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SCUSF 0806 "Phase II placebo-controlled trial of lisinopril and Coreg CR® to reduce cardiotoxicity in patients with breast cancer receiving (neo)adjuvant chemotherapy with trastuzumab (Herceptin®)"

NCT #: 01009918

08/31/2012 **Cancer Control Credit: 1.0**

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All CCOP/MBCCOPs may participate
SunCoast CCOP Research Base Affiliates
11/19/2010 CTSU Affiliated Institutions

Activation Date: March 01, 2010

Amendment #1: September 24, 2010

Amendment #2: October 08, 2010

Amendment #3: November 19, 2010

Amendment #4: June 3, 2011

Amendment #5: August 31, 2012

(See next page)

Amendment #1: September 24, 2010	Name changed from Moffitt CCOP Research Base to SunCoast CCOP Research Base, Added logo and toll free number. All changes made throughout protocol.
Amendment #2: October 08, 2010	Standardize title, pt schedule to 13 weeks +/- (3 months) [protocol, App I ICF, App III Data Forms], new co-investigator, added Refill study agent directions (4.15), added Medication Order Form – Site Stock (table of contents, 4.6.8, 6.5.2.4, Appendix III), added LVEF Reimbursement Form (App III Data Collection Forms), added Refill Worksheet & sample email App II IVR), added FDA IND Exemption letter & Herceptin® prescribing information (Appendix IV), CTCAE V4.0 (8.7, 8.9, App III), administrative clarifications & formatting (4.6.2, 4.6.3, 4.6.10, 4.7.2, 4.8.1, 4.10.3, 5.65, 5.68.1, 6.1, 6.5.2, 9.1, 9.2, all appendices
Amendment #3: November 19, 2010	Added participation through CTSU: cover, TOC., CTSU support page, , §,4.0, 6.5.1, 6.5.4.2, App 1-ICF, App II-IVR, App III-Data forms, updated LVEF 6.5.1. administrative 4.8.2.
Amendment #4: June 3, 2011	Added troponin I (biomarker) [schema, §,2.10, 3.2.4, 6.1, 6.5.4, 10.8, and App III-Data forms]; Clarified patient schedule of events [protocol, App I ICF, App III Data Forms]; requesting de-identified ECHO results submitted for central review [§ 6.1, 6.5.7, 9.2, App III Data Forms]
Amendment #5: August 31, 2012	Includes males (§2.12.1, §4.8.8); Stratified based on chemotherapy regimen - with/without an anthracycline (schema, §2.9.8, §3.2.2); Pertuzumab allowed in chemo regimen (§4.8.2); Use of ARBs, such as losartan, now allowed (§4.9.4); No metastatic disease (§4.9.1); Chemistry profile is a non-fasting sample (schema, §2.10, §6.8.4); Expanded study plan tables (§6.1-6.4); Examples of MUGA scan/ECHO calculations for study failure (§7.1, §7.2); Revised reportable adverse events (§8.0); Process of payment for LVEF testing not considered standard of care (§12.9). Revised ICF (Appendix I).

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11/19/2010

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with the SunCoast (SCUSF) CCOP Research Base will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix (Appendix VIII).

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the members' section of the CTSU Web site located at www.ctsu.org.
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the SCUSF CCOP Research Base Data Management Center (DMC). **Case report forms** (with the exception of patient enrollment forms)**, signed consents, clinical reports, symptom/ medication diaries, quality of life questionnaires, and transmittals** must be sent via mail or fax to the SCUSF CCOP Research Base DMC unless otherwise directed by the protocol. Your institution's standard fax transmittal cover sheet should accompany all data submissions. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by SCUSF CCOP Research Base DMC. Please send query responses and delinquent data to SCUSF CCOP Research Base DMC and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the SCUSF CCOP Research Base DMC.

11/19/2010

CANCER TRIALS SUPPORT UNIT (CTSU)
CONTACT INFORMATION FOR SCUSF-0806

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to SunCoast CCOP Research Base unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]	SCUSF CCOP Research Base Operations Center: FAX: 813-910-5998 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions contact Viki Huegel by phone or by email: 1-813-396-9503, or Viki.Huegel@epi.usf.edu.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at: www.ctsu.org. CTSU logistical information is located in Appendix VIII.		

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Schema

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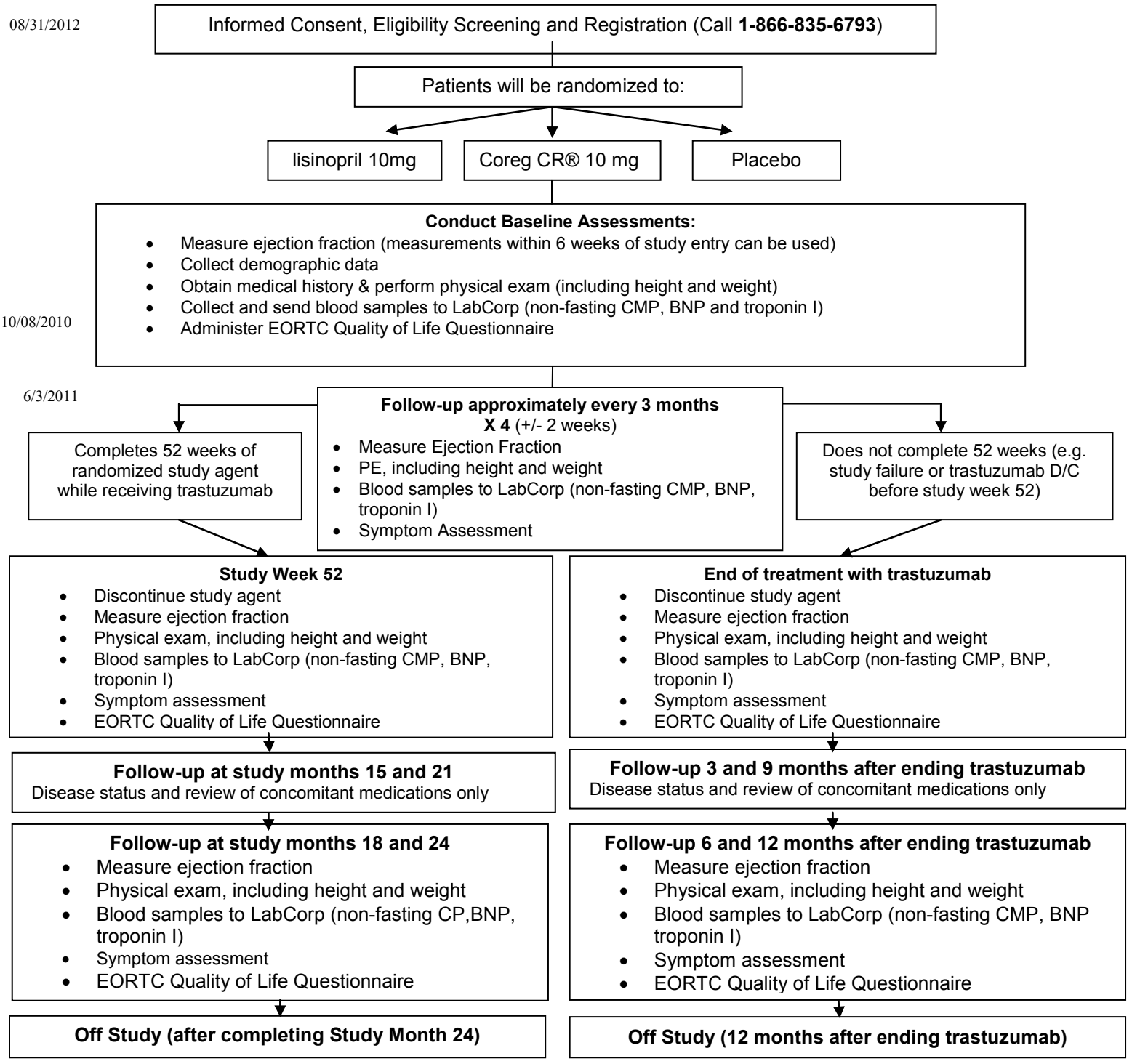
This Phase II placebo-controlled study will enroll 468 subjects to evaluate the effect of lisinopril or Coreg CR®, compared to placebo, on trastuzumab-induced cardiotoxicity in patients with breast cancer who are receiving adjuvant or neoadjuvant therapy. The study will enroll to 2 separate cohorts; patients who received an anthracycline-containing regimen and patients whose treatment regimen did not contain an anthracycline. Should accrual to a cohort reach 281, that cohort will be closed to new accrual and the study will be completed with accrual to the remaining cohort. Study agent will be administered daily for 52 weeks OR until the end of trastuzumab therapy, if it is discontinued prior to week 52. Primary response, change in LVEF, will be evaluated at baseline, every 3 months X 4 while on trastuzumab therapy, then at study months18 and 24 (or 6 and 12 months after last dose of trastuzumab). Study failure is defined as an absolute decrease ≥ 10% in LVEF at study follow-up OR an absolute decrease ≥ 5% in LVEF if it is < 50% at study follow-up.



Glossary of Terms:

	Angiotensin-Converting Enzyme Inhibitor	ACE Inhibitor
	B-Type Natriuretic Peptide	BNP
	Beta Blocker	*β*-Blocker
	Cancer Therapy Evaluation Program	CTEP
	Carvedilol phosphate extended-release	Coreg CR®
11/19/2010	Clinical Trials Support Unit	CTSU
	Common Terminology Criteria and Adverse Events	CTCAE
	Community Clinical Oncology Program	CCOP
	Comprehensive Metabolic Panel	CMP
	Confidence Intervals	CI
	Continuous Release	CR
	Ejection Fraction	EF
	European Organization for Research and Treatment of Cancer's Quality of Life	EORTC QLQ-C30
	Extended Release	ER
	Food and Drug Administration	FDA
	Health Insurance Portability and Accountability Act	HIPAA
	Heart Failure	HF
	Heart Outcomes Prevention Evaluation	HOPE
	Human Epidermal Growth Factor -2	HER2
	Institutional Review Board	IRB
	Interactive Voice Response system	IVR system
	Investigational New Drug	IND
	Left Ventricular	LV
	Left Ventricular Ejection Fraction	LVEF
	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure	MERIT-HF
	National Cancer Institute	NCI
	New York Heart Association	NYHA
	Power	p=
	Private Health Information	PHI
	Quality of Life	QOL
	Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot trial	RESOLVD
	Relative Risk	RR
	Studies of Left Ventricular Dysfunction	SOLVD
	Survival and Ventricular Enlargement	SAVE
	Trastuzumab	Herceptin®
6/3/2011	Troponin I	TnI

1.0 Introduction

1.1 Chemotherapy-induced cardiotoxicity is a well-established treatment side effect, most notably of anthracycline-based treatment regimens. It is also a side effect of trastuzumab (Herceptin®), which is now standard in adjuvant treatment regimens for women with human epidermal growth factor -2 (HER2) positive breast cancers. The projected number of women who will have HER2-positive disease and who can benefit from trastuzumab therapy, well exceeds 50,000 per year

1.2 A decrease in left ventricular ejection fraction (LVEF) has been reported in as many as 28-34% of women when trastuzumab is combined with standard chemotherapy.[1-3] As new agents are introduced into clinical practice and treatment outcomes improve, there will be more long-term survivors of breast cancer. As the number of survivors increases, it is likely that treatment-induced cardiotoxicity will be more prevalent.

