

# Research Base Protocols

## Quick Reference Guide

**60A02**

A Phase II Randomized Placebo Controlled, Double Blinded Trial to Evaluate the Effects of Fruit and Vegetable Extracts on Intermediate Biomarkers in *Head and Neck Cancer* Patients

**71103**

Phase II Study of Single Agent Depsipeptide (FK228) in *Metastatic or Unresectable Soft Tissue Sarcomas*

**97102**

A Phase III Randomized Study Comparing the Effects of Oxandrolone (Oxandrin)<sup>®</sup> and Megestrol Acetate (Megace)<sup>®</sup> On Lean Body Mass, Weight, Body Fat, and Quality Of Life in Patients with *Solid Tumors and Weight Loss Receiving Chemotherapy*

**97202**

A Phase III Randomized Double-Blind Placebo-Controlled Study of Oral Coenzyme Q10 to Relieve Self-Reported Cancer Treatment Related Fatigue in *Breast Cancer Patients*

**98301**

A Phase II Study of St. John's Wort for the Treatment of Hot Flashes in Women with a History of *Breast Cancer*

**97405**

Randomized Study of Soy Protein and Effexor<sup>™</sup> on Vasomotor Symptoms of *Men with Prostate Cancer*

### Clinical Office Staff:

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## Ineligibility

- Concomitant malignancy other than curatively treated HNSCC within last 5 years, except non-melanoma skin cancer, carcinoma in situ of the cervix or distant metastases (IVc M1)
- Serious medical or psychiatric illness which would prevent informed consent
- Expected survival < 6 months
- Nausea  $\geq$  grade 2 by NCI Common Toxicity Criteria (CTC) Version 3.0
- Current supplementation of high-dose vitamins within the last 2 months.
  - Vitamin A > 10,000 IU daily (3440 mcg)
  - Vitamin C > 1,000 mg daily
  - Vitamin E > 800 IU daily (537 mg)

## Objectives

The proposed research will use a randomized, double-blind, placebo-controlled trial to evaluate the effects of fruit and vegetable (F&V) extracts on surrogate endpoint biomarkers (SEBs) that are associated with the development of SPTs in patients with previous HNSCC.

1. To test the hypothesis that F&V extracts can modulate SEBs in patients with previous HNSCC. The primary endpoint is the expression of a cell cycle regulatory protein, p27, which is associated with disease-free survival. The secondary endpoints are cell proliferation (Ki-67), DNA damage (strand breaks), and immune function (T-cell function), which are associated with the development of HNSCC.
2. To evaluate whether the augmentation of SEBs by F&V extracts is influenced by other factors, such as characteristics of the original tumor (i.e., site and stage), continued tobacco/alcohol use, or depression. Our working hypothesis is that current tobacco/alcohol use and/or depression may modify the effects of F&V extracts on SEBs. Therefore, tobacco/alcohol use and depression will be evaluated at baseline and post treatment.
3. To determine serum carotenoids and antioxidant levels (vitamins A, C, and E) at baseline and post treatment. This evaluation tests the hypothesis that F&V extracts can increase plasma antioxidant levels which may contribute to biomarker changes. We will also assess whether the augmentation of plasma antioxidant levels is influenced by tobacco use and/or alcohol consumption.

The proposed research will use a novel complementary and alternative (CAM) approach to cancer chemoprevention. The results will provide critical information on: (1) the use of surrogate endpoint(s) in monitoring the biological effects of F&V extracts, (2) the mechanisms of F&V in preventing HNSCC, and (3) the feasibility of using supplementation of F&V extract supplementation with HNSCC patients. Promising study results from this Phase II chemoprevention trial will lay the groundwork for a larger Phase III trial to assess the application of F&V extracts in preventing SPTs for patients with HNSCC.

## Study Design

This study is a two arm, placebo controlled double-blind, Phase II chemoprevention trial assessing the effects of F&V extracts on biomarkers in 200 patients with previous HNSCC.

## Treatment Schedule

**The CCOP/non-CCOP site must contact Andrea Rice at 336-716-2573 immediately upon patient receiving Run-in placebo. This will insure Biomarker/Biopsy collection kits will be shipped to you prior to the patient's return visit.**

A research nurse will conduct a screening interview to collect information on medical history, tobacco use, alcohol consumption history, and to administer a food frequency questionnaire. After the interview, the research nurse will collect approximately 1 ½ tablespoons of blood for screening evaluation. Patients with normal blood chemistry will be invited to initiate the 1-week run-in procedure. Study subjects with  $\geq$ 75% compliance will be randomly assigned to receive either F&V extracts or placebo.

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# Post Treatment

Participants in the treatment group will receive two fruit and vegetable capsules in the morning and two fruit and vegetable capsules in the late afternoon or very early evening each day; participants in the placebo arm will receive 2 placebo capsules in the morning and two placebo capsules in the late afternoon or very early evening each day. The study plane includes two blood draws and two biopsies, 1 at baseline and one at 12-week after intervention. Supplements will be stopped after the 12-week treatment period. Patients will be given a \$10 gift certificate after baseline visit and a \$40 gift certificate when they complete the study. Patients may have treatment discontinued for any of the following reasons: (1) histological progression, either as dysplasia or invasive carcinoma; (2) development of unacceptable gastrointestinal (GI) toxicity ( $\geq$  grade 3); (3) illness necessitating premature termination; (4) protocol violation; and (5) death. The investigator will make every effort to perform the final evaluation at 12 weeks.

## Study Parameters

	Screening*	Run-In/ Baseline	1	(Week)				8	12	q year x5 off- study f/u
Medical History	X									
Signed Informed Consent	X									
Physical Exam	X							X		
Performance Status	X							X		
Hemoglobin	X									
WBC	X									
Platelets	X									
Bilirubin	X									
Creatinine	X									
SGOT	X									
SGPT	X									
Serum Pregnancy Test**	X									
Biomarkers		X							X	
Oral Biopsies		X							X	
CESD		X							X	
PSS		X							X	
Baseline H&N Questionnaire		X								
Food Questionnaire		X							X	
GI Toxicity Telephone Interviews***			X	X	X	X	X			
Post Treatment H&N Questionnaire									X	
Medication/ placebo Diary	X						X			
Pill Count		X						X		
Follow-up Form									X	

\*Within 28 days of registration

\*\* Within 10 days of registration

\*\*\*To be performed at the completion of each week of study drug.

The CCOP/non-CCOP site must contact Andrea Rice at 336-716-2573 immediately upon patient receiving Run-in placebo. This will insure Biomarker/Biopsy collection kits will be shipped to you prior to the patient's return visit.

**Initial labs to be drawn: CBC w/diff,plts, CMP, SGOT, SGPT, and serum pregnancy tests if applicable.**

**Run-In/ Baseline: Juice Plus Biomarkers and Oral Biopsy**

**Study medications: Provided Free.** Storage and distribution of Juice Plus™ and placebo will be handled by Biologics, Inc. (625 Oberlin Road, Raleigh, NC, 27605; 1-800-850-4306). **Upon registration of the patient, Biologics, Inc. will receive notification to initiate shipment of either Juice Plus™ or placebo to the participant's address provided.** Each shipment will include a twelve week supply of test agent or placebo. If patients choose to take Juice Plