record. Because there is a short window of time (1 week) for all the pre-treatment assessments before systemic breast cancer treatment is initiated, some

potentially eligible patients may not be seen again by the treating oncologist until after they are no longer eligible for the study. In such cases, women who have had all their questions about the trial answered on the day they first learn about the study, and who wish to volunteer for the trial, may be consented to participate in the study the same day they are first informed of the research.

After consent has been obtained, clinical research staff will complete a full eligibility checklist and compile the support documents from patient medical records, including laboratory reports, medical history, physician notes, and current medications list. The oncologist, study cardiologist, or other physician-investigator will review the patient's eligibility checklist, medical history, and supporting documentation. Patients with a history of heart disease or cardiomyopathy and patients > 50 years old who are eligible for statin therapy based on the 2013 ACC/AHA guidelines (LDL cholesterol >190, or LDL <190 and ASCVD risk >7.5%; http://tools.acc.org/ASCVD-Risk-Estimator/) will be excluded from the trial. Patients 40-50 years old who are eligible for statin therapy based on the 2013 ACC/AHA guidelines and want to be placed on statins will also be excluded.

A Clinical Research Office (CRO) designee will conduct a final eligibility check prior to registration. Consented patients who qualify for the study after the pre-study eligibility evaluations and CRO confirmation of eligibility will be registered for the trial, enrolled in the study, randomized to the intervention (atorvastatin or placebo), and scheduled for Visit 1, the baseline testing.

4.2 Study Treatment Protocol

All women will receive their usual care under the guidance of their oncologist. Importantly, this will include 2-D echo to allow us to compare current screening practice with the innovative CMRI. Breast cancer patients scheduled for systemic breast cancer treatment are recommended to undergo a 2D-echocardiogram prior to starting treatment, and 3 months and 9 months after initiation of treatment for standard of care monitoring.

There will be three research study visits (Visits 1, 4, and 6) to collect endpoint data: baseline measurements and initiation of the statin intervention, from 2 weeks before the patient starts systemic breast cancer treatment (trastuzumab with or without anthracycline) up to 3 weeks after starting treatment; and follow-up visits 6 and 12 months after initiation of the statin intervention. Each research visit will include a medical history, medications, and laboratory test results review; vital signs assessment and measurement of weight; ECOG performance status; blood draw; pregnancy test for women who are able to become pregnant (during the pre-study evaluations visit and at each research visit; see 4.3 Study Measurements for pregnancy test details); cardiac magnetic resonance imaging (CMRI); interviewer-administered questionnaire; quality of life assessments, QLQ-C30 and QLQ-BR23; eligibility criteria review; dispensing the study drug (atorvastatin or placebo, no dispense at 12-month visit; compliance and adverse events assessment; and review of the study diary.

There will be three additional encounters during standard of care oncologist visits (1 month, 3 months, and 9 months after initiation of the statin intervention) that include a medical history, medications, and laboratory test results review; physical exam; symptom assessment; ECOG performance status; clinical labs for a Complete Blood Count and Automated Differential (CBDF) and a Comprehensive Metabolic Panel (CMPL); eligibility criteria review; compliance and adverse events assessment; review of the study diary; and dispensing the study drug. See Section 7.0 Clinical Evaluations and Procedures for a detailed description of the study treatment protocol.

Research visits will coincide whenever practicable with usual care clinic appointments to reduce travel time and increase compliance with the study protocol. The study visit will be scheduled as early in the morning as possible. Each subject will be offered $100 at the completion of each research study visit as reimbursement for their time, transportation, parking, and other expenses related to the study. Participants who complete all three research study visits will receive $300. A packet of material, including an appointment letter, a map, and parking instructions for the visit will be provided to the subject prior to the scheduled study visit. A day or two prior to the scheduled study visit, the participant will be contacted by telephone to confirm or reschedule her visit. If a subject misses her study visit, she will be called promptly to reschedule. The study coordinator will have a database which tracks

active participants who do not have a scheduled visit or who have missed their targeted visit date. Study visits will be rescheduled for up to 3 months until the participant is considered lost to follow-up.

4.3 Study Measurements

Following is a brief description of study measurements. See Section 7.7 for a more detailed description.

Cardiac magnetic resonance imaging (CMRI). CMRI will be performed at baseline and at the 6-month and 12-month research visits (Visits 1, 4, and 6). CMRI will be used to measure the primary outcome, global circumferential strain (GCS) and the secondary outcomes, myocardial diastolic function, and fibrosis. CMRI is a non-invasive, non-radiation imaging modality that is the gold standard cardiac imaging technique for cardiac structure (atrial and ventricular size and volume, valves, pericardium, edema, fibrosis) and function (myocardial blood flow quantification, systolic and diastolic function). CMRI can also detect myocardial fibrosis with late gadolinium enhancement and T1 mapping. Patients with claustrophobia may pre-medicate as needed prior to the CMRI. Women who have breast reconstruction surgery after enrollment/completion of the baseline visit that includes metallic breast expanders prohibiting MRI will not be required to do the CMRI while the breast expanders are in place.

Blood specimen. A blood specimen will be collected from each participant at every research visit. Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations, and 5 mL will be drawn for laboratory blood tests to monitor for potential adverse effects of the intervention. An additional (optional) 28 mL blood sample will be collected from subjects who consent to have their blood samples banked for future studies of blood biomarkers.

Pregnancy test. Because statins are known to be teratogenic and MRI is contraindicated in pregnant women, women < 60 years of age who have not had a menstrual period in the last 30 days will be required to have a urine pregnancy test during the pre-study evaluations and at every research visit. However, women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.

Physical assessment. Participants will have a physical assessment at every standard of care and research study visit. Each assessment will include vital signs, including blood pressure, heart rate, and temperature; measurement of weight; and ECOG performance status. The oncologist will perform a physical exam and an interval symptom history at every standard of care visit.

Medical record review. Medical history, concomitant medications, and laboratory test results will be reviewed at every standard of care and research study visit. Specific information regarding the type of treatment regimen and dose received will be obtained through the electronic medical record, including Taxotere (docetaxel), carboplatin, and trastuzumab (TCH); TCH with pertuzumab (TCHP); and anthracycline and trastuzumab regimen doxorubicin (or epirubicin), cyclophosphamide, and taxane followed by trastuzumab (AC-TH). Information regarding breast or chest wall radiation, including right vs. left sided radiation, total dose, and number of fractions of radiation, as well as technique and dosimetry will be collected. BRCA mutation information will also be collected.

Baseline and follow-up questionnaires. A structured interview, developed for this investigation and including risk factor and clinical assessment, will be administered by the research staff at Visit 1 (baseline). The questionnaire will obtain information regarding race/ethnicity; education; anthropometry including weight at different decades of life; medical history, including history of cancer and BRCA testing; menstrual and pregnancy histories; use of oral contraceptives and hormones; adult recreational physical activity; tobacco smoking history; and history of alcoholic beverage consumption. A shorter questionnaire will be administered at the 6 and 12 month visits to assess changes in exposures and behaviors between visits.

Quality of life and symptoms assessment. We will measure quality of life and symptoms using the QLQ-C30 and QLQ-BR23. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a 30-item measure developed to assess the quality of life of cancer patients [78]. The measure includes three scales: global health status, functional status (physical, role, emotional, cognitive, and social), and physical symptoms.

The EORTC QLQ-BR23 is a 23-item measure specifically for patients with breast cancer that assesses disease symptoms and emotional problems related to breast cancer [79,80]. Participants will self-administer the QLQ-C30 and QLQ-BR23 assessments.

5.0 AGENT ADMINISTRATION

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

5.1 Dose Regimen and Dose Groups

- Agent(s): Atorvastatin calcium and placebo
- Daily dose(s) and regimen(s) for each agent: One capsule atorvastatin calcium 20 mg or placebo per day

Sixty participants with newly diagnosed stage 1-3 breast cancer will be randomized into one of 2 groups: 30 participants will receive 20 mg atorvastatin and 30 participants will receive a placebo identical in color, consistency, and appearance to atorvastatin. Atorvastatin 20 mg and matching placebo will be supplied as over-encapsulated capsules for oral administration.

The recommended starting dose of atorvastatin is 10 to 20 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily.

5.2 Study Agent Administration and Duration of Therapy

Patients will self-administer one capsule of atorvastatin 20 mg or placebo daily. Atorvastatin calcium can be administered as a single dose at any time of the day, with or without food. Patients will be instructed to take the study agent at bedtime or with an evening meal. In the absence of treatment delays due to adverse events, treatment for each agent will extend for 12 months.

5.3 Run-in Procedures

None.

5.4 Contraindications

Patients are advised not to consume grapefruit while on atorvastatin. Grapefruit contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (> 1 liter per day). Participants enrolled in the study will be instructed to avoid all forms of grapefruit (e.g., juice, fruit, grapefruit seed extract, dietary supplements containing grapefruit) during the trial.