1.3 One of the new challenges in oncology and cardiology is safe and effective short and long-term use of trastuzumab. In addition to improving progression-free survival in women with metastatic breast cancer that overexpresses HER2, trastuzumab also has been shown to reduce the risk of recurrence in the adjuvant setting for early stage breast cancers that are HER2-positive.[4]

1.4 Trastuzumab is the prototype of novel targeted molecular chemotherapeutic agents. HER2 is amplified or overexpressed in up to 30% of breast cancers[5] and is also expressed in myocardial cells.[6] Inhibition of signaling through the myocardial receptor may cause cardiotoxicity secondary to disrupted cardiac contractile function and structure[6], especially in the previously stressed heart; however, the exact mechanism of cardiotoxicity is under intense investigation.

1.5 While studies have demonstrated improved disease-specific and overall survival in patients with HER2 overexpressing disease, treated with trastuzumab,[5, 7] oncologists commonly interrupt or discontinue trastuzumab therapy when there is evidence of cardiotoxic changes. Cardiotoxicity is commonly manifested by an asymptomatic decrease in the left ventricular ejection fraction (LVEF) and less commonly by clinical heart failure.[3] Unlike anthracycline-induced cardiotoxicity, trastuzumab-induced changes are not dose-dependent,[3] and may be substantially reversible,[3,8] despite continuation of trastuzumab in the face of cardiotoxic changes or a subsequent drug rechallenge.[9] Endomyocardial biopsies from patients with trastuzumab-induced cardiac dysfunction also do not have the typical anthracycline-related ultrastructural changes.[10, 11] Evidence has suggested that LVEF recovery is evident within six months of discontinuing trastuzumab therapy for the majority of patients who demonstrate a decrease in LVEF.[12] However, the data on long-term sequelae of these changes are still being gathered.

1.6 Cardiac side effects of trastuzumab have, like anthracycline therapy, prompted mandatory screening practices before and during treatment with trastuzumab. Evaluation of LVEF is the most common screening procedure conducted.

1.7 Due to the recognition of increased cardiac toxicity observed with anthracyclines and trastuzumab combinations, there has been much emphasis on finding alternative treatments that will reduce the incidence of cardiotoxicity. Even with changes in breast cancer treatment regimens that may reduce its prevalence, cardiotoxicity will remain a concern for oncologists.

1.8 Recent studies have demonstrated the effectiveness of angiotensin-converting enzyme (ACE) inhibitors and beta blockers (β-blockers) in preventing anthracycline-induced cardiotoxicity.[13, 14] The majority of patients who develop trastuzumab-induced cardiotoxicity respond to standard treatment for chronic heart failure, which usually consists of diuretics, ACE inhibitors, β-blockers, cardiac glycosides and other inotropic agents.[2, 3] Optimal treatment of these patients includes identification of individuals at risk for and the prevention of cardiotoxicity, as well as early diagnosis and effective treatment of cardiotoxic changes.

1.9 This is a randomized, phase II placebo-controlled trial evaluating the effects of an ACE inhibitor (lisinopril) and a β-blocker Coreg CR® on cardiotoxicity in patients with breast cancer who are receiving adjuvant trastuzumab. If we can demonstrate that the use of an ACE inhibitor or a β-blocker can reduce the degree of trastuzumab-induced cardiotoxicity, it is hoped that patients will receive complete and uninterrupted therapy for breast cancer.

2.0 Background and Significance

2.1 The clinical significance of cardiotoxicity associated with trastuzumab is acknowledged as a serious concern within the oncology community. While a recent review reported the incidence of trastuzumab-induced cardiotoxicity to range from 6.5% to 34%,[2] large adjuvant trastuzumab trials (NSABP B-31, BCIRG 006, HERA, NCCTG N9831. FinHER) report the incidence to range from 0-17%.[15] The variation in incidence within studies is a result of inconsistent definitions and measurements of cardiotoxicity. It also depends on whether trastuzumab was used in a treatment or adjuvant setting; with higher incidence in patients receiving concurrent anthracycline and cyclophosphamide (AC). Based on these past studies and anecdotal clinical experience, a conservative incidence estimate of cardiotoxicity in our study population is approximately 15%.

2.2 To further assess trastuzumab-induced cardiotoxicities, the study co-chair (Dr. Guglin, Cardiologist) conducted a retrospective study at the H. Lee SunCoast Cancer Center in Tampa, Florida in patients receiving trastuzumab therapy for breast cancer in two settings (adjuvant n = 118; metastatic n = 38).[2] Patients in the adjuvant group receiving concomitant cardiac medications, including ACE inhibitors, angiotensin receptor blockers, statins, and β-blockers, were more likely to receive uninterrupted trastuzumab therapy ($p = 0.0335$), had less change in ejection fraction ($p = .0083$), and had fewer symptoms of heart failure ($p = 0.0083$). Adjuvant patients who were receiving these medications for hypertension alone had significantly less cardiotoxicity ($p = .0063$), less change in ejection fraction ($p = 0.0466$), and fewer symptoms of heart failure ($p= .0466$). This was less evident in patients with one or more co-morbidities aside from hypertension alone ($p = 0.0915$). In the adjuvant group, cardiotoxicity was observed in one-third of patients (n=39) evaluated. Seventeen patients (14.4%) demonstrated a decrease in ejection fraction to < 50%. Of these, only seven patients exhibited signs and symptoms of heart failure. Nineteen patients (16.1%) exhibited a decline in ejection fraction by ≥ 10% during trastuzumab therapy; however, none of these patients were symptomatic. Three patients had signs and symptoms heart failure in the presence of normal systolic function. Data from the metastatic group were less consistent. Of the 38 patients, 34.2% developed cardiotoxicities. Two of the patients initiated trastuzumab with a baseline EF of 48% and 30%.

2.3 The exact mechanism of trastuzumab-induced cardiotoxicity has yet to be elucidated. Several hypotheses have been proposed, including; inhibition of HER2 signaling in cardiac tissues, drug-drug interactions, an induction of immune mediated destruction of cardiomyocytes, and indirect consequences of trastuzumab-induced affects outside of the heart.[16-18] In a recent study by Grazette *et. al*., cultures of neonatal rat ventricular myocytes were exposed to anti-erbB2 (HER2) antibody.[19] There was a time-dependent increase in mitochondrial translocation and oligomerization of Bcl-associated protein, as indicated by 1,6-bismaleimidohexane cross linking. This process was associated with cytochrome C release and caspase activation. These alterations induced mitochondrial dysfunction, a loss of mitochondrial membrane potential, a 35% decline in adenosine triphosphate levels, and a loss of redox capacity. Anti-erbB2 activates the mitochondrial apoptosis pathway through a modulation of Bcl-xL and -xS, which was previously not described, causing impairment of mitochondrial function and integrity, and disruption of cellular energetics. Evidence also supports a direct cardiotoxic effect of HER2 blockade. Mice were generated with ventricular-restricted knockout of the HER2 gene.[17] These mice developed signs of a dilated cardiomyopathy, and their cardiomyocytes showed enhanced susceptibility to anthracycline-induced cell death. Thereby concluding that the signaling

cascade associated with HER2 in cardiomyocytes is essential for the prevention of dilated cardiomyopathy. This data provides evidence that the cardiotoxicity induced from exposure to trastuzumab is presumably due to its direct effects on the HER2 receptor.

2.4 There are strong indicators from existing literature and in related topics that suggests how ACE inhibitors and β-blockers might effectively reduce trastuzumab-induced cardiotoxicity.

2.5 Angiotensin Converting Enzyme (ACE) Inhibitors:

2.5.1 Angiotensin converting enzyme (ACE) inhibitors are a standard therapy for heart failure (HF) and asymptomatic left ventricular (LV) systolic dysfunction, regardless of etiology.[20] Multiple, large, prospective, randomized trials have consistently demonstrated a significant reduction in mortality and morbidity after therapy with ACE inhibitors.[21, 22] Further, the use of ACE inhibitors in the treatment of trastuzumab-induced cardiotoxicity was observed in the retrospective data collected by the study co-chair with promising results.[2] The exact mechanism of action in this treatment setting is not clearly understood, but several explanations have been suggested. The primary effect includes the limiting of oxidative stress, largely mediated through angiotensin II suppression.[23] In addition to interrupting the renin-angiotensin system, ACE inhibitors also enhance the action of kinins and augments kinin-mediated prostaglandin production.[24]

2.5.2 ACE inhibitors are an important class of agents that have multiple benefits in the treatment, as well as prevention, of heart failure in susceptible populations. The benefits are a class effect, as the same benefits have been demonstrated in many agents of this class. We chose lisinopril for this study because it has been shown to be superior to alternative ACE inhibitors in this regard.[25, 26]

2.5.3 The efficacy of ACE inhibitors in patients with asymptomatic LV dysfunction was demonstrated in the SOLVD[27] prevention and the SAVE[22] trials. The Studies of Left Ventricular Dysfunction (SOLVD) prevention trial included 4,228 patients with asymptomatic LV dysfunction with an LVEF ≤ 35%. The combined incidence of symptomatic HF or cardiovascular death was reduced by enalapril (30% versus 39% for placebo) and the risk reduction of 29% (95% CI 21% to 36 %, $p < 0.001$) was demonstrated with a mean follow-up of just over three years. In the XSOLVD, extension of the SOLVD prevention trial, there were significant reductions in all-cause mortality (51% versus 56% for placebo, $p = 0.001$) and cardiovascular mortality (37% versus 42% for placebo, $p = 0.0008$) at 11 years.[21]

2.5.4 The Survival and Ventricular Enlargement (SAVE) trial demonstrated that when administered 3 to 16 days after acute myocardial infarction in select patients, captopril (an ACE inhibitor) led to a reduction in risk of 21% for death from cardiovascular causes (95% confidence interval, 5% to 35%; $p = 0.014$). It also led to a 37% risk reduction for the development of severe HF (95% confidence interval, 20% to 50%; $p < 0.001$).[22]

2.5.5 The analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial suggests that 10 mg daily ramipril therapy may reduce the risk of developing HF in high-risk patients without LV dysfunction.[28] Two prospectively defined endpoints (HF death and HF hospitalization) were combined with two post hoc endpoints (HF leading to open label ACE inhibitor use or development of signs and symptoms of HF). Ramipril significantly reduced the event rate from 11.5% to 9.0% (RR 0.77, 95% CI 0.68 to 0.87, $p < 0.0001$).

2.5.6 Studies have evaluated the effect of ACE inhibitors in anthracycline induced-cardiotoxicity. The value of treatment with ACE inhibitors was demonstrated in a prospective series of patients who were being monitored for evidence of LV dysfunction while on epirubicin for metastatic breast cancer.[29] In contrast, there was only one such response among 33 cases treated with a digitalis preparation

plus a diuretic. Seven of eight (88%) patients treated with an ACE inhibitor had a sustained increase in LVEF of ≥ 15% as compared to one of 33 (8%) in those who were not treated with an ACE inhibitor ($p < 0.001$). The patients with decreased cardiac function did not spontaneously recover during the observation period. Cardiac function could only be reversed by treatment with ACE inhibitors for several months. Three patients in this study stopped ACE inhibition therapy after years of stabilized cardiac function, after which all three experienced a deterioration of cardiac function. Sixty additional patients with severe HF from anthracyclines have since been successfully treated with ACE inhibition, with a remarkably long-lasting recovery evaluated clinically and by LVEF determination.[29]

2.5.7 The potential protective effect of ACE inhibitors for preventing the development of left ventricular dysfunction in response to chemotherapy has since been evaluated. Cardinale, *et. al*., report a randomized trial of patients after high-dose chemotherapy.[13] One hundred fourteen adult patients who had elevated troponin-I soon after high-dose chemotherapy were randomized to enalapril (target of 20 mg/day) or open-label control, with treatment initiation delayed until one month after chemotherapy and continued for one year. The results were impressive; 43% of the control and 0% in the enalapril group had a more than 10% drop in LVEF ($p < 0.001$), and clinical cardiac events were likewise nearly eliminated with enalapril, from 30 events in the control population to one event in the enalapril group ($p < 0.001$). This was primarily attributable to reductions in heart failure and arrhythmias. There were some weaknesses in the trial such as the trial was a single-center, open-label trial, the diversity of cancer diagnoses and chemotherapy regimens included in the study, and possible bias because of the lack of pre-specified and clearly defined clinical endpoints.

2.5.8 A study conducted by Silber *et. al*., evaluated the use of enalapril in 135 pediatric cases who already had one anthracycline-induced cardiac abnormality.[30] Treatment with enalapril demonstrated that during the first year of treatment, the rate of reduction in LV end-systolic wall stress was greater in the enalapril group than in the placebo group (-8.59 versus 1.85 g/cm^2; $p = 0.033$). This difference was maintained over the study period, resulting in a 9% reduction in estimated LV end-systolic wall stress by year five in the enalapril group. There was no change in the functional capacity.

2.5.9 An animal study conducted by Boucek *et. al*., demonstrated that treatment with an ACE inhibitor, lisinopril, reduces the time-dependent effects of an anthracycline on cardiac gene expression and myocellular apoptosis.[31] Rabbits were randomized to one of four treatment groups; saline (control) +/- lisinopril or anthracycline +/- lisinopril. After a 10-week intervention, histopathology demonstrated a reduced number of cardiomyocytes relative to interstitial cells in the LV of the anthracycline treated group compared to the control and the anthracycline + lisinopril groups. Gene expression of the pro-atrial naturetic peptide (ANP) increased approximately 12-fold ($n = 10$; $p < 0.05$) in the LV of the anthracycline treated group compared to the control and anthracycline + lisinopril groups.

2.6 Beta Blockers (β-Blockers):

2.6.1 The increase of sympathetic activity in HF may have deleterious effects. A number of trials have shown that blockade of β-adrenergic receptors leads to symptomatic improvement and enhanced survival in many patients with HF.[32] The use of β-blockers has consistently been associated with a 30% reduction in mortality and a 40% reduction in hospitalization in patients with HF.[33-37] As a result of this compelling evidence, β-blockers are now considered an important component of standard therapy in HF. β-blockers primarily act to inhibit the

adverse effects of the sympathetic nervous systems in patients with HF.[24] β-Blockers also reduce cardiotoxicities by preventing free radical mediated lipid oxidation and intracellular calcium overload.

2.6.2 The MERIT-HF trial[38] and the RESOLVD pilot study[39] demonstrated that the use of sustained release metoprolol has a mortality benefit. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), 3,991 patients with class II to IV HF and an LVEF ≤ 40% who were receiving any combination of diuretic and ACE inhibitor, were randomly assigned to therapy with extended-release metoprolol, beginning with 12.5 or 25 mg daily and titrated up to 200 mg/day, or placebo. The study was terminated early when it showed a 34% relative risk reduction in all-cause mortality at 12 months (7.2% versus 11% for placebo, p = 0.0062). There was also a reduction in cardiovascular deaths in the metoprolol group, (6.4% versus 10.1%; RR 0.62, 95% CI 0.50-0.78, p = 0.00003) and deaths from aggravated HF (1.5% versus 2.9%; RR 0.51, 95% CI 0.33-0.79, p = 0.0023). The total risk reduction of deaths related to cardiovascular and aggravated HF was 38% and 49%, respectively. While the proportion of sudden cardiac deaths decreased, when grouped by the New York Heart Association (NYHA) functional class, a greater proportion of deaths were observed in subjects who exhibited increasing severity of HF. The study agent was well tolerated.

2.6.3 In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot trial (RESOLVD) study metoprolol CR showed a significant improvement in measures of LV function with an attenuation in the increase in LV end-diastolic volume (+6±61 mL versus +23±65 mL, p = 0.01) and LV end-systolic volume (-2±51 mL versus +19±55 mL, p < 0.001) after 24 weeks of therapy.[39] LVEF was unchanged (-0.05%) in the placebo group but increased by 2.4% in the metoprolol CR–treated patients (p = 0.001). There were fewer deaths in the group receiving β-blockers (3.4% versus 8.1%, not significant).

2.6.4 Animal studies have suggested that the β-blocker, Coreg CR®, may protect against the cardiotoxicity of anthracyclines.[40] Further support for this possibility comes from a small randomized trial of 50 patients undergoing anthracycline chemotherapy for a variety of malignancies.[14] Patients were randomly assigned to carvedilol, 12.5 mg daily, or placebo. All patients underwent echocardiography prior to and six months after chemotherapy. Among the patients assigned to carvedilol, there was no change in the mean LVEF after chemotherapy (70% before and after therapy). In contrast, patients assigned to placebo had a statistically significant absolute reduction in LVEF by 17% (69 to 52%, p < 0.001). The incidence of cardiotoxicity observed was unusually large (20%) in the control group as compared to 4% in the treatment group, which may be from the high doses of anthracycline used in the study for both groups. However the standard deviation of the doses was not reported and it could greatly affect the significance of the study.

2.6.5 Several studies have been completed comparing the efficacy of various β-blockers.[41-47] Use of carvedilol is associated with a greater improvement of LVEF, longer estimated median survival, a reduction in the total number of hospitalizations, and hospitalizations for cardiovascular reasons and those for HF.

2.6.6 Coreg CR® is a nonselective beta-adrenergic blocking agent approved to treat essential hypertension, impaired left ventricular function related to acute myocardial infarction, and heart failure. Coreg CR® is indicated for the treatment of mild-to-severe congestive heart failure of ischemic or cardiomyopathic origin. It has been shown to reduce symptoms and clinical progression of heart failure[45, 48] and to improve left ventricular function.[49] The

mechanism by which Coreg CR® produces a beneficial effect in patients with congestive heart failure and left ventricular dysfunction following an acute myocardial infarction is not known (Prod Info Coreg CR® (carvedilol phosphate, extended-release) oral capsules, 2006).

2.6.7 In a retrospective study, M. Guglin *et al*. demonstrated that being on cardiac medications thought to prevent cardiac remodeling (ACE-inhibitors, angiotensin receptor blockers, statins, beta-blockers) was possibly associated with less cardiomyopathy (RR=0.69; p 0.092) and less HF symptoms (RR=0.38; p 0.086) in adjuvant patients with one or more cardiovascular comorbidities. The use of these medications was significantly associated with less cardiomyopathy (RR=0.35; p = 0.0063), less EF drop < 50% (RR=0.13; p 0.0083), less heart failure symptoms (RR=0.13; p = 0.0083), and less trastuzumab discontinuation (RR=0.25; p = 0.034) in adjuvant patients with hypertension alone.[2]

2.7 Using the same strategies that have demonstrated promising results in anthracycline-induced cardiotoxicity, this study will evaluate and compare the effect of an ACE inhibitor, lisinopril, and a β-blocker, Coreg CR®, on trastuzumab-induced cardiotoxicity in women with breast cancer. Participants will start study agent at the same time as they start trastuzumab treatment and continue on study agent for 52 weeks (or end of trastuzumab if it is discontinued prior to week 52). The efficacy of ACE inhibitors and β-blockers in the treatment of chemotherapy-induced cardiotoxicity, specifically LVEF, are equivalent. Therefore, a study to compare the efficacy of these agents is warranted. Should either intervention prove effective, fewer patients will experience the deleterious effects of cardiotoxicity; and, more patients will be able to complete optimal therapy for breast cancer treatment.

2.8 Measurement of Left Ventricular Ejection Fraction (LVEF):

2.8.1 Multiple Gated Acquisition (MUGA) scans and echocardiograms (ECHO) are routinely used to monitor and assess cardiac function and LVEF of patients with cancer who are treated with cardiotoxic-inducing chemotherapeutic agents. LVEF provides an overall assessment of cardiac function, and is a measure of the proportion of blood that is expelled from the ventricle with each heartbeat.

2.8.2 A MUGA is a noninvasive assessment that produces a moving image of the heart, which can accurately assess the activity of the left ventricle and provides a reproducible measure of LVEF. The MUGA scan involves the introduction of a radioactive marker into the bloodstream, which can be scanned to determine the circulation dynamics of the marker and blood flow.

2.8.3 An ECHO is a noninvasive ultrasound assessment of sound waves to examine the structure and motion of the heart. It provides a real-time image of the heart and can produce accurate assessments of the velocity of the blood and cardiac tissues, as well as calculate cardiac output and EF.

10/08/2010

2.8.4 Ejection fraction will be assessed at baseline, every 3 months (+/- 2 weeks) through study week 52, (or until the end of trastuzumab, if discontinued prior to week 52) and at study month 18 and 24 (or 6 and 12 months after the last dose of trastuzumab, if it was discontinued prior to study week 52).

6/3/2011

2.9 Biomarkers of cardiotoxicity will be evaluated in an effort to identify patients at risk for cardiomyopathy prior to development of cardiac symptoms and before the drop of ejection fraction (EF) can be appreciated by echocardiography or MUGA.

<u>Brain natriuretic peptide (BNP)</u>

2.9.1 Brain natriuretic peptide (BNP) concentration is a measurement of the amount of BNP hormone in the blood and is an indicator of heart function. Normal levels of BNP are low (0-99 pg/mL) and the concentration increases as a consequence of

HF severity (≥ 100 pg/mL). The concentration of BNP is also used to measure the response to treatment for HF. Monitoring BNP has been demonstrated to measure changes of heart function during and after trastuzumab treatment.[50, 51] The concentration of BNP will be assessed at baseline and compared every 3 months (+/- 2 weeks) through study week 52 throughout the duration of the study. An additional BNP assessment will be completed at the six and 12 month post treatment visit and compared to previous concentrations.