The combined use of atorvastatin with gemfibrozil, cyclosporine, lipid-modifying doses of niacin, azole antifungals, or strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, erythromycin, the hepatitis C protease inhibitor telaprevir, or combinations of HIV protease inhibitors), and fibric acid derivatives) is contraindicated due to an increased risk for myopathy. Patients will be screened for contraindications to atorvastatin 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 use of any contraindicated medication is unavoidable. Concomitant medications will be reviewed at study visits and during follow-up telephone calls. Participants will be closely monitored for symptoms and side effects to the study drug and will be instructed to call the study doctor immediately if they have a serious adverse reaction.

5.5 Concomitant Medications

Medications known to interact with atorvastatin will be documented on the concomitant medication case report form (CRF) and will include start and stop date, dose and route of administration, and indication. Taking these medications would exclude the patient from study participation. These medications include: gemfibrozil, cyclosporine, clarithromycin, itraconazole, erythromycin, the hepatitis C protease inhibitor telaprevir, HIV protease inhibitors, colchicine, and red yeast rice. Any medications taken by the patient that are deemed clinically significant in relation to the study, including medications started, stopped, or dose-modified to treat AEs considered at least possibly related to the study drug, will also be recorded on the concomitant medication CRF.

5.6 Dose Modification

The study agent will be stopped in the event of an AE ≥ grade 3 considered possibly, probably, or definitely related to the study agent. The study agent will be restarted after resolution. One of the common side effects of statin medication is myalgia (muscle pain with normal 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 (including atorvastatin 20 mg), the risk is very low. We will measure levels of creatine phosphokinase (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 cardiologist on trial will determine whether the symptoms or an elevation in CPK warrants the participant to discontinue taking the study drug. The study agent will be permanently discontinued in subjects who experience grade 3 or greater myopathy (unexplained muscle symptoms *and* CPK > 5 times ULN) or persistent hepatotoxicity (ALT or AST > 3 times ULN) that is considered possibly, probably, or definitely related to the study agent.

If a participant experiences elevated liver enzymes (AST/ALT > 3x ULN), we will continue the study agent and repeat the liver function tests (LFTs) 7-10 days later. If AST/ALT values resolve (≤ 3x ULN), the participant will continue on the study agent. If AST/ALT values are still elevated (> 3x ULN), the participant will discontinue the study agent. We will measure LFTs 4 weeks later. If AST/ALT values are still elevated (> 3x ULN), the study agent will be permanently discontinued. If AST/ALT values resolve (≤ 3x ULN), we will restart the study agent at half the dose, atorvastatin 10 mg or placebo, and continue to closely monitor all clinically obtained LFTs.

5.7 Adherence/Compliance

Compliance will be measured by pill (capsule) counts and patient diaries. Compliance is defined as 85% of the total dose with all doses of the study agent taken during the week before Visit 6 (the final visit). A patient diary will be used to monitor daily compliance (Appendix B). Participants will be instructed to record the time the study drug was taken each day in the diary, as well as any missed doses and potential side effects. Diaries will be reviewed and compliance will be assessed at every study visit.

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

The participant will be asked at registration if they would like to receive reminder emails or text messages regarding the study medication. Messages will be sent daily for the first week; in following weeks, messaging will be targeted to participants having difficulty remembering their dose. Since agent compliance is very important during the final week of the intervention, text/email messages will be sent to all study participants who opt to receive these reminders. In addition, phone calls will be made to all study participants during the week before their final visit (Visit 6) to remind them to take the study drug every day until the visit. Participants will also be reminded to bring any leftover study drugs and the study diary with them to every visit.

Pill counts will be performed at Study Visits 2, 3, 4, 5, and 6 to assess compliance. If less than 85% of the dose has been consumed during the study period, the subject will be considered non-compliant. All participants that receive a study agent for any period of time will be evaluable for toxicity.

6.0 PHARMACEUTICAL INFORMATION

6.1 Study Agent

Atorvastatin calcium, a synthetic lipid-lowering agent, 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 cholesterol biosynthesis.

The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol. Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose, NF; lactose monohydrate; magnesium stearate; microcrystalline cellulose; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80; and simethicone emulsion.

6.2 Reported Adverse Events and Potential Risks

The most common (incidence ≥ 5.0% in patients) reported adverse events (AEs) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection. Other AEs reported in clinical trials (< 5%) were dyspepsia, nausea, musculoskeletal pain, muscle spasms, myalgia, insomnia, and pharyngolaryngeal pain.

Persistent increases in serum transaminases (to more than 3 x ULN) have occurred in 0.7% of patients who received atorvastatin calcium tablets in clinical studies (0.2% for atorvastatin 20 mg). One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae [7]. It is recommended that liver function tests be performed before initiating therapy with atorvastatin calcium, and thereafter when clinically indicated.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values above 10 x ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment. The concomitant use of higher doses of atorvastatin with certain drugs such as fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis. Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

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. Atorvastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs which inhibit this metabolic pathway can raise the plasma levels of atorvastatin and may increase the risk of myopathy [6,81]. These include erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, and combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, or grapefruit products. Combination of these drugs with atorvastatin is contraindicated [Table 2] [7]. If short-term treatment with strong CYP3A4 inhibitors is unavoidable, therapy with atorvastatin must be suspended during the course of treatment.

Table 2. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting Agents	**Prescribing Recommendations**
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily
*Use with caution and with the lowest dose necessary	

- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin calcium tablets.
- Digoxin: Patients should be monitored appropriately.
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased.
- Rifampin should be simultaneously co-administered with atorvastatin calcium tablets.
- Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of atorvastatin calcium tablets with gemfibrozil should be avoided.

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

6.3 Agent Availability, Packaging, and Labeling

Atorvastatin 20 mg and matching placebo are investigational agents for oral administration supplied to investigators by the Cedars-Sinai Medical Center Department of Pharmacy. Generic atorvastatin 20 mg tablets will be over-encapsulated and the capsules will be filled with an inert excipient (generally lactose powder). The placebo capsules are identical looking capsules but only filled with lactose powder. The amount of lactose will range from 700 mg-1 g per capsule (less if the capsule contains an atorvastatin tablet).

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

The study agent will be dispensed to the participant five times: One bottle of 44 capsules (30-day supply + 14 days buffer) at baseline, one bottle of 74 capsules (60-day supply + 14 days buffer) at 1 month, and one bottle of 104 capsules (90-day supply + 14 days buffer) at 3 months, 6 months, and 9 months after initiation of the intervention.

6.4 Storage

Study agents will be stored in a safe, secure, temperature monitored limited access drug storage area specifically for research medication at the Cedars-Sinai Medical Center Department of Pharmacy. Study agents shall be maintained at a controlled room temperature [between 15-25°C] by the Pharmacy and once dispensed, the subjects will be instructed to store the drug in their homes protected from light, heat, and moisture.

6.5 Agent Accountability

The Investigator is required to maintain adequate records of receipt, inventory, dispensing, and disposition of the study agent. This responsibility has been delegated to the study research pharmacist, Suwicha Limvorasak, Pharm.D., Investigational Drug Pharmacist at the Samuel Oschin Comprehensive Cancer Institute (SOCCI). The receipt record will include from whom the agent was received, date, quantity and batch or lot number. The dispensing record will note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Blinding and Unblinding

The research pharmacist will manage the investigational agent. The blind will be maintained through the effort of the research pharmacist, and the pharmacy. Unblinding will only occur when it is deemed medically necessary. The date and reason for breaking the blind will be documented by the Principal Investigator.

In the event that the Principal Investigator and treating physician have determined that it is medically necessary to unblind the participant due to life threatening or emergent clinical issues, a summary of the clinical history and request for unblinding will be forwarded to Dr. Howard Sandler, Medical Director, for final review and final approval. Documentation of unblinding approval will be provided to the research pharmacy and maintained in research chart.