2.9.2 Biomarkers like natriuretic peptides have been widely used for monitoring of heart failure of any etiology. Natriuretic peptides levels are more sensitive than symptoms and become elevated even in asymptomatic left ventricular dysfunction. Specifically, brain natriuretic peptide (BNP) is produced primarily in cardiac atria and ventricles. Its levels rise in response to stretch of ventricular myocytes or increases in wall tension and reflect the severity of heart failure. [52, 53]

2.9.3 In the setting of chemotherapy-induced cardiomyopathy, early detection of these markers may identify "high-risk" group which can benefit from close observation.[54] During the evolution of doxorubicin-induced left ventricular dysfunction the secretion of natriuretic peptides is more closely associated with the impairment of left ventricular diastolic filling than with the deterioration of left ventricular systolic function.[55]

2.9.4 Brain natriuretic peptide and not NT-proBNP was chosen to be measured for this study because the difference between the two is subtle, and the use of BNP is more common.[56] The objective for measuring BNP is to allow for early detection of LVEF in subjects receiving trastuzumab therapy.

6/3/2011

Troponin I (TnI)

2.9.5 Cardiac troponin I is a well established early marker of myocardial injury, including injury related to high-dose chemotherapy.[57] Even minimal elevations of TnI is predictive of late changes in ejection fraction;[58] and, increases soon after high-dose chemotherapy is considered a strong predictor of poor cardiac outcome.[13] Most recently the utility of TnI as a predictor of unforeseeable and refractory cardiotoxicity in patients treated with trastuzumab for breast cancer has been reported.[59]

2.9.6 In a single center study by Cardinale et al.[59] evaluated TnI before and after each course of trastuzumab as adjuvant therapy or treatment of metastatic breast cancer. Only 5% of patients without TnI elevation in the course of treatment developed cardiomyopathy. On the other hand, 62% of those with elevated TnI later demonstrated reduced left ventricular ejection fractions. Moreover, there was less recovery of cardiac function in those patients who had elevated TnI, the strongest predictor of cardiotoxicity reported in this study.

2.9.7 We believe this prospective randomized controlled clinical trial presents an ideal opportunity to compare the specificity, sensitivity, positive and negative predictive value of both BNP and TnI in patients with breast cancer who are receiving trastuzumab. If TnI is a more sensitive marker of trastuzumab-induced cardiomyopathy, the practice of screening with cumbersome and costly cardiac imaging every three months could change to selectively imaging only those patients in whom a screening TnI was abnormal.

08/31/2012

2.9.8 Given the large difference in cardiac toxicity between anthracycline- and non-anthracycline-containing regimens,[60] the protocol seeks to approximate the sample size of each regimen to ensure that the power of the study wlll be sufficient.

6/3/2011 2.10 Non-fasting comprehensive metabolic panel (CMP)

2.10.1 For safety monitoring purposes, a comprehensive metabolic panel (CMP) will be collected at each follow-up visit during active therapy monitor renal and liver function for potential adverse reactions

2.11 Quality of Life:

2.11.1 Cardiotoxicity is often associated with adverse symptoms, including fatigue, coughing spells, and shortness of breath. Therefore, an assessment of health related quality of life (HRQL) will be measured as a secondary objective to determine whether the hypothesized reduction of cardiotoxicity in patients randomized to lisinopril or Coreg CR® correlates with HRQL. An improvement in HRQL or at least stable HRQL should accompany prevention of cardiotoxicity. Measurement of HRQL can also be correlated to the possible onset of LVEF changes measured by ECHO or MUGA and/or the change in troponin I and/or BNP.

6/3/2011

2.11.2 The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-30) will be used to assess quality of life at baseline, at study week 52 (or at the end of trastuzumab therapy, if it is given for less than one year), and at study months 18 and 24 (or 6 and 12 months after the last dose of trastuzumab, if given for less than one year). The EORTC QLQ-C30 is a validated, multidimensional, self-administered questionnaire developed to assess the quality of life in cancer patients across a range of cultural settings.[60-62] It will be used to assess quality of life as a secondary endpoint. The questionnaire consists of 30 questions that pertain to the patient and their health. Questions are answered using a scale of 1 to 4, with 1 being “not at all” and 4 being “very much”, except for questions 29 and 30, which are answered using a 7 point scale ranging from 1 “very poor” to 7 “excellent”. Approximately 10 to 15 minutes are required to complete the questionnaire.

2.12 Gender and Ethnicity:

08/31/2012 2.12.1 Entry into this study is open to males and females of all ethnic backgrounds. SunCoast CCOP Research Base members estimate that approximately 20% of accrual to CCOP Research Base studies in general will be patients with minority backgrounds. A similar distribution is anticipated for this protocol.

3.0 Objectives:

3.1 The primary objective of this study is to determine if administration of lisinopril or Coreg CR®, compared to placebo, will reduce the incidence of trastuzumab-induced cardiotoxicity, as measured by LVEF, in patients receiving adjuvant, or neoadjuvant, therapy for HER2 positive breast cancer.

3.2 The secondary objectives of this study are to determine:

3.2.1 determine whether subjects randomized to active agent have fewer interruptions in trastuzumab therapy due to cardiomyopathy

08/31/2012 3.2.2 determine whether the treatment effect is consistent in anthracycline and non-anthracycline patient cohorts

3.2.3 compare changes in HRQL among the treatment groups during the study intervention

3.2.4 evaluate the long term effects on the prevention of cardiomyopathy and impact on HRQL for either or both study agents

6/3/2011 3.2.5 compare the predictive value of troponin I and BNP in the identification of trastuzumab-induced cardiotoxicity

4.0 Regulatory, Subject Selection (§4.7), Registration & Randomization

11/19/2010

4.1 CTSU sites should refer to Appendix VIII, CTSU Logistics, for CTSU registration and randomization procedures.

Regulatory:

4.2 Send the Intent to Participate form (available on the SunCoast CCOP Research Base website (http://www.SunCoastccop.org) by fax [**813-910-5998**] or email (ccop@epi.usf.edu) to the SunCoast CCOP Research Base Operations Center at the time of submission to IRB to begin site set-up needed to activate each institution.

4.3 Forms will be available through the SunCoast CCOP Research Base website (http://www.SunCoastccop.org) via PDF to download and printout as a Master forms packet

4.4 The sample informed consent contains all of the NCI required elements and is available on the SunCoast CCOP Research Base website (http://www.SunCoastccop.org) as a Word document to download and add the local IRB language.

4.5 When preparing the consent for local IRB review, be sure all information in the sample informed consent is included. Additional information may be added, but information may not be deleted or changed significantly. Contact the SunCoast CCOP Research Base Operations Center for questions (email ccop@epi.usf.edu or telephone **1-800-909-1242**).

4.6 Modifications and inclusion to site-specific language made to the informed consent must be approved by the SunCoast CCOP Research Base Operations Center. The Word version of the site-specific informed consent should be emailed to ccop@epi.usf.edu at the time of IRB submission.

4.7 Prior to enrollment of patients, Affiliation regulatory paperwork for each institution must be on file with the SunCoast CCOP Research Base Operations Center, which include:

4.7.1 A signed letter of collaboration or affiliation agreement.

10/08/2010

4.7.2 HHS Form 1572 and CV for Responsible Investigator.

4.7.3 HHS Form 1572 for all participating physicians who will receive drug shipment, noting the address for drug shipment

4.7.4 SCUSF CCOP Research Base Financial Disclosure / Conflict of Interest Form for Responsible Investigator

4.7.5 The SunCoast CCOP Research Base Operations Center requires evidence of training on the Protection of Human Research Subjects.

4.7.6 List of all enrolling centers covered under the IRB review process with shipping address, Responsible Investigator and Primary contact telephone, fax and email information for each enrolling center

4.7.7 FWA and IRB numbers for all enrolling centers

10/08/2010

4.7.8 Medication Order Form – Site Stock; have the investigator responsible for this study sign the form and return to the SunCoast CCOP Research Base Operations Center by fax (813-910-5998) or email (ccop@epi.usf.edu). The Operations Center will release to the investigational pharmacy at the time of activation so site stock can be shipped at the time each institution enrolls their first patient.

4.7.9 Send the current IRB approval (HHS Form 310 or IRB approval letter) by email (ccop@epi.usf.edu) or fax (**813-910-5998**) to begin site activation.

10/08/2010

4.7.10 At receipt of the IRB approval and activation processes completed, the SunCoast CCOP Research Base Operations Center will release a “Welcome Letter”

providing site identification code, any study-specific materials and/or study agent at this time.

Subject Selection:

4.8 Inclusion Criteria:

08/31/2012 4.8.1 Males and Females ≥ 18 years old diagnosed with HER2 positive breast cancer

10/08/2010 4.8.2 Scheduled to receive neoadjuvant or adjuvant trastuzumab (Herceptin®) therapy (anthracycline-containing regimens are permitted). Patients receiving 11/19/2010 Herceptin® with their chemotherapy are permitted for eligibility work-up. Taxanes are permitted. Trastuzumab (Herceptin®) therapy may be given with or after primary chemotherapy. Pertuzumab may be used in conjunction with 08/31/2012 trastuzumab.

4.8.3 Left Ventricular Ejection Fraction (LVEF) ≥ 50% by MUGA scan or echocardiogram

08/31/2012 4.8.4 Adequate renal function for administration of trastuzumab-containing chemotherapy regimen.

4.8.5 Sitting systolic blood pressure of > 90 mm Hg

4.8.6 Pulse ≥ 60 beats/minute

4.8.7 Not pregnant or breastfeeding

08/31/2012 4.8.7.1 Female patients of childbearing potential, who are sexually active, must have a negative pregnancy test before starting the study

4.8.8 Both men and women must be willing to use effective contraception during the study. Teratogenicity is documented for both active study agents

4.8.9 Able to swallow capsules

4.8.10 Able and willing to give informed consent

4.8.11 Signed HIPAA compliant research authorization (or equivalent for international sites) to release Personal Health Information to the SunCoast CCOP Research Base.

4.9 Exclusion criteria:

08/31/2012 4.9.1 Patients with metastatic disease

10/08/2010 4.9.2 Prior treatment with trastuzumab or anthracyclines prior to this chemotherapy regimen

08/31/2012 4.9.3 Current treatment with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), such as losartan, β-blockers or digoxin

4.9.4 Known cardiac history: heart failure, myocardial infarction, radiation-induced cardiac dysfunction

4.9.5 Known allergy to either ACE inhibitors or β-blockers

4.9.6 History of bronchial asthma or related bronchospastic conditions

4.9.7 Hereditary or idiopathic angioedema

4.9.8 History of severe hypersensitivity reactions to drugs or other causes, i.e. bee stings

4.9.9 This protocol does not exclude patients who are participating on other investigational studies. Refer to the local IRB guidelines.