7.0 CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Time and Events

Study Procedures	**Pre-Study***	**Visit 1^ (Baseline)** From 2 weeks before patient starts systemic breast cancer treatment up to 3 weeks after starting treatment: initiation of the statin intervention	**Visit 2*** 1 month ± 2 weeks after initiation of the statin intervention	**Visit 3*** 3 months ± 2 weeks after initiation of the statin intervention	**Visit 4^** 6 months ± 2 weeks after initiation of the statin intervention	**Visit 5*** 9 months ± 2 weeks after initiation of the statin intervention	**Visit 6^** 12 months ± 2 weeks after initiation of the statin intervention	**Follow-Up** Days 30 ±7, 60 ±7, and 90 ±7 after completion of the statin intervention
Assess eligibility and recruitment	X							
Informed Consent and HIPAA authorization	X							
Registration and randomization to atorvastatin or placebo	X							
Review inclusion/exclusion criteria and study requirements	X	X	X	X	X	X		
Review medical history, medications, and laboratory test results	X	X	X	X	X	X	X	
Demographics (birth date, race, ethnicity, education)	X	X						
Physical exam and symptom assessment	X		X	X		X		
Vital signs, measure weight	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	
2D-echocardiogram[1]	X			X		X		
Urine pregnancy test[2]	X	X			X		X	

Study Procedures	**Pre-Study***	**Visit 1^ (Baseline)** From 2 weeks before patient starts systemic breast cancer treatment up to 3 weeks after starting treatment: initiation of the statin intervention	**Visit 2*** 1 month ± 2 weeks after initiation of the statin intervention	**Visit 3*** 3 months ± 2 weeks after initiation of the statin intervention	**Visit 4^** 6 months ± 2 weeks after initiation of the statin intervention	**Visit 5*** 9 months ± 2 weeks after initiation of the statin intervention	**Visit 6^** 12 months ± 2 weeks after initiation of the statin intervention	**Follow-Up** Days 30 ±7, 60 ±7, and 90 ±7 after completion of the statin intervention
Blood test: Complete Blood Count and Automated Differential (CBDF)	X		X	X		X		
Blood test: Comprehensive Metabolic Panel (CMPL)	X		X	X	X	X	X	
Blood test: Lipid panel[3]	X	X			X		X	
Blood test: Creatine phosphokinase (CPK)		X						
Blood tests: hematocrit and creatinine[4]		X			X		X	
Collect blood for future research[5]		X			X		X	
Cardiac Magnetic Resonance Imaging (CMRI)		X			X		X	
Risk factor questionnaire		X			X		X	
QLQ-C30 and QLQ-BR23		X			X		X	
Dispense study agent and diary		X	X	X	X	X		
Collect study agent and diary			X	X	X	X	X	
Review study diary			X	X	X	X	X	
Assess compliance (pill count)			X	X	X	X	X	
Assess adverse events			X	X	X	X	X	X
Telephone contact[6]	X	X	X	X	X	X	X	X

**Pre-Study evaluations and Visits 2, 3, and 5 are standard of care visits.*

^Visits 1, 4, and 6 are research visits to collect endpoint data and will coincide with standard of care visits when possible.

[1] A 2D-echocardiogram will be done for standard of care monitoring before the patient starts systemic breast cancer treatment, and 3 months and 9 months after initiation of treatment.

[2] Because statins are known to be teratogenic and MRI is contraindicated in pregnant women, women < 60 years of age who have not had a menstrual period in the last 30 days will be required to have a urine pregnancy test at the pre-study evaluations and at Visits 1, 4, and 6. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.

[3] Lipid panel: If lipid panel results within the past 12 months are not available, a lipid panel will be done to confirm eligibility prior to registration. The lipid panel will not be done at Visit 1 if a lipid panel was done at the pre-study evaluations or if lipid panel results within 30 days prior to the visit are available.

[4] Less than 1 mL of blood will be drawn from each participant at Visits 1, 4, and 6 for measurement of hematocrit and creatinine levels used for CMRI calculations.

[5] Blood collection for future research: An additional (optional) 28 mL blood sample will be collected at Visits 1, 4, and 6 from participants who consent to have their blood samples banked for future studies of blood biomarkers.

[6] Telephone contact every four weeks (± 7 days) during the intervention to assess compliance and adverse events. Follow-up telephone contact on days 30 ± 7, 60 ± 7, and 90 ± 7 after completion of the statin intervention to assess adverse events.

7.2 Pre-Study Evaluation

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.

7.2.1 Pre-Screen Medical Chart Review and Initial Determination of Eligibility

Clinical research staff will identify potential participants via a review of participating oncologist-investigator schedules to identify breast cancer cases that would be appropriate to screen via medical records. A protocol specific checklist will be used to determine initial eligibility as specified in the inclusion and exclusion criteria. Medical records will be reviewed for:

1. Age
2. Breast cancer diagnosis (stage; HER2, ER, and PR status)
3. Medical contraindications and laboratory results that impact inclusion in the study
4. Prior or current use of statin medication, and current use of prohibited concomitant medications

Research staff will indicate if the patient appears to meet the general criteria, i.e., yes or no response, and will not record specific test results or other detailed data points on the checklist. The names of the patients who appear to meet the study eligibility criteria will be recorded along with the name of their treating physician. Research staff will contact the oncologist-investigator and advise that the patient has been identified as a potential research participant, and the eligibility checklist will be forwarded to the oncologist for review.

7.2.2 Recruitment and Consent

Potentially eligible patients with newly diagnosed stage 1-3 breast cancer will be scheduled for a consult with an oncologist.

- The oncologist will introduce the study to breast cancer patients recommended for trastuzumab treatment (with or without anthracycline) during the treatment planning visit after standard care options have been presented.
- Patients will receive a study information packet to take home that includes the study information leaflet, the IRB approved study informed consent form and HIPAA authorization, and the Learning More about Research Opportunities brochure to advise them of the voluntary nature of participation. Clinical research staff will be present at the clinic during this visit and will be available to review the study information packet with the patient.
- 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 she receives, and that she can withdraw from the study at any time. The study coordinator will follow up with the patient a few days later by phone to address any additional questions.
- Patients who are interested and want to volunteer for the trial will be consented to participate in the study by the oncologist at their next standard of care visit, or by one of the study physician-investigators present during the patient's baseline pre-study standard of care echocardiogram.

Because there is a short window of time (1 week) for all the pre-treatment assessments before systemic breast cancer treatment is initiated, some potentially eligible patients may not be seen again by the treating oncologist until after they are no longer eligible for the study. In such cases, women who have had all their questions about the trial answered on the day they first learn about the study, and who wish to volunteer for the trial, may be consented to participate in the study the same day they are first informed of the research.

7.2.3 Pre-Study Evaluations

Consented patients will undergo the following tests to confirm eligibility and safety of statin initiation:

- Physical exam including vital signs assessment, measurement of height and weight

- Symptom assessment and ECOG performance status
- Clinical labs for a Complete Blood Count and Automated Differential (CBDF) and a Comprehensive Metabolic Panel (CMPL)
- Lipid panel. If lipid panel results within the past 12 months are available, the lipid panel will not be required.
- Urine pregnancy test for women < 60 years of age who have not had a menstrual period in the last 30 days. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
- Baseline 2D-echocardiogram

Women who are pregnant, who have an abnormal 2D-echocardiogram, or who have AST/ALT > 3x ULN or creatinine > 1.8 mg/dL will be excluded from the trial.

7.2.4 Final Determination of Eligibility, Registration, and Randomization

After consent has been obtained, clinical research staff will complete a full eligibility checklist and compile the support documents from patient medical records, including laboratory reports, medical history/physician notes, and current medications list. The oncologist, study cardiologist, or other physician-investigator will review the patient's eligibility checklist, medical history, and supporting documentation.

Patients with a history of heart disease or cardiomyopathy and patients > 50 years old who are eligible for statin therapy based on the 2013 ACC/AHA guidelines (LDL cholesterol >190, or LDL <190 and ASCVD risk >7.5%; http://tools.acc.org/ASCVD-Risk-Estimator/) will be excluded from the trial. Patients 40-50 years old who are eligible for statin therapy based on the 2013 ACC/AHA guidelines and want to be placed on statins will also be excluded.

A Clinical Research Office (CRO) designee will conduct a final eligibility check prior to registration. Consented patients who qualify for the study after the pre-study eligibility evaluations and CRO confirmation of eligibility will be registered for the trial, randomized to the intervention (atorvastatin or placebo), and scheduled for Visit 1, the baseline testing.

7.3 Baseline Testing and Evaluation During the Study Intervention

7.3.1 Visit 1 – Baseline Testing and Initiation of the Statin Intervention

Visit 1 (baseline measurements) will occur from 2 weeks before the patient starts systemic breast cancer treatment (trastuzumab with or without anthracycline) up to 3 weeks after starting treatment. Participants will be asked to refrain from eating for 3 hours before the visit. The following procedures will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Vital signs assessment and measurement of weight
3. ECOG performance status
4. Blood collection for CMRI and clinical labs: Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations. Fasting for 3 hours prior to the CMRI is recommended. Five mL of blood will be drawn for laboratory blood tests for a lipid panel and creatine phosphokinase (CPK). If a lipid panel was done at the pre-study evaluations or if lipid panel results within 30 days prior to this visit are available, the lipid panel will not be done. A CMPL will not be required because one will be done at the pre-study evaluations.
5. Optional blood collection (28 mL) from participants who consent to have their blood samples banked for future studies of blood biomarkers
6. Urine pregnancy test for women < 60 years of age who have not had a menstrual period in the last 30 days. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.