Registration and Randomization:

4.10 Patients must not start protocol treatment prior to registration.

4.11 Treatment should start within ten (10) working days after registration; however, there may be unanticipated and justifiable delays.

09/24/2010

4.11.1 For unanticipated delays contact the SunCoast CCOP Research Base Operations Center (by email ccop@epi.usf.edu or telephone **1-800-909-1242**) and document the reason for delay in the participant's research chart for audit purposes. Each unanticipated delay will be evaluated for study continuation.

4.11.2 If a participant does not receive any assigned protocol treatment, the baseline (On Study Form – see Appendix III) and off-study data (Off Study Form – see Appendix III) will still be collected and must be submitted according to the Records to be Kept section (see Section 9.0). Document the reason for not starting protocol treatment on the Off Study Form.

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4.11.3 Screening workup can be completed within 14 days before registration
4.11.3.1 Except LVEF which can be done ≤ 6 weeks before enrollment

Eligibility Verification:

4.12 Study candidates must meet all of the eligibility requirements listed in Section 4.0.

4.13 After obtaining informed consent, patients will be registered and randomized. **CTSU sites must refer to the CTSU Logistical Appendix VIII for patient enrollment instructions.** All other site will register by calling the SunCoast CCOP Research Base Interactive Voice Response (IVR) system at (**1-866-835-6793**) (Appendix II). The following information will be requested:

4.13.1 SunCoast CCOP Research Base study number **0806**

4.13.2 Site identification/institution code (unique to each institution)

4.13.3 First letter of the subject's first name (see numeric code Appendix II)

4.13.4 First letter of the subject's last name (see numeric code Appendix II)

4.13.5 Subject date of birth (MM/DD/YYYY)

4.13.6 Does the subject live in the United States?

4.13.7 (if yes) Subject five-digit Zip Code (XXXXX).

4.13.8 (if no) Country Code __ __ (see CTEP Country Code Appendix II)

4.13.9 Does the subject meet all eligibility requirements?

4.13.10 Has the patient signed a HIPAA compliant authorization to release of private health information (PHI), or equivalent for international sites, to the SunCoast CCOP Research Base Operations Center?

4.13.11 Did the subject sign the informed consent?

4.14 The SunCoast CCOP Research Base Operations Center Interactive Voice Response (IVR) telephone system will assign a unique study identification number (sequence number) and treatment randomization for each patient entered on study.

4.15 **When the first patient is being enrolled by an institution:** Fax the Medication Order Form (Appendix III) to the investigational pharmacy at **1-866-992-9966.** Order forms will be processed within one week for shipping via express courier to the site.

08/31/2012

Calling for Study Agent Refills or Stop Study Agent:

10/08/2010

4.15.1 Patients must complete the LVEF cardiac monitoring criteria prior to requesting refill study agent

4.15.2 Call through the IVR system **1-866-835-6793**

4.15.3 Use the REFILL REQUEST IVR worksheet (see Appendix II)

You will be asked:

4.15.4 Study Number: 0806

4.15.5 Site identification/institution code (unique to each institution)

4.15.6 Has the subject previously been enrolled? If Yes:

4.15.7 Subject Sequence Number:

IVR system will confirm:

4.15.8 First letter of the subject's first name (see numeric code Appendix II)

4.15.9 First letter of the subject's last name (see numeric code Appendix II)

4.15.10 Subject date of birth (MM/DD/YYYY)

You will need to answer:

08/31/2012

4.15.11 For which study visit are you requesting a refill or stop study agent?
- 4.15.11.1 Press "1" for 3-month study agent follow-up
- 4.15.11.2 Press "2" for 6-month study agent follow-up
- 4.15.11.3 Press "3" for 9-month study agent follow-up

4.15.12 Date of LVEF (MUGA / echocardiogram) assessment: MM/DD/YYYY

4.15.13 Is the patient eligible to continue on study per protocol section 7.0?

IVR system will respond:

4.15.14 The patient should continue taking study agent

OR: IVR system will respond

4.15.15 The patient should stop taking study agent

4.15.16 Discontinue Study Agent

4.15.17 Complete assessments per the study plan table

4.15.18 Patient moves into Follow-up for 12 months

5.0 Study Agent Information (FDA IND 102825 exemption granted)

Lisinopril:

Product Description

5.1 Lisinopril is an oral long acting angiotensin converting enzyme inhibitor, which inhibits the conversion of angiotensin I to angiotensin II.

Manufacturer:

5.2 Lupin Limited

Supplier:

5.3 Carter's Park and King Pharmacy, Inc.

Clinical Pharmacology:

5.4 A copy of the package insert is included in Appendix IV for reference.

Dose selection:

5.5 Lisinopril10 mg will be administered once daily. This dosage was based on the commonly used dose for asymptomatic left ventricular systolic dysfunction.

Pharmacokinetics:

5.6 Following oral administration, the concentration of lisinopril peaks within 7 hours. Absorption of lisinopril is approximately 25% (6-60%), of which the consumption of food is not affected.

5.7 Lisinopril is not metabolized and is excreted in the feces (69%) and urine (29%) unchanged.

5.8 The effective half-life of accumulation of lisinopril is 12 hours after multiple dosing.

Storage and Stability:

5.9 Store at controlled room temperature 20-25°C (68-77°F). Protect from moisture, freezing and excessive heat.

5.10 Dispense in a tight, light resistant container.

Specifications:

5.11 Lisinopril is FDA approved for the treatment of adult acute myocardial infarction, heart failure and hypertension.

5.12 See product information (Appendix IV).

Known toxicity/dose limiting toxicity:

5.13 Cardiovascular effects: Angina, chest pain, orthostatic effects, palpitations, peripheral edema, tachycardia, arrhythmias, vasculitis.

5.14 Dermatologic effects: Angioedema, rash, flushing, urticaria, diaphoresis, pruritis, toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), photosensitivity, psoriasis.

5.15 Endocrine/metabolic effects: Acute intermittent prophyria, body temperature above normal, gynecomastia, hyperglycemia, hyperkalemia, hyperuricemia, hypoglycemia, hyponatremia, abnormal lipids.

5.16 Gastrointestinal effects: Drug-induced acute pancreatitis, diarrhea, nausea, vomiting, dyspepsia, abdominal pain, anorexia, constipation, dry mouth, taste disturbances, flatulence, gastrointestinal ulcer, intestinal angioedema.

5.17 Hematologic effects: Pancytopenia, eosinophilia, thrombocytopenia, reduced hemoglobin and hematocrit, hemolytic anemia, Schonlein-Henoch Purpura.

5.18 Hepatic effects: Hepatoxicity, abnormal liver enzymes.

5.19 Immunologic effects: Drug-induced neutropenia, immune hypersensitivity reaction, sarcoma, systemic lupus erythematosus (SLE)

5.20 Musculoskeletal effects: Arthralgia, articular gout, muscle cramps, back pain, joint pain, shoulder pain.

5.21 Neurologic effects: Dizziness, headache, asthenia, vertigo, lassitude, fatigue, insomnia, paraesthesias, stroke, nervousness, confusion, depression, somnolence. Ophthalmic effects: Blurred vision, diplopia, photophobia.

5.22 Otic effects: Tinnitus

5.23 Renal effects: Nephrotoxicity, urinary tract infections

5.24 Reproductive effects: Impotence in males, decreased libido

5.25 Respiratory effects: Cough, upper respiratory infections

5.26 Other: Angioedema of the head and neck, withdrawal signs/symptoms

5.27 Teratogenicity: Category C (1st trimester); Category D (2nd trimester); Category D (3rd trimester)

Contraindications, Drug Interactions and Precautions:

5.28 See package insert – Appendix IV.

Coreg CR® (carvedilol phosphate, extended-release):
Product Description:

5.29 Coreg CR® is a non-selective β-adrenergic blocking agent with α_1-blocking activity.

Manufacturer:

5.30 GlaxoSmithKline

Supplier:

5.31 Carter's Park and King Pharmacy, Inc.

Clinical Pharmacology:

5.32 A copy of the package insert is included in Appendix IV for reference.

Dose selection:

5.33 Coreg CR® 10 mg will be administered once daily. This dosage was based on the commonly used dose for asymptomatic left ventricular systolic dysfunction.

Pharmacokinetics:

5.34 Coreg CR® is readily absorbed following oral administration. Approximately 25-35% of the compound is absorbed, the concentration of which peaks after five hours. Consumption with food significantly improves absorption.

5.35 Less than two percent of Coreg CR® is excreted through the urine unchanged. Approximately 60% of Coreg CR® is excreted through feces.

5.36 The effective half-life of Coreg CR® is seven to ten hours.

Storage and Stability:

5.37 Store Coreg CR® at 25°C (77°F).

5.38 Dispense in a tight, light resistant container.

Specifications:

5.39 Coreg CR® is FDA approved for the treatment of adult acute myocardial infarction, heart failure and hypertension.

5.40 See product information (Appendix IV).

Known toxicity/ dose limiting toxicity:

5.41 Cardiovascular effects: Angina, atrioventricular block, bradyarrhythmnia, edema, hypotension, palpitations, peripheral edema, rebound hypertension, shock, syncope.

5.42 Dermatologic effects: Rash, pruritis, edema, photosensitivity, Stevens-Johnson Syndrome (SJS)

5.43 Endocrine/metabolic effects: Diabetes mellitus, disorder of glucose regulation, insulin resistance, hyperinsulinemia, hyperglycemia, abnormal lipids, hyperkalemia, weight gain.

5.44 Gastrointestinal effects: Diarrhea, nausea, vomiting

5.45 Hematologic effects: Reduced hemoglobin and hematocrit, thrombocytopenia

5.46 Hepatic effects: Hepatoxicity, abnormal liver enzymes

5.47 Immunologic effects: Immune hypersensitivity reaction

5.48 Musculoskeletal effects: Arthralgia

5.49 Neurologic effects: Cerebrovascular accident, dizziness, headache, insomnia, somnolence

5.50 Ophthalmic effects: Abnormal vision, blurred vision

5.51 Psychiatric effects: Fatigue

5.52 Renal effects: Kidney disease, microalbuminuria

5.53 Reproductive effects: Erectile dysfunction, impotence and Peyronie's disease in males, sexual dysfunction

5.54 Respiratory effects: Asthma with status asthmaticus, bronchospasm, dyspnea

5.55 Other: Withdrawal signs/symptoms

5.56 Teratogenicity: Category C (All trimesters)

Contraindications, Drug Interactions and Precautions:

5.57 See package insert – Appendix IV

Placebo:

Product Description:

5.58 The placebo capsule contains potato starch as filler. It will appear identical to lisinopril and Coreg CR®.

Supplier:

5.59 Carter's Park and King Pharmacy, Inc.

Storage and Stability:

5.60 Store at 25°C (77°F).

5.61 Dispense in a tight, light resistant container.

Specifications:

5.62 The supplier has certified that the placebo contains no active agent. The weight of the capsule, with contents, is equivalent to the active agent capsules.