7. Cardiac magnetic resonance imaging (CMRI)
8. Interviewer-administered questionnaire to obtain demographic information (detailed race and ethnicity, education); medical history, including history of cancer and BRCA testing; reproductive history, oral contraceptives and hormones; alcoholic beverage consumption and tobacco smoking histories; physical activity; and anthropometry
9. Self-administered QLQ-C30 and QLQ-BR23 to assess quality of life and symptoms
10. Review inclusion and exclusion criteria
11. Dispense the study agent and review instructions for how to take it
12. Dispense the study diary and review instructions for completing it

7.3.2 Visit 2 – Month 1 Standard of Care Visit

A standard of care oncologist visit for routine monitoring will occur 1 month (± 2 weeks) after initiation of the statin intervention. The following procedures will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Physical exam including vital signs assessment and measurement of weight
3. Symptom assessment and ECOG performance status
4. Clinical labs for CBDF and CMPL
5. Review inclusion and exclusion criteria
6. Collect study agent and assess compliance (pill count)
7. Collect and review study diary
8. Assess adverse events
9. Dispense study agent and diary

7.3.3 Visit 3 – Month 3 Standard of Care Visit

A standard of care oncologist visit for routine monitoring will occur 3 months (± 2 weeks) after initiation of the statin intervention. The following procedures will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Physical exam including vital signs assessment and measurement of weight
3. Symptom assessment and ECOG performance status
4. Clinical labs for CBDF and CMPL
5. Follow-up 2D-echocardiogram (may be on a different day)
6. Review inclusion and exclusion criteria
7. Collect study agent and assess compliance (pill count)
8. Collect and review study diary
9. Assess adverse events
10. Dispense study agent and diary

7.3.4 Visit 4 – Month 6 Research Visit

A research visit will occur 6 months (± 2 weeks) after initiation of the statin intervention. Participants will be asked to refrain from eating for 3 hours before the visit. The following procedures will be performed during this visit. Participants with metallic breast expanders in place will not be required to do the 6-month CMRI and the blood collection for CMRI.

1. Review medical history, medications, and laboratory test results
2. Vital signs assessment and measurement of weight

3. ECOG performance status
4. Blood collection for CMRI and clinical labs: Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations. Fasting for 3 hours prior to the CMRI is recommended. Five mL of blood will be drawn for laboratory blood tests for a CMPL and a lipid panel. If CMPL results within 30 days prior to this visit are available, the CMPL will not be done.
5. Optional blood collection (28 mL) from subjects who consent to have their blood samples banked for future studies of blood biomarkers
6. Urine pregnancy test for women < 60 years of age who have not had a menstrual period in the last 30 days. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
7. Cardiac magnetic resonance imaging (CMRI)
8. Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors between visits
9. Self-administered QLQ-C30 and QLQ-BR23 to assess quality of life and symptoms
10. Review inclusion and exclusion criteria
11. Collect study agent and assess compliance (pill count)
12. Collect and review study diary
13. Assess adverse events
14. Dispense study agent and diary

7.3.5 Visit 5 – Month 9 Standard of Care Visit

A standard of care oncologist visit for routine monitoring will occur 9 months (± 2 weeks) after initiation of the statin intervention. The following procedures will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Physical exam including vital signs assessment and measurement of weight
3. Symptom assessment and ECOG performance status
4. Clinical labs for CBDF and CMPL
5. Follow-up 2D-echocardiogram (may be on a different day)
6. Review inclusion and exclusion criteria
7. Collect study agent and assess compliance (pill count)
8. Collect and review study diary
9. Assess adverse events
10. Dispense study agent and diary

7.3.6 Telephone Calls and Email/Text Messages

Study participants will be followed during the intervention via telephone calls every four weeks (± 7 days) by the clinical research staff to assess compliance and adverse events. Participants who report having taken < 85% of the study drug doses between phone calls, or whose pill count at a study visit reveals < 85% compliance, will be called every two weeks (± 3 days) to monitor compliance until compliance resolves to at least 85%. In addition, participants will receive a phone call the day before each scheduled research visit to remind them to refrain from eating for 3 hours prior to the visit. Participants will also be reminded to bring any leftover study drugs and the study diary with them to every visit. Study participants will also be called during the week before their final visit (Visit 6) to remind them to take the study drug every day until the visit appointment.

Participants who opt to receive reminders for study medication intake via email or text messages will be contacted by the study staff during the first week of the study and further as needed. The study staff will send emails or text messages on cellular phone; participants will be encouraged to respond to these messages indicating if the study

drug has been taken. These responses will be used to assess compliance and will be reviewed during phone contacts. For participants who miss more than one dose of the study drug in a week, the email/text reminders will continue further into dosing period. Since agent compliance is very important during the final week of the intervention, text/email messages will be sent to all study participants who opt to receive these reminders.

The following information with be collected during the telephone calls:

- Medication compliance review. Participants will be asked if they missed any doses of medication, and the dates of all missed doses will be recorded.
- Concomitant medication review
- Adverse events. Participants will be asked if they have experienced any of the following symptoms to assess adverse events:
    - Joint pain
    - Mild muscle aches
    - Diarrhea
    - Upper respiratory infection
    - Nausea
    - Urinary tract infection (painful or difficult urination)
    - Pain in extremity (feet, ankles, hands, wrists)
- Additional symptoms experienced by participants will be recorded to assess adverse events

7.4 Evaluation at Completion of the Study Intervention

7.4.1 Visit 6 – Month 12 Research Visit

The final research visit will occur 12 months (± 2 weeks) after initiation of the statin intervention. Participants will be asked to refrain from eating for 3 hours before the visit. The following procedures will be performed during this visit. Participants with metallic breast expanders in place may be scheduled for the 12-month CMRI and blood collection for CMRI up to 3 months later (15 months) to allow for the final CMRI to be done.

1. Review medical history, medications, and laboratory test results
2. Vital signs assessment and measurement of weight
3. ECOG performance status
4. Blood collection for CMRI and clinical labs: Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations. Fasting for 3 hours prior to the CMRI is recommended. Five mL of blood will be drawn for laboratory blood tests for a CMPL and a lipid panel. If CMPL results within 30 days prior to this visit are available, the CMPL will not be done.
5. Optional blood collection (28 mL) from subjects who consent to have their blood samples banked for future studies of blood biomarkers
6. Urine pregnancy test for women < 60 years of age who have not had a menstrual period in the last 30 days. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
7. Cardiac magnetic resonance imaging (CMRI)
8. Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors between visits
9. Self-administered QLQ-C30 and QLQ-BR23 to assess quality of life and symptoms
10. Collect study agent and assess compliance (pill count)
11. Collect and review study diary
12. Assess adverse events

7.5 Post-intervention Follow-up Procedures

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

7.6 Removal of Subjects from Study

Patients can be taken off the study intervention 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:

7.6.1 Patient voluntarily withdraws (follow-up permitted);

7.6.2 Patient withdraws consent (termination of intervention and follow-up);

7.6.3 Patient is unable to comply with protocol requirements;

7.6.4 Patient becomes ineligible for the trial;

7.6.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

7.6.6 Treating physician judges continuation on the study would not be in the patient's best interest;

7.6.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

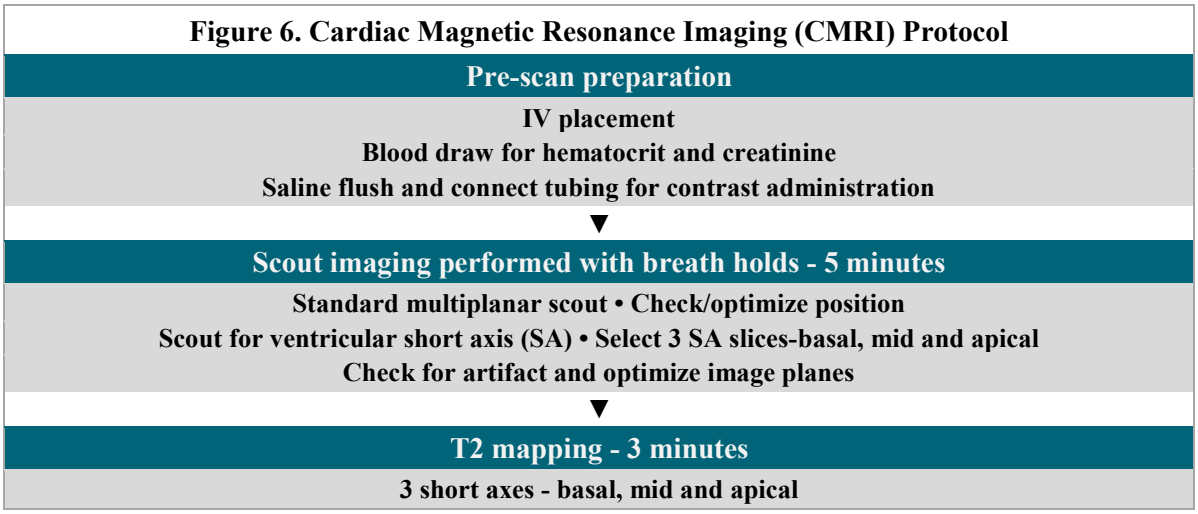
7.6.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