Study Agent Procurement:

5.63 Study agents will be provided by the SunCoast CCOP Research Base Operations Center to enrolling centers at no cost to the patient or clinical center.

5.64 Patient-specific drug supply will be filled by Carter's Park and King Pharmacies with prescriptions from enrolling center using the Medication Order Form included in Appendix III Data Collection Forms.

10/08/2010

5.65 Disposition of Study Agent

5.65.1 Any study agent remaining after the participant completes active study agent (up to week #52) may be disposed on site according to local institutional guidelines.

Dosing and Administration:

5.66 Study agents will be blinded and indistinguishable by locking, over-encapsulation with potato starch as filler for weight equivalency. Patients who cannot swallow pills should not be enrolled, as capsules may not be opened.

10/08/2010 5.67 Begin study agent starting on the same day as trastuzumab therapy

5.67.1 Preventative agents (SCUSF 0806 Study agent) should be administered before the offending agent (Herceptin®) is introduced.

5.68 Administer 1 capsule by mouth once daily, instructing patient to take study agent around the same time each day, and to take it with food

5.69 The plan outlined in Section 8.0. “Toxicity Assessment and Adverse Event Reporting” will be utilized to inform the patient about adverse events and limit the exposure to lisinopril should a patient present with a serious adverse event

5.70 Participants will document the number of capsules taken, the time of administration and any side effects on the Study Medicine Daily Log (see Appendix III)

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6.0 Study Plan Tables

6.1 Study Requirements **WHILE RECEIVING STUDY AGENT and ADJUVANT TRASTUZUMAB** (See table 6.3 if neoadjuvant)

10/08/2010
11/19/2010
6/3/2011
08/31/2012

Study Requirements	Screen	Pre-Treatment	Tx follow up every 3 months X 3 (+/- 2 weeks)	Trastuzumab or study agent D/Cd before study week 52 (≤ 1 month since last LVEF)	Trastuzumab or study agent D/Cd before study week 52 (> 1 month since last LVEF)	Study Week 52
Signed informed consent/HIPAA form	X					
Measurement of left ventricular ejection fraction (LVEF)[1]	X[1, 2]		X[2]		X[2]	X[2]
History & physical (height and weight)	X		X		X	X
Eligibility form	X					
Registration / randomization	X					
On-study form		X				
Patient assessment form		X	X		X	X
Blood samples to LabCorp: • Non-fasting CMP • Troponin I • BNP		X[3] X[3] X[3, 4]	X X X[4]		X X X[4]	X X X[4]
QOL questionnaire (EORTC QLQ C-30)		X		X	X	X
Order study agent refills, using IVR			X			
Follow-up Form			X	X	X	X
Concomitant Medication Form		X	X	X	X	X
Study Medicine Daily Log		X[5]	X[5]	X	X	X
Adverse Events Form			X	X	X	X

[1] May be done within 6 weeks of study entry, using a MUGA scan (CMPT code 78472] **or** an ECHO [CMPT code 93306 without contrast]. The method of assessing LVEF must be same for the study duration, and be performed at the same institution as screening.

[2] Send de-identified copies of ECHO reports to the SunCoast CCOP Research Base.

[3] Draw and send pretreatment labs to LabCorp AFTER study registration and BEFORE starting study agent and Herceptin®

[4] Contrast material used for MUGA Scan may alter BNP results. Draw samples as long as possible after the MUGA scan (or before the MUGA if for a follow-up visit). If labs are drawn within 1 week after the MUGA, please list "contrast for MUGA" on the concomitant medication form.

[5] Distribute and instruct patients to start a new log each week. Logs are to be returned and reviewed at least every 3 months (if logs are returned more frequently, review and submit at that time). Review Study Medicine Daily Logs with patients and document any side effects on the Adverse Events Form. Study Medicine Daily Logs will be used as a measure of compliance.

** A patient-specific medication order form and a site stock medication order form must be submitted ONLY when the first patient at an institution is being enrolled. Study agent for all subsequent participants and all study refills will be dispensed from institution's site stock, which is replenished automatically**

08/31/2012 6.2 Study requirements **WHILE IN 12-MONTH FOLLOW-UP AFTER ADJUVANT TRASTUZUMAB**:

Study Requirements	Follow up every 3 months X 3 (+/- 2 weeks)			Completed 12-month FU (Off Study)
	Month 3 (phone)	Month 6 (clinic)	Month 9 (phone)	
Measurement of left ventricular ejection fraction (LVEF)[1]		X[2]		X[2]
History & physical (height and weight)		X		X
Blood samples to LabCorp: • Non-fasting CMP • Troponin I • BNP		X X X[3]		X X X[3]
QOL questionnaire (EORTC QLQ C-30)		X		X
Patient assessment form	X	X	X	X
Follow-up Form	X	X	X	X
Concomitant Medication Form	X	X	X	X
Adverse Events Form	As Needed			
Off-Study Form				X

[1] A MUGA scan (CMPT code 78472] **or** an ECHO [CMPT code 93306 without contrast] may be used. The method of assessing LVEF must be same for the study duration, and be performed at the same institution as screening.

[2] Send de-identified copies of ECHO reports to the SunCoast CCOP Research Base.

[3] Contrast material used for MUGA Scan may alter BNP results. Draw samples before the MUGA scan if possible. If labs are drawn within 1 week after the MUGA, please list “contrast for MUGA” on the concomitant medication form.

6.3 Study Requirements **WHILE RECEIVING STUDY AGENT and NEOADJUVANT TRASTUZUMAB**

11/19/2010
6/3/2011
08/31/2012

Study Requirements	Screen	Pre-Treatment	Prior to surgery	When resuming trastuzumab	Tx follow up every 3 mo X 3 (+/- 2 weeks)	Study agent or trastuzumab D/Cd before 52nd dose of TZB (≤ 1 month since last LVEF)	Study agent or trastuzumab D/Cd before 52nd dose of TZB (≤ 1 month since last LVEF)	Post dose 52 of TZB
Signed informed consent/HIPAA form	X							
Measurement of left ventricular ejection fraction (LVEF)[1]	X[1, 2]		X[2]		X[2]		X[2]	X[2]
History & physical (ht and wt)	X		X		X		X	X
Eligibility form	X							
Registration / randomization	X							
On-study form		X						
Patient assessment form		X	X		X		X	X
Blood samples to LabCorp: • Non-fasting CMP • Troponin I • BNP		 X[3] X[3] X[3, 4]	 X X X[4]		 X X X[4]		 X X X[4]	 X X X[4]
EORTC QLQ C-30		X				X	X	X
Order study agent refills, using IVR			X	X	X			
Follow-up Form			X		X	X	X	X
Concomitant Medication Form		X	X	X	X	X	X	X
Study Medicine Daily Log		X[5]	X[5 & 6]	X	X[5]	X	X	X
Adverse Events Form			X	X	X	X	X	X

[1] May be done within 6 weeks of study entry, using a MUGA scan (CMPT code 78472] **or** an ECHO [CMPT code 93306 without contrast]. The method of assessing LVEF must be same for the study duration, and be performed at the same institution as screening.

[2] Send de-identified copies of ECHO reports to the SunCoast CCOP Research Base.

[3] Draw and send pretreatment labs to LabCorp AFTER study registration and BEFORE starting study agent and Herceptin®

[4] Contrast material used for MUGA Scan may alter BNP results. Draw samples as long as possible after the MUGA scan (or before the MUGA if for a follow-up visit). If labs are drawn within 1 week after the MUGA, please list "contrast for MUGA" on the concomitant medication form.

[5] Distribute and instruct patients to start a new log each week. Logs are to be returned and reviewed at least every 3 months (if logs are returned more frequently, review and submit at that time). Review Study Medicine Daily Logs with patients and document any side effects on the Adverse Events Form. Study Medicine Daily Logs will be used as a measure of compliance**.** [6] **Continue to give study agent during the surgical recovery period.**

** A patient-specific medication order form and a site stock medication order form must be submitted ONLY when the first patient at an institution is being enrolled. Study agent for all subsequent participants and all study refills will be dispensed from institution's site stock, which is replenished automatically**

08/31/2012 6.4 Study requirements **WHILE IN 12-MONTH FOLLOW-UP AFTER NEOADJUVANT TRASTUZUMAB**:

Study Requirements	Follow up every 3 months X 3 (+/- 2 weeks) after resuming trastuzumab post-operatively			Completed 12-month FU (Off Study)
	Month 3 (phone)	Month 6 (clinic)	Month 9 (phone)	
Measurement of left ventricular ejection fraction (LVEF)[1]		X[2]		X[2]
History & physical (height and weight)		X		X
Blood samples to LabCorp: • Non-fasting CMP • Troponin I • BNP		X X X[3]		X X X[3]
QOL questionnaire (EORTC QLQ C-30)		X		X
Patient assessment form	X	X	X	X
Follow-up Form	X	X	X	X
Concomitant Medication Form	X	X	X	X
Adverse Events Form	As Needed			
Off-Study Form				X

[1] A MUGA scan (CMPT code 78472] **or** an ECHO [CMPT code 93306 without contrast] may be used. The method of assessing LVEF must be same for the study duration, and be performed at the same institution as screening.

[2] Send de-identified copies of ECHO reports to the SunCoast CCOP Research Base.

[3] Contrast material used for MUGA Scan may alter BNP results. Draw samples before the MUGA scan if possible. If labs are drawn within 1 week after the MUGA, please list “contrast for MUGA” on the concomitant medication form.

6.5 Discontinuation of study agent criteria

Completion of study week 52

6.5.1 Follow-up with LVEF at study month 18 and 24.

6.5.2 Report disease status and concomitant medications every 3 months X 4 (study months 15, 18, 21 and 24)

6.5.3 Discontinuation of trastuzumab prior to study week 52

6.5.4 Follow-up with LVEF in 6 and 12 months after the last dose of trastuzumab.

6.5.5 Report disease status and concomitant medications every 3 months X 4 (3, 6, 9, and 12 months after last dose of trastuzumab)

Treatment (study agent) failure (section 7.0)

6.5.6 Follow-up with LVEF in 6 and 12 months after determination of treatment (study agent) failure

6.5.7 Report disease status and concomitant medications every 3 months X 4 (3, 6, 9 and 12 months after treatment failure)

6.5.8 Patients may be rechallenged with trastuzumab per ASCO guidelines; however they will be considered study failures and discontinue study agent

08/31/201

Other: (e.g. symptomatic bradycardia or hypotension attributable to study agent)

6.5.9 Do not rechallenge study agent

6.5.10 Follow-up with LVEF in 6 and 12 months after discontinuing study agent

6.5.11 Report disease status and concomitant medications every 3 months X 4 (3, 6, 9 and 12 months after discontinuing study agent)

6.6 Forms are due to the SunCoast CCOP Research Base Operations Center **within 14 days of protocol visit** (see Records to be Kept section 9.0). Forms can be faxed to **813-910-5998**.

6.7 To prevent biasing the outcome of the study, this is a double-blind study design, where both the clinical staff and the participants are blinded to the specific nature of the product (study agent and placebo).