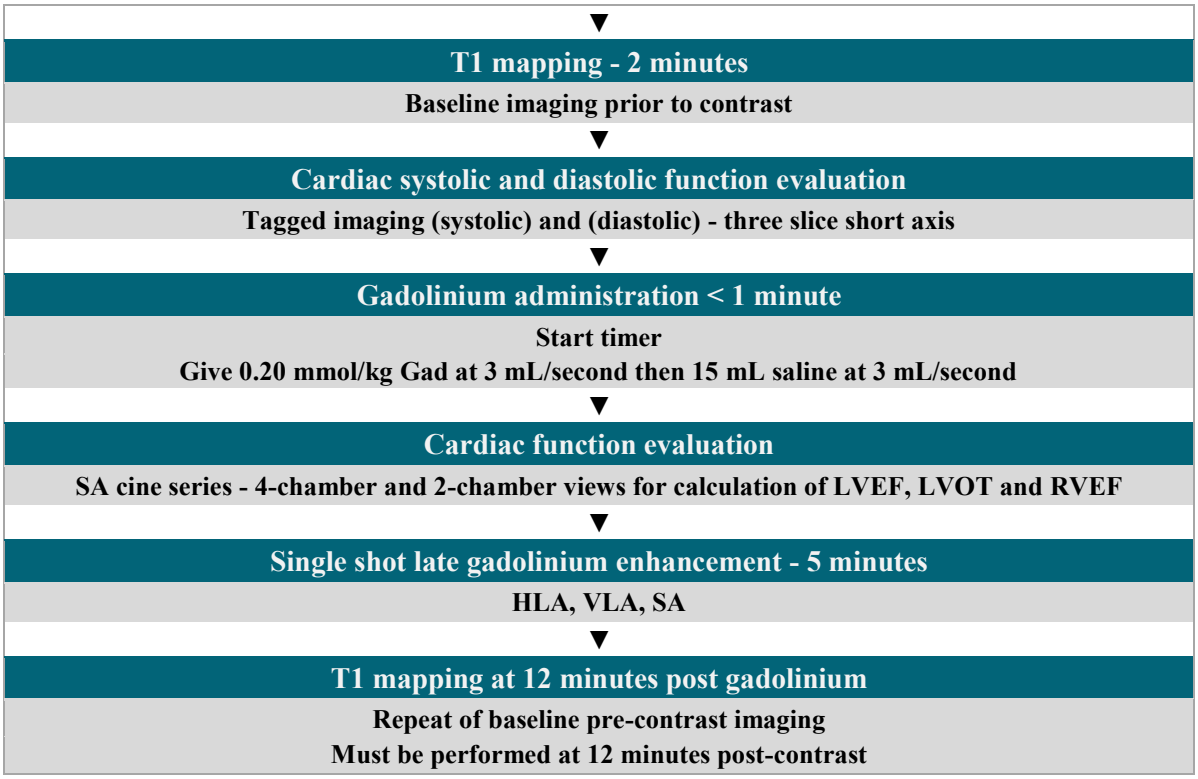
7.6.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

7.7 Methods for Clinical Procedures

Cardiac magnetic resonance imaging (CMRI). CMRI will be performed at each visit using the 3 Tesla system devoted to research. The protocols prepared and tested by Dr. Li's team will be used for imaging [82-84]. Comprehensive CMRI examination will include: (1) tomographic views in cine mode using electrocardiogram (ECG) gated steady-state-free-precession (SSFP), (2) grid tag (tissue tagging) imaging, (3) scout imaging, (4) single shot late gadolinium contrast enhancement, (5) T2 mapping, and (6) T1 mapping [Figure 6].

Figure 6. Cardiac Magnetic Resonance Imaging (CMRI) Protocol





Prior to the CMRI an IV will be inserted and a small blood sample (< 1 mL) will be drawn from participants. An i-STAT blood analyzer at the CSMC Research Imaging Core will be used to measure hematocrit and creatinine. The hematocrit value is used to calculate myocardial extracellular volume (ECV) with the T1 mapping. The creatinine value is used to calculate the glomerular filtration rate (GFR). If the GFR is < 60, the CMRI will be performed without gadolinium. Women < 60 years of age who have not had a menstrual period in the last 30 days will be required to have a urine pregnancy test before the CMRI. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test. The Research Imaging Core will do an onsite urine pregnancy test. Women who are pregnant will not undergo the CMRI.

After the pregnancy test, hematocrit, and GFR have been evaluated, scout images will be obtained for ventricular short axis and whole heart imaging, followed by T2 mapping. Baseline pre-contrast short axis imaging will be performed for T1 mapping. This will be repeated at 12 minutes post-contrast. Cine imaging for calculation of left and right ventricular ejection fraction and characterization of regional wall motion will occur after administration of gadolinium contrast. This will be followed by single shot late gadolinium enhancement, and then T1 mapping at 12 minutes post-contrast. In brief, with the patient in the supine position, high resolution, perpendicular images through the chest will be collected to locate the heart. Images will be acquired with a breath-hold at the end of expiration. The time required for the entire MRI protocol will be approximately 75 minutes. Images will be evaluated by consensus of skilled interpreters trained in CMRI imaging. A cardiac imaging physician blinded to clinical information of the subjects will read the CMRIs and evaluate them for any incidental findings. Myocardial blood flow quantitation at rest and calculation of T1 relaxation time for the myocardium will be performed using in-house dedicated analysis software as previously published [85]. We will analyze T1 mapping using quantitative parametric images of myocardial extracellular blood volume using MOLLI recovery images to generate a $\Delta R1$ map [69]. Information on LV filling, peak filling rate (PFR), and time to peak filling rate (tPFR), will be obtained by cine imaging. Quantitative analyses will use tissue tagging grid imaging for calculation of indices of strain and relaxation from systolic and diastolic optimized tagged cine images to obtain global circumferential strain (GCS), its time derivative in systole (CSs rate) and diastole (CSd rate), and the peak rate of basal to apical untwisting (UTR).

Gadolinium Contrast (Gadavist). Intravenous contrast agents such as Gadavist are an extracellular gadolinium-based chelate. All of the clinically approved intravenous contrasts that might be used in this study have excellent

safety profiles and are commonly used in CMRI studies. Unlike iodinated contrast agents used in CT, gadolinium-based CMRI contrast agents do not cause nephrotoxicity. Allergic reactions are extremely rare, but may be more common in persons with a history of allergic reactions to iodinated contrast. Studies support a rate of serious allergy reactions of 1 in 20,000.

Blood specimen. A blood specimen will be collected from each participant at Visits 1, 4, and 6. Participants will receive a phone call reminder the day before the visit to refrain from eating for 3 hours prior to the visit. Five mL of blood will be collected for laboratory blood tests into one 5 mL gold top SST tube. The time and date of the blood draw and of the participant's last meal will be recorded. Blood tests will be done for a lipid panel at Visits 1, 4, and 6. The lipid panel will not be done at Visit 1 if a lipid panel was done at the pre-study evaluations or if lipid panel results within 30 days prior to the visit are available. A CMPL will be done at Visits 4 and 6. A CMPL will not be required at Visit 1 because one will be done at the pre-study evaluations. If CMPL results within 30 days prior to Visit 4 or Visit 6 are available, the CMPL will not be done at that visit. Lab values within the past 30 days are sufficient for monitoring, and we wish to prevent patients having to undergo unnecessary repeat tests. A blood test for creatine phosphokinase (CPK) will be done at Visit 1 only. Depending on where the participant visit occurs, the blood testing will be done at the CSMC Clinical Laboratory or at the Tower Hematology Oncology Medical Group laboratory.

Prior to the CMRI, less than 1 mL of blood will be drawn at the CSMC Research Imaging Core for measurement of hematocrit and creatinine levels used for CMRI calculations. An i-STAT blood analyzer at the Imaging Core will be used to measure the hematocrit and creatinine. Fasting for 3 hours prior to the CMRI is recommended for optimal contrast enhancement.

An additional (optional) 28 mL blood sample will be collected before the CMRI from subjects who consent to have their blood samples banked for future studies of blood biomarkers. Fasting for 10 hours before the optional blood collection is recommended but is not required. The blood will be drawn at the CSMC Research Imaging Core into four vacutainers, including one 10 mL green top heparinized tube, one 10 mL red top serum tube, and two 4 mL lavender top EDTA tubes. The vacutainers will be placed on ice in a cooler and transported to the CSMC Clinical Research Office (CRO) Research Laboratory for processing within 2 hours of collection. The four vacutainers will be centrifuged as specified in the blood processing SOP. After centrifugation, cryovials will be prepared from the blood specimens including plasma, serum, red blood cells, and buffy coat for DNA extraction. Processed specimens will be stored at -80^{o}C for future studies of cardiac blood biomarkers. If the participant fasted for 10 hours prior to the visit for the optional blood collection, she may have a snack after the blood draw and before the CMRI if desired.

8.0 MEASUREMENT OF EFFECT AND CRITERIA FOR EVALUATION

8.1 Prevention of Cardiotoxicity Due to Breast Cancer Treatment

This randomized clinical trial aims to evaluate the impact of statin on preventing cardiotoxicity due to trastuzumab treatment (with or without anthracycline) in breast cancer patients. Cardiac function will be primarily measured by global circumferential strain (GCS), a sensitive measure of cardiac function, which is predictive of future cardiac events. Secondary outcomes will include additional global measures of cardiac function (e.g. left ventricular ejection fraction), cardiac morphology (mass, wall thickness, internal dimensions), diastolic function, and tissue viability (fibrosis, edema, inflammation). We anticipate that trastuzumab treatment will impair GCS, and increase markers of fibrosis, edema, and/or inflammation. We hypothesize that there will be less change in GCS and secondary outcomes measures with atorvastatin intervention compared to placebo.

8.2 Methods for Evaluation of Cardiac Function

Cardiac MRI will be performed at baseline, 6 months and 12 months after randomization as outlined in Section 7.7. Imaging will include: (1) conventional cinematic imaging, to assess myocardial morphology and global function; (2) magnetic resonance tissue tagging, to assess GCS, along with other secondary endpoint measures like global longitudinal strain (GLS), peak left ventricular (LV) twist and torsion, as well as diastolic endpoints

such as strain rate and untwisting rate; (3) T1 mapping (before and after the administration of gadolinium), to assess myocardial fibrosis and tissue viability; (4) T2 mapping, to assess myocardial edema and inflammation; and (5) late gadolinium enhancement, to assess focal scar.

Table 3. Summary of Endpoints Measured by Cardiac Magnetic Resonance Imaging (CMRI)	
CMRI procedure	**Measurement**
Cine-imaging + tissue tagging	
Systolic function	*GCS (primary endpoint),* GLS, peak LV twist and torsion
Diastolic function	Untwisting rate
Cardiac function and morphology	Left ventricular ejection fraction (LVEF), LV end diastolic volume (LV EDV), LV end systolic volume (LV ESV), cardiac output (CO), LV mass, LV concentricity
T1 mapping + Gadolinium enhancement	Myocardial fibrosis and tissue viability, extracellular volume
T2 mapping	Edema and inflammation

8.3 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, concomitant medications, or medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. As described in section 7.5, clinical research staff will 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, echocardiogram 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. If feasible, we will conduct a research visit to collect final measurements for participants who permanently discontinue the study agent early. An end-of-study research visit will be conducted 12 months after initiation of the statin intervention (Visit 6). All CMRI procedures will be done at this visit. The blood collections for clinical labs and future research, and the follow-up risk and quality of life questionnaires, will not be done. The following procedures will be performed during the end-of-study visit:

1. Review medical history, medications, and laboratory test results
2. Vital signs assessment and measurement of weight
3. ECOG performance status
4. Blood collection for CMRI: Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations.
5. Urine pregnancy test for women < 60 years of age who have not had a menstrual period in the last 30 days. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
6. Cardiac magnetic resonance imaging (CMRI)

8.4 Off-Study Criteria

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

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

- Other

Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants will be removed from study agent if investigators feel it is in the interest of subject to do so. As described in section 7.5, clinical research staff will follow up by telephone on days 30 ± 7, 60 ± 7, and 90 ± 7 after the participant goes off-study to assess symptoms and adverse events. Standard of care data (medical history, laboratory test results, concomitant medications, echocardiogram 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. If feasible, we will conduct a research visit to collect final measurements for participants who go off-study early. An end-of-study research visit will be conducted 12 months after initiation of the statin intervention (Visit 6). All CMRI procedures will be done at this visit. The blood collections for clinical labs and future research, and the follow-up risk and quality of life questionnaires, will not be done. The following procedures will be performed during the end-of-study visit:

1. Review medical history, medications, and laboratory test results
2. Vital signs assessment and measurement of weight
3. ECOG performance status
4. Blood collection for CMRI: Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations.
5. Urine pregnancy test for women < 60 years of age who have not had a menstrual period in the last 30 days. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
6. Cardiac magnetic resonance imaging (CMRI)

9.0 CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

Cardiac magnetic resonance imaging (CMRI) is considered the gold standard imaging technique for accurate quantification of systolic and diastolic function, and the addition of tissue tagging helps determine specific myocardial structural changes related to twist and torsion of the left ventricle during systole and diastole. CMRI can also detect fibrosis with late gadolinium enhancement and T1 mapping. Reliance on 2-dimensional echocardiography (2-D echo) for the identification of cardiac damage is limited as it lacks the requisite sensitivity to detect subtle changes in left ventricular (LV) function. Newer sophisticated echocardiographic imaging techniques, including myocardial strain and speckle tracking can identify early pre-clinical LV systolic dysfunction pre- and post-treatment, but the quality is sonographer-dependent and is limited by patient body habitus. Moreover, early myocardial injury, edema, and fibrosis are missed on echocardiography.

9.2 Laboratory Correlates and Biomarkers

A blood specimen will be collected from participants at each research visit. Less than 1 mL of blood will be drawn for measurement of hematocrit and creatinine levels used for CMRI calculations. Five mL of blood will be collected for clinical blood tests. An additional (optional) 28 mL blood sample will be collected from subjects who consent to have their blood samples banked for future studies of blood biomarkers.

Clinical blood tests (5 mL). Blood tests will be done at all research visits for statin monitoring. A lipid panel will be done at Visits 1, 4, and 6. The lipid panel will not be done at Visit 1 if a lipid panel was done at the pre-study evaluations or if lipid panel results within 30 days prior to the visit are available. A CMPL will be done at Visits 4 and 6. A CMPL will not be required at Visit 1 because one will be done at the pre-study evaluations. If CMPL results within 30 days prior to Visit 4 or Visit 6 are available, the CMPL will not be done at that visit. Creatine phosphokinase (CPK) will be measured at Visit 1 to establish a patient-specific reference for this indicator of muscle toxicity. During the trial, if the patient reports unexplained muscle pain or weakness, CPK will be tested again to check for elevation.

Optional banked samples for future studies (28 mL). Processed blood will be stored at -80°C for future studies of blood biomarkers. Future studies may include: (a) investigation of high-sensitivity troponin (hs-TnT), a biomarker of myocardial injury; (b) studies of two novel biomarkers of cardiac fibrosis, galectin-3 (GAL3) and apoptosis / inflammation, growth differentiation factor 15 (GDF15), which play regulatory roles in extracellular matrix remodeling and are associated with impaired cardiac function and chronic heart failure; (c) investigation of brain naturetic peptide (BNP), a biomarker of myocardial stretch; and (d) examination of pro-inflammatory markers IL-6 and hs-CRP.

9.3 Specimen Banking

Patients participating in this trial will be invited to participate in an optional repository study, MetaBank (Pro35861). Subjects who consent for MetaBank will provide an additional 28 mL of blood at each research visit, and the blood, as well as their leftover specimens collected during this trial, will be stored and maintained in the MetaBank for use in future research. Specimens will be retained in MetaBank freezers, equipped with temperature activated alarms, located in the Shuman Basement of the Davis Research Building at CSMC. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

The Principal Investigator will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Cedars-Sinai Medical Center. Collaborators will be required to complete the MetaBank Data and Specimen Usage Agreement specifying the planned use of the specimens, and a Material Transfer Agreement that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of Cedars-Sinai Medical Center for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by Cedars-Sinai Medical Center, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Description

This phase II randomized, double-blinded, placebo-controlled trial evaluates the effect of statin use versus placebo on global circumferential strain (GCS), a measure of LV dysfunction, in women newly diagnosed with breast cancer using state-of-the-art imaging (CMRI). Secondary outcomes will include additional global measures of cardiac function (e.g. left ventricular ejection fraction), diastolic function, cardiac morphology (mass, wall thickness, internal dimensions), and tissue viability (fibrosis, edema, inflammation). Assuming a 20% drop-out rate, 60 women diagnosed with stage 1-3 breast cancer recommended to undergo trastuzumab treatment, with or without anthracycline, will be randomized to 12 months of atorvastatin intervention or placebo resulting in a final sample of 48 women completing both follow-up visits. Measurements will be taken at three time points: Baseline, from 2 weeks before the patient starts systemic breast cancer treatment (trastuzumab with or without anthracycline) up to 3 weeks after starting treatment; Follow-up, 6 months and 12 months post-initiation of the statin intervention. At each of the three time points, information regarding the participant’s medical history, medication use, risk factors, physical functioning, and quality of life will be obtained as adjustment variables.