6.8 After consenting to participate in the study, the following steps will occur:

6.8.1 Subjects will be registered and randomized by calling the automated Interactive Voice Response (IVR) telephone System at **1-866-835-6793**, which is available 24 hours/day and 7 days/week. (Note: CTSU sites should contact the CTSU registration to perform the enrollment, per Appendix VIII).

11/19/2010

10/08/2010

6.8.2 For the first patient enrolled at each site:

6.8.2.1 Research staff will complete the Medication Order Form for treating physician's signature, and then fax the form to the investigational pharmacy at **1-866-992-9966**.

6.8.2.2 If the form is received for processing by 12:00pm noon, study agent will be released to the site the same day for courier two-day delivery.

6.8.2.3 If the form is received after 12:00pm, the study agent will be processed within 1 business day for shipment by courier two-day delivery.

10/08/2010

6.8.2.4 With the first patient registration, "site stock" study agent will be released to the site for future patients and for patient refills. Patient-Specific Medication Order Forms need to be faxed to the investigational pharmacy at 1-866-992-9966 for the first patient only.

08/31/2012

6.8.3 Research staff will complete the On-Study Form (See Appendix III) at baseline, collecting demographic information, personal and medical history.

6.8.4 Laboratory assessments CMP (non-fasting comprehensive metabolic panel) (CMPT code 80053),Troponin I (CMPT code 84484) and BNP [B-Type Natriuretic Peptide] (CMPT code 83880) will be submitted to LabCorp using pre-printed forms supplied by the SCUSF CCOP Research Base Operations Center at no charge. CMP, Troponin I and BNP will be collected at baseline, every 3 months X 4 (+/- 2 weeks), study week 52 (or end of trastuzumab therapy if discontinued before week 52 or if study agent is stopped before week #52), study month 18 (or 6 months after the last dose of trastuzumab or stopped study agent) and Study month 24 (or 12 months after the last dose of trastuzumab or stopped study agent).

08/31/2012

6.8.4.1 BNP and Troponin I should be drawn AFTER registration and BEFORE patient receives study agent and trastuzumab

6.8.4.2 Laboratory specimens should be drawn BEFORE contrast material is administered for a MUGA Scan, as test results may be altered.

08/31/2012

6.8.4.3 Laboratory specimens will be submitted to the local LabCorps. Preliminary and final results will be sent directly to the site as indicated on the Intent to Participate Form (or, for CTSU sites, the Site Contact Form). LabCorp will submit Final results directly to the SunCoast CCOP Research Base Operations Center. LabCorp will invoice the SunCoast CCOP Research Base Operations Center for the tests.

11/19/2010

6.8.5 MUGA scan [CMPT code 78472] or ECHO [CMPT code 93306 without contrast] LVEF will be used to measure cardiac function at baseline, every 3 months X 4 (+/- 2 weeks), Study week 52 (or end of trastuzumab therapy if discontinued before week 52 or study agent is stopped before week #52), study month 18 (or 6 months after the last dose of trastuzumab or stopped study agent) and Study month 24 (or 12 months after the last dose of trastuzumab or stopped study agent).

10/08/2010

08/31/2012

6.8.5.1 Baseline LVEF within 6 weeks of study entry is acceptable. The same measurement test (MUGA or ECHO) must be used throughout the study.

6/3/2011

6.8.6 For sites using ECHO**,**de-identified copies of the ECHO report will be submitted with the Patient Assessment form for a central review by the study's Principle Investigator of the mitral regurgitation, tricuspid regurgitation and velocity, mitral inflow E' & A' velocities, tissue Doppler E' and A' velocities, mitral annulus E' & A' velocities, and septal side E' & A' velocities.

6.8.7 Participants will complete the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire (EORTC QLQ-C30), supplied by the Research Base (see Appendix III). The EORTC QLQ-C30 will be completed at pre-treatment visit, study week 52 (or end of trastuzumab therapy if discontinued before week 52 or study agent is stopped before week #52) and study months 18 and 24 (or 6 and 12 months after the last dose of trastuzumab or stopped study agent. EORTC QLQ-C30 should be completed AFTER registration and BEFORE patient receives study agent and trastuzumab

08/31/2012

10/08/2010

6.8.8 Physical examination, including height and weight will be performed at baseline, every 3 months X 4 (+/- 2 weeks), study week 52 (or end of trastuzumab therapy if discontinued before week 52) and study months 18 and 24 (or 6 and 12 months after the last dose of trastuzumab. Reports of disease status will be requested every 3 months until the study ends (3, 6, 9 and 12 months after discontinuation of study agent).

10/08/2010

6.8.9 Research Staff will complete a baseline Concomitant Medication Form (see Appendix III) at baseline and every 3 months X 4 (+/- 2 weeks), study week 52 (or end of trastuzumab therapy if discontinued before week 52), and every 3 months following discontinuation of study agent at each subsequent study visit. Reports of disease status will be requested and concomitant medications will be submitted every 3 months until the study ends (3, 6, 9, and 12 months after discontinuation of study agent). Concomitant Medications should include chemotherapy agents and any medications listed in Appendix V.

08/31/2012

6.8.10 Research staff will instruct participants to begin taking their study medicine on the morning of the day they are scheduled to begin trastuzumab treatment. Participants will be instructed to take study agent once daily with food at about the same time each day.

6.8.11 For monitoring of compliance, patients will complete Study Medicine Daily Logs. Instructions for completing the forms will be given each time study agent is dispensed. Research staff will collect and review Study Medicine Daily Logs at all follow-up visits and the off-treatment visit (see Appendix III) for compliance, documentation of blood pressure monitoring and adverse event reporting.

08/31/2012

6.8.12 Discrepancies noted on the Study Medicine Daily Logs will be addressed and documented. If a discrepancy is evident, research staff will clarify with the patient, and instruct on how to prevent future discrepancies.

6.8.13 Study Medicine Daily Logs are to be submitted to the Research Base Operations Center at least every 3 months. If the logs are being collected more frequently, they may be submitted at any time.

6.8.14 Adverse events will be documented, using the Adverse Event (AE) Form (Appendix III), graded using the Common Terminology Criteria for Adverse Events(CTCAE) version 4.0, and reported per guidelines in section 8.11.

6.8.15 Patients will be instructed to take their blood pressure every day during the first week of study medicine, three times a week the second week of the study, and then weekly while taking the study medicine. Blood pressure results will be documented on the Study Medicine Daily Log.

6.8.15.1 Blood pressure cuffs will be provided to the patient by the SunCoast CCOP Research Base at no charge.

10/08/2010

6.8.16 Follow-up visits will be scheduled every 3 months X 4 (+/- 2 weeks) through Study week 52 (or when trastuzumab therapy ends, if it is discontinued before week 52). Follow-up visits should occur within +/- 10 working days of the expected visit schedule.

6.8.17 Patients who fail treatment or discontinue study agent prematurely, will continue in study follow-up for 12 months, having LVEF measurements 6 and 12 months after study agent was discontinued. An additional report of concomitant medications and disease status will be requested every 3 months X 4 after discontinuing study agent.

6.8.17.1 Patients may be re-challenged with trastuzumab per ASCO guidelines; however they will be considered study failures and discontinue study agent.

7.0 Treatment Response Assessment:

Study failure is defined as:

7.1 An absolute decrease in LVEF from baseline of ≥ 10% at follow-up (for example– if MUGA is 80% at baseline, then 70% is a 10% decrease in LVEF and study failure; if ECHO is 60 – 65%, then 50 – 55% is a 10% decrease in LVEF and study failure).

7.2 An absolute decrease of ≥ 5% in LVEF from baseline for individuals with < 50% LVEF at follow-up (for example– if MUGA is 52% at baseline, then 47% is a 5% decrease in LVEF and study failure).

Criteria for discontinuing study agent:

7.3 Treatment failure

7.4 Treatment with trastuzumab discontinued

7.5 Symptomatic bradycardia or hypotension

7.6 Withdrawal of consent to participate in study

7.7 All data acquired prior to discontinuation will be included in the primary analysis. Every effort will be made to conduct a final study visit with the participant. Participants will be followed clinically until adverse events resolve, if applicable.

8.0 Toxicity Assessment, Adverse Event Reporting and Unblinding Procedures

Toxicity Assessment:

09/24/2010 8.1 CTCAE version 4.0 will be used to evaluate all toxicities. All appropriate treatment areas should have access to a copy of the CTCAE. To access the CTCAE version 4.0 click http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

09/24/2010 8.2 For help in determining AE categories, you may access Safety Profiler at: http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx.

8.3 Definitions:

8.4 An adverse event is defined as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in this research study."

8.5 Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

8.6 An unexpected adverse event is defined as "any adverse experience…the specificity or severity of which is not consistent with the risks of information described in the literature (protocol and package inserts)."

8.7 Expected adverse events are those that are "identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study."

Adverse Event (AE) Reporting Requirements (**FDA IND Exemption #102,825)**:

09/24/2010 8.8 This study utilizes drugs that are commercially available

08/31/2012 8.9 Adverse events will be reported using FDA Guidelines

8.10 Serious and unexpected adverse events:

8.10.1 Events that are both serious and unexpected with possible, probable or definite attribution to study agent:

8.10.1.1 Notify the Research Base Operations Center within 24 hours of learning about the event by telephone **(800-909-1242**), fax (**813-910-5998)** or email (ccop@epi.usf.edu)**.**

8.10.1.2 Report known details of event to the Research Base using the FDA MedWatch Adverse Reaction (ADR) Form FDA 3500A (see Appendix III), which must be signed by the treating Investigator. Update the form as more information becomes available and submit to the Research Base Operations Center.

8.10.1.2.1 All follow-up information referencing a reported adverse event will go through the SunCoast CCOP Research Base Operations Center.

8.10.1.2.2 The SunCoast CCOP Research Base Operations Center ensures that the FDA is notified according to the Code of Federal Regulations.

8.10.1.3 Supply written documentation of the event to the Research Base within 10 days (include the event on the Adverse Event Reporting Form, which provides information on grading and attribution).

8.10.1.3.1 Notify the local IRB within 10 days or per IRB institutional guidelines.

8.11 Reportable adverse events:

8.11.1 An adverse event is defined as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in this research study." As such:

8.11.1.1 Adverse events, such as hospitalization with febrile neutropenia, are not reportable events on this study. In this example, the event is associated with administration of cytotoxic chemotherapy, which would be administered regardless of participation in this study.

8.11.1.2 In this same example, if the severity of neutropenia is higher than expected, and if a clinician determines that it is possibly, probably or definitely related to administration of a study agent, the event would be reportable.

8.11.2 Review the patient's Study Medicine Log regularly for patient reported AEs that may be related to administration of study agent. In particular, document the incidence of:

8.11.2.1 Shortness of breath

8.11.2.2 Diarrhea

8.11.2.3 Tiredness

8.11.2.4 Fainting/Dizziness

8.11.3 Document toxicity grade using CTCAE V4.0

8.11.3.1 The Adverse Event Reporting Form captures both toxicity grade and attribution, which is determined by the treating clinician.