10.2 Sample Size and Accrual

Sample size: Intervention = 60 (30 statin:30 placebo) randomized sample; Analytic sample after 20% drop out = 48 (24:24).

The planned duration of accrual is 24 months with an expected accrual rate of 2-3 subjects per month. We anticipate that all evaluable participants will have completed all study procedures within three years. Power and precision arguments are provided below.

10.3 Randomization and Intervention

Randomization will be carried out by the SOCCI Research Pharmacy among consented subjects who meet all eligibility criteria after the eligibility evaluations and CRO confirmation of eligibility, and who are registered for the trial. A secure web-based system maintained by the Biostatistics and Bioinformatics Core at CSMC will randomly assign women to either statin or placebo based on sequences that minimize imbalances between the arms on diagnosis. Study personnel will be blinded to actual assignment. The randomization algorithm computes real-time marginal totals according to the method of Pocock and Simon [86], which ensures near equal allocation to the two treatment strategies. Intention-to-treat analysis is initiated at the time of randomization. Based on the literature cited above, a lipophilic statin, atorvastatin calcium, was selected for the intervention. Independent pharmacists will dispense either active or placebo atorvastatin according to the computer-generated assignment. The placebo is designed to be identical in color, consistency, and appearance to atorvastatin. Dosing and administration of atorvastatin will be consistent with the recommended regimen: 20 mg once a day.

10.4 Endpoints/Statistical Considerations

Our primary outcome, global circumferential strain obtained by CMRI, is a composite measure of myocardial deformation as the heart contracts and relaxes. The non-parametric Wilcoxon-Mann-Whitney test will be used to test the equality of statin treatment (atorvastatin) to placebo in reducing or preventing LV dysfunction through comparison of change in GCS values (Δ length / original length, expressed as % / seconds) measured from 2 weeks prior to start of systemic breast cancer treatment to 1 year post-initiation of the statin intervention. Power calculations use a two group t-test based on previously published data [87], which indicate a standard deviation of 4.3 for baseline GCS and 3.1 for GCS 1 year post treatment initiation. A conservative estimate of the standard deviation of the difference of these two random variables will assume no correlation between pre- and post-treatment GCS, which gives an estimated standard deviation of 5.3 $=\sqrt{(4.3^2 + 3.1^2)}$. With 20% dropout rate, we plan to enroll a total of 60 patients with each group having 30 patients, leaving 24 per group after loss to follow up. Based on the asymptotic efficiency of a Mann-Whitney test under non-normal distributions in the groups, the minimum detectable differences in the power calculations have been done using an adjusted sample size that is 15% smaller than that anticipated, or 20 per group. Assuming the same standard deviation for both groups, a two-sided two sample t-test would allow us to detect a minimum detectable difference in means between treatment and placebo groups for the change in GCS ranging from 4.8 to 2.4 units depending on the actual post- versus pre-GCS correlation (0 to 0.8), assuming 80% power and a 5% significance level. Other minimum detectable differences that assume higher correlation between pre- and post-treatment GCS are shown in Table 4.

Table 4. Minimum detectable differences for repeated measures design. A two-group t-test assumes 80% power, 5% significance, and 20 patients per group. It is also assumed that the standard deviation is 4.32 at baseline and 3.12 at 1 year post-treatment, and that the paired differences standard deviation is the same for treatment and placebo groups. Selected values of correlation between a pair of observations made on the same subjects are presented.

Correlation of post vs. pre-GCS	Standard Deviation of post vs. pre-GCS	Minimum Detectable Difference
0	5.3	4.8
0.2	4.8	4.3
0.4	4.2	3.8
0.6	3.5	3.2
0.8	2.6	2.4

10.5 Statistical Analysis Plan

Primary analyses will be conducted on an intention-to-treat basis on all patients who complete the 12-month CMRI. The distribution of the covariates, including age, race, dose of trastuzumab treatment (and anthracycline if

applicable), laterality, radiation dose, smoking status, BMI, baseline measures of fibrosis, hormone use, 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. The assumptions of the t-test and regression will be examined for the distribution of the difference in 1 year post-treatment initiation GCS minus pre-treatment GCS. Non-normal distribution or unequal variance between groups will be corrected using a transformation (e.g. log, arcsin, Box-Cox). If a transformation is inadequate for the t-test a Wilcoxon-Mann-Whitney test will be used instead. Patients may not receive a uniform dose of trastuzumab treatment, given that some patients may be enrolled for up to 3 weeks after starting systemic breast cancer treatment and patients undergoing an AC-TH regimen will receive anthracycline first, followed by trastuzumab. While our primary analysis will be with all patients assumed to have received homogeneous trastuzumab treatment, we plan to conduct sub-analyses in participants randomized to atorvastatin to evaluate whether patients who initiate statin after receiving one or more doses of trastuzumab treatment experience a different level of cardioprotection than patients who initiate statin before receiving any trastuzumab treatment.
Secondary analyses. Secondary analyses will compare the statin and placebo groups regarding differences from baseline to 12 months follow-up in the following outcomes using a similar approach to the main outcome: (1) myocardial structural changes through CMRI and pre- and post-gadolinium myocardial T1 values for fibrosis; and (2) myocardial functional changes, through cine CMRI and tissue tagging. As described above, we will take note of any chance difference in covariates and adjust for factors in a multiple regression analysis. Assumptions of the regression models for GCS and two secondary outcome measures will be examined primarily through analysis of residuals after adjustment for potential covariates. If necessary, transformations to the outcomes will be made as described for the main analysis. **Missing data.** Care will be taken to minimize missing data to the extent possible. Assuming ≤ 10% missing data, multiple imputation on covariates (not primary or secondary outcomes) will be considered for statistical analysis. In the unlikely event of > 10% missing values, we will consider a missing data mechanism [88]. After diagnosing the possible missing data mechanism, we will evaluate the potential influence of missing data by conducting sensitivity analyses under several assumptions of missingness [89].

10.6 Contamination (Cross-Over) and Drop-Outs

We anticipate some contamination from the statin intervention to placebo due to non-compliance and this will be monitored and managed through blood tests. We do not expect cross-over from the placebo to statin group as women will be aware that they might be on statins already and would not want to jeopardize their safety and care. However, current clinical guidelines for prescription of statins may also influence drop-outs among women who wish to reduce the risk of cardiovascular disease [10]. These guidelines recommend targeting women with cardiovascular disease, LDL cholesterol ≥ 190 mg/dL, and women ages 40-75 years with diabetes or a 10-year cardiovascular disease risk ≥ 7.5%. Most of these women would not meet the eligibility criteria for study participation. The drop-out rate is conservatively expected to be 20% from baseline to 1 year follow-up.

10.7 Evaluation of Toxicity

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

10.8 Evaluation of Response

Changes in global circumferential strain obtained by CMRI will be evaluated for all randomized participants.

10.9 Interim Analysis

There will be no planned interim analyses.

11.0 ADVERSE EVENTS

11.1 Experimental Therapy

The study intervention, atorvastatin calcium, is a standard drug and dose commercially available for primary and

secondary prevention of cardiovascular disease. Atorvastatin has a widely accepted tolerability profile with few serious side effects [6]. A list of adverse events (AEs) that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6.2, Pharmaceutical Information, as well as the Investigator Brochure or package insert.

11.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

AEs will be collected throughout the study period and at follow-up time points. Grade 1 and 2 laboratory abnormalities/AEs will not be collected, with the exception of AST or ALT > 3x the upper limit of normal, which are known AEs related to statin use and indicate that a participant must be evaluated for possible discontinuation of the study agent. Only lab abnormalities graded 3 or above and that are considered at least *possibly* related to the study agent will be collected and reported. All serious adverse events (SAEs) will continue to be collected, regardless of attribution.

All patients experiencing an adverse event, considered at least *possibly* related to the study drug with the exception of grade 1 and 2 laboratory abnormalities, 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; or
- death.

11.3 Definitions

11.3.1 Definition of 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.

11.3.2 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. The CTCAE v4 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.

11.3.3 Serious Adverse Events

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

11.3.3.1 Results in death. If death results from (progression of) the disease, the disease should be reported as a serious adverse event (SAE) itself.

11.3.3.2 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).