Submit the Adverse Event Reporting Form to the Research Base Operations Center within the timeframes addressed in Section 9.2.

Notify the local IRB as required per IRB institutional guidelines.

Unblinding procedure:

8.12 A patient's treatment may be unblinded if an event requires knowledge of the assigned treatment in order to deliver appropriate medical care. An investigator, who feels this is the case, should contact the SunCoast CCOP Research Base Operations Center. If the biostatistician is in agreement, treatment will be unblinded and the investigator will be informed. This action will be reported to the Data Monitoring Committee.

8.13 At the conclusion of the study, all investigators will be unblinded with respect to their patient's treatments. They should inform their patients of their actual treatment.

9.0 Records to be Kept / Data Collection Forms Submission Guidelines

10/08/2010

9.1 Fax (**813-910-5998**) or email (ccop@epi.usf.edu) forms to the SunCoast CCOP Research Base Operations Center **within 14 days of each protocol visit**:

08/31/2012

9.2 Records to be Kept Table

Type of form	Time due
Study Agent Accountability Record	**Do not submit – This form is to be updated each time study agent is received and dispensed.**
Intent to Participate Form	At IRB submission
Eligibility Form	**Within 14 days** of registration
Registration & Randomization Worksheet	**Within 14 days** of registration
Demographics Form	**Within 14 days** of registration
Patient Assessment Form	**Within 14 days** of protocol visit
Follow-up Form	**Within 14 days** of protocol visit
Medication Order Forms (to Carter King Pharmacy)	At first patient registration to Carter King dispensing pharmacy
Concomitant Medications Form	**Within 14 days** of protocol visit
EORTC QLQ C-30 Quality of Life Form	**Within 14 days** of protocol visit
Study Medicine Daily Log	**Within 14 days** of protocol visit
Off Study Form	**Within 14 days** of protocol visit
Adverse Events Form	**Within 14 days** of protocol visit
MedWatch Adverse Events Report copy	Within 5 days of completion if required

08/31/2012

10.0 Statistical considerations

Primary Outcome Variables:

10.1 The primary aim of this study is to determine if treatment with lisinopril or Coreg CR® can reduce the incidence of trastuzumab-induced cardiotoxicity in patients with HER2-positive breast cancer after 52 weeks of treatment as measured by the preservation of left ventricular ejection fraction (LVEF). Patients who demonstrate an LVEF < 50% at follow-up and a ≥ 5% absolute decrease in EF from baseline, or a ≥ 10% absolute decrease in LVEF after initiating trastuzumab therapy will be considered failures.

08/31/2012

10.2 We will compare the LVEF of each treatment group with the placebo arm. In addition, a comparison of the two study agents will be completed, recognizing that we do not have sufficient power for this secondary analysis. Linear regression with treatment and anthracycline regimen (yes/no) as independent factors will be used to compare the changes of LVEF, a continuous measure between the two arms (treatment arms with placebo). Logistic regression with treatment and anthracycline regimen (yes/no) will be

used to compare the proportions of cardiac failures in each arm. For comparisons of each treatment with placebo, we will consider one-sided 0.025 significant levels to adjust for the multiple testing. A mixed linear model will be utilized to analyze the pattern of LVEF change during the course of this study using the data from all follow-up visits. Furthermore, a multiple regression model will be used to control for potential confounders such as use of other agents (i.e. pertuzumab).

Sample Size:

10.3 The sample size calculation is based on the comparisons of each treatment with placebo. Using a conservative incidence estimate, we hypothesize that 15% of women treated for breast cancer with adjuvant or neoadjuvant trastuzumab will have decreased-LVEF in the placebo arm as compared to 5% of the women on the treatment arms. To detect a 10% difference in women who exhibit a decrease in LVEF in response to study agent, lisinopril or Coreg CR®, a sample size of 141 participants for each of the three arms is required to achieve 80% power for a one-sided Pearson's chi-square test at the 0.025 significance level. Assuming a 10% drop-out rate, 468 subjects will be randomized to one of the three arms.

08/31/2012

10.4 Given the large difference in cardiac toxicity between the regimens,[60] the protocol seeks to approximately balance the regimens by enrollment to 2 separate cohorts; patients who received an anthracycline-containing regimen and patients whose treatment regimen did not contain an anthracycline. A minimum of 187 subjects will be enrolled to each cohort. As such, should accrual to a cohort reach 281, that cohort will be closed to new accrual and the study will be completed with accrual to the remaining cohort.

Intent-to-Treat Principle:

10.5 As possible, all statistical analyses will be based on the intent-to-treat principle. Subjects will be analyzed according to their randomized assignment.

Secondary Outcome Variables

10.6 Interruptions of trastuzumab therapy caused by a decrease of LVEF will be evaluated by comparing the number of trastuzumab cycles completed without interruption by patients within each treatment group. Poisson regression will be utilized to compare the number of trastuzumab cycles completed. Furthermore, the proportion of patients completing uninterrupted trastuzumab therapy will be compared. Logistic regression will be utilized to compare the proportion of patients completing trastuzumab therapy between treatment arms. The frequency of all trastuzumab interruptions categorized by the criteria for study agent discontinuation (Section 7.0) and 95% confidence interval will be reported and compared by treatment group. A Fisher's exact test or chi-square test, depending on cell size, will be utilized to compare the frequency of categorized trastuzumab interruptions between the treatment arms.

10.7 Quality of life changes will be evaluated using the EORTC QLQ-C30 V 3.0 at baseline and at the end of treatment (end of trastuzumab therapy or week 52). The analysis plan will follow a linear regression model to consider the treatment effects on these measurements (dependent variables) adjusted for baseline age and potentially other covariates to compare the treatment arms. The observed data will be evaluated for normality and appropriate transformation introduced prior to conducting the analysis.

10.8 To assess the long term effect of the study agents, follow-up measurements will be collected at study months 18 and 24 (or 6 and 12 months after the last dose of trastuzumab, if it was discontinued before week 52). This exploratory analysis will be completed to determine the long term effects on the prevention of cardiomyopathy and

impact on QOL for either or both study agents. The treatment groups will be compared to using appropriate two sample tests.

6/3/2011

10.9 Receiver operating characteristic (ROC) curves will be used to determine the predictive value of two most common biomarkers in predicting trastuzumab-induced cardiotoxicity: Brain natriuretic peptide (BNP) vs. Cardiac troponin I. The null hypothesis is that areas under ROC (AUCROC) for the two biomarkers regarding identification of trastuzumab-induced cardiotoxicity (primary endpoint) are equal. Areas under the ROC curves will be tested using Delong's nonparametric approach, applying generalized U-statistics to generate an estimated covariance matrix for correlated ROC curves [63]. Due to the uncertainty about the treatment effect of the active drugs, this analysis will be limited to the placebo group only. With approximate 15% incidence rate in the placebo group, the proposed sample size will achieve a power greater than 80% to reject the null if the true difference between two ROCAUCs is 20% or more, assuming the correlation between BNP and Troponin I is 0.60.

Adverse Events

10.10 Adverse Events and side effects will be tabulated and compared for all patients. Adverse Events experienced will be compared with respect to frequency using the Fisher's exact test or chi square test if the cell size is sufficient between arms. Estimates of the AE rates as well as exact 95% confidence intervals for AEs will also be reported by treatment arm. All available AE data will be summarized and reviewed by the SCUSF CCOP Research Base Data Monitoring Committee at least every six months.

11.0 Data Safety Monitoring Plan

11.1 This protocol will be monitored in accordance with the SunCoast CCOP Research Base Data Safety Monitoring plan on file with the NCI last updated June 09, 2009.

11.2 The Data Monitoring Committee will review this project at least every six months.

12.0 Study Feasibility: Role of participating CCOPs

12.1 Member CCOPs and SunCoast affiliates will be responsible for enrolling **468** subjects during this study, which is expected to accrue for **3** years.

12.2 This study will be conducted in the community setting where this patient population is seen.

12.3 Study forms are available via the SunCoast CCOP Research Base website (http://www.SunCoastccop.org)

12.4 An automated registration/randomization system is available 24/7.

12.5 Study agent will be provided at no cost to the patient or clinical center by the SunCoast CCOP Research Base.

12.6 Laboratory testing will be provided at no cost to the patient or clinical center by the SunCoast CCOP Research Base. Specimens will be submitted to the local LabCorp for processing. Preliminary and final reports will be submitted directly to the site by LabCorp and final results will be submitted directly to the SunCoast CCOP Research Base Operations Center by LabCorp.

12.7 Blood pressure cuffs will be provided at no cost to the patient or clinical center.

12.8 EORTC QLQ-C30 Quality of Life Forms will be provided at no cost to the patient or clinical center by the SunCoast CCOP Research Base.

08/31/2012

12.9 Funds are available to reimburse clinical centers in the event payment of follow-up LVEF testing is not covered as standard of care. Using Medicare reimbursable rates, a clinical center may invoice the Research Base, using the Reimbursement Request From in Appendix III, for $300 if other payment is denied.

12.10 Evidence of training in Responsible Conduct of Research shall be on file at the SunCoast Research Base Operations Center prior to study start-up.

12.11 Informed consent will be obtained and documented prior to initiation of any study related procedures.

12.12 Basic guidelines for confidentiality and medical ethics will be closely adhered to during the study.

12.13 Data submission guidelines addressed in Section 9.0 will be followed. Queries will be generated by the SunCoast Research Base Operations Center for missing or unclear data elements.

12.14 CCOPs and enrolling SunCoast affiliates will be audited within 18 months of the first accrual and at least once every three years thereafter.

12.15 Subjects may be enrolled on other research studies if the studies do not impact eligibility criteria or protocol treatment for this study and is permitted by the local site Institutional Review Board.

12.16 This trial is feasible to conduct in the community setting. To determine the feasibility of completing this trial under the CCOP mechanism, we surveyed our adult CCOP members for interest and estimated annual accrual. We received an enthusiastic response to this study. Of the 17 members surveyed, 11 members plan to participate in this study. Based on the feedback we received from our adult CCOP members, and allowing for a reasonable start up period, we estimate that the protocol will accrue at a rate of 12 patients per month. We anticipate that recruiting for this study will take approximately 39 months to reach the accrual goal of 468.

12.17 We are aware of 6 treatment trials in patients with HER-2 positive breast cancer that employ trastuzumab in the treatment regimen. While the cardiotoxic effects of study therapy will be evaluated, only 2 studies will include this in their primary objectives. Furthermore, these trials do not include the use of supportive care agents such as those listed in this study. SCUSF 0806 differs from the BETH trial (NSABP B-44-1) in that SCUSF 0806 allows neoadjuvant chemotherapy (including anthracycline-containing regimens) the pathology requirements are not as stringent, no tissue samples are required and the LVEF entry criterion is lower for SCUSF 0806 (≥ 50% vs. ≥ 55%). As such, we do not anticipate any effect on our accrual potential.

13.0 References:

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