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

11.3.3.4 Results in persistent or significant disability or incapacity.

11.3.3.5 Is a congenital anomaly/birth defect.

11.3.3.6 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.

11.4 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 v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

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 – 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

11.5 Reporting Requirements for Adverse Events

11.5.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

- The CSMC IRB must be notified no later than 10 business days after the investigator becomes aware of the event or receives an external report of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO). The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths, or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

11.5.2 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.

11.6 Stopping Rules

There are no formal stopping rules. The study agent, atorvastatin calcium, is a commonly prescribed drug indicated for long-term use. The study agent will be stopped in the event of an AE ≥ grade 3 considered possibly, probably, or definitely related to the study agent. The study agent will be restarted after resolution unless the subject experiences grade 3 or greater myopathy (unexplained muscle symptoms *and* CPK > 5 times ULN) or persistent hepatotoxicity (ALT or AST > 3 times ULN) that is considered possibly, probably, or definitely related to the study agent, in which case the study agent will be permanently discontinued.

12.0 STUDY MANAGEMENT

12.1 Conflict of Interest

All investigators will follow the Cedars Sinai Medical Center conflict of interest policy. There are no conflicts of interest to report.

12.2 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.

12.3 Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. 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 at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (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 (S01, S02, etc.). Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered.

12.3.1 Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the SOCCI Clinical Research Office (CRO). The following documents will be completed and provided for review:

- Registration form (or equivalent)
- Copy of required laboratory tests
- Copy of required imaging reports
- Eligibility checklist (signed by investigator)
- Signed patient consent form and Subject's Bill of Rights
- HIPAA authorization form

12.3.2 Registration

After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Assign the patient a dose as determined through communication with Biostatistics and the principal investigator
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

Oversight by the principal investigator is required throughout the entire registration process.

12.4 Record Keeping and Data Management

Data storage and tracking systems will be developed using the Research Electronic Data Capture (REDCap) application, stored and maintained on a secure CSMC Enterprise Information Systems (EIS) server. REDCap is a web-based application that is HIPAA compliant (secure location, automatic encryption, authentication, authorization, and audit trail) and is only accessed via password. Appropriate administrative, physical, and technical safeguards are in place to ensure the confidentiality, integrity, and security of electronic protected health information (EPHI). Security measures for the databases include password management, transmission security, and data encryption to guard against unauthorized access to EPHI while it is being transmitted over the network. Only certified research personnel who are listed on the approved IRB application will be given access to the data. Questionnaire data will be entered into the REDCap database. The data will be checked for missing data and reviewed for accuracy by clinical research staff. Programs will be developed to prevent data entry errors and to perform extensive data edits, including checks for inconsistences and permissible variable values. A data dictionary will document all database activities, and contain detailed information about each database variable. A secure OnCore database will be developed to track the storage locations and status of study biospecimens.

12.5 Data and Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will be convened and will meet every six months 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 DSMB Charter. There will be interim reviews conducted by the DSMB 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 DSMB 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 Cedars-Sinai Medical Center IRB.

12.6 Executive Committee and Internal Advisory Board (IAB)

The project investigators with the assistance of the study coordinator will have day-to-day responsibility for the trial. They will ensure that recruitment and scientific goals are met according to the milestone schedule. The Executive Committee, including Drs. Goodman, Wei, Mita, and Bairey Merz; and Ms. Travis-Teague, will have monthly teleconferences and quarterly in-person meetings. Meeting agendas will include the following content areas:

a) Present and review data obtained and evaluate progress toward achieving recruitment and follow-up goals;
b) Identify and resolve all impediments to the successful implementation and completion of the project;
c) Review and discuss interim data to assist in planning the remaining work;
d) Discuss, coordinate, and delegate presentations to community and advocacy groups regarding the growing importance of cardioprotection among women with breast cancer;
e) Promote enthusiasm and maintain the momentum of the project.

An IAB will review the study and assist the investigators in protocol development, problem solving, evaluating scientific progress, identifying research opportunities, and guiding future research planning. The IAB will meet annually with the Executive Committee, although each IAB member will be available for consultation and advice on an ad hoc basis. The composition of the IAB includes Dr. Armando Giuliano, Co-director of the Brandman Breast Center, a breast surgeon who promulgated the practice of the sentinel node biopsy and a recent recipient of the Susan Komen Brinker Award for Scientific Distinction in Clinical Research, their highest award for clinical research; Dr. Beth Karlan, an oncologist and Director of the Women's Cancer Program who sits on the National Cancer Advisory Board; Dr. Debiao Li, Director of the Biomedical Imaging Research Institute and President of the International Society for Magnetic Resonance in Medicine; and Dr. Steven Piantadosi, immediate past Director of the Samuel Oschin Comprehensive Cancer Institute and one of the world's leading experts in the design and analysis of clinical trials for cancer research. Following the end of the meeting, the IAB will prepare a written report to the Executive Committee.

12.7 Adherence to the Protocol

Adherence to the protocol, Good Clinical Practice (GCP) and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). In addition, the SOCCI CRO Quality Management Core (QMC) will conduct the following:

1) Audit preparations (AP) prior to audit conducted by any external auditing agency (i.e., NCI or FDA). The purpose of an AP is to ensure adequate source documentation to support protocol compliance and data integrity are present and organized, and to identify and correct any major findings prior to the external audit, if possible.
2) A thorough review of selected subject cases, regulatory files, and Investigational Product (IP) accountability records (if applicable) within 2-3 months after the first subject is enrolled and annually thereafter while subjects are receiving investigational intervention. Reviews will include a representation of cases, pharmacy, and regulatory files from external sites.
3) Central eligibility verification for all subjects enrolled as described in protocol section 12.3.1 Eligibility Verification.
4) Central review of all eligibility waivers and exception requests by a SOCCI Medical reviewer to assess appropriateness and risk to ensure quality data and ensure subject safety protections for investigator initiated research.
5) For multi-site studies, a central review of subject registration and eligibility verification.

For any protocol, the QMC has the authority to request more frequent reviews or closer safety monitoring if it is deemed appropriate for any reason. Additionally, to monitor data quality and protocol compliance once all subjects have discontinued intervention, decreased monitoring may be implemented.

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

12.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. 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.

12.9 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring 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. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.10 Obligations of Investigators

The Principal Investigator is 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 Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator 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 Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator 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 Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	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.
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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

APPENDIX B

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.

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

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

Study Drug Dispensed for:

☐ Visit 1 (Baseline) – Visit 2 (Month 1) ☐ Visit 2 (Month 1) – Visit 3 (Month 3)
☐ Visit 3 (Month 3) – Visit 4 (Month 6) ☐ Visit 4 (Month 6) – Visit 5 (Month 9)
☐ Visit 5 (Month 9) – Visit 6 (Month 12)

Instructions

Complete one line in the table for each day you take the study drug.
Please contact the study research staff at «staff phone number» if you have any questions.

- Take your study drug once per day at bedtime or with an evening meal. Please swallow the capsule whole and do not chew, crush, or open it. Take the capsule at the same time every day.
- Record the date and time of day you took the study drug.
- 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.
- If you notice any side effects such as joint pain, mild muscle aches, diarrhea, nausea, respiratory infection, painful or difficult urination, pain in feet, ankles, hands, or wrists, or if you have any other symptoms, please write them in the Comments column and report them to the study staff when they call you.

Day	Date	Time Study Drug Taken	Check if Dose Missed	Comments
1		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
2		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
3		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
4		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
5		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
6		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
7		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
8		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
9		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
10		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
11		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
12		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
13		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
14		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
15		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
16		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	

Day	Date	Time Study Drug Taken	Check if Dose Missed	Comments
17		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
18		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
19		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
20		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
21		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
22		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
23		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
24		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
25		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
26		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
27		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
28		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
29		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
30		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
31		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
32		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
33		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
34		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
35		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
36		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
37		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
38		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
39		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
40		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
41		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
42		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
43		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
44		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
45		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
46		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
47		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
48		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
49		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
50		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	

Day	Date	Time Study Drug Taken	Check if Dose Missed	Comments
51		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
52		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
53		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
54		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
55		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
56		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
57		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
58		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
59		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
60		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
61		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
62		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
63		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
64		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
65		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
66		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
67		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
68		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
69		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
70		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
71		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
72		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
73		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
74		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
75		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
76		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
77		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
78		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
79		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
80		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
81		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
82		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	

Day	Date	Time Study Drug Taken	Check if Dose Missed	Comments
83		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
84		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
85		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
86		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
87		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
88		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
89		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
90		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
91		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
92		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
93		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
94		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
95		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
96		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
97		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
98		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
99		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
100		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
101		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
102		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
103		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	
104		____:____ ☐ a.m. / ☐ p.m.	☐ Dose not taken today	

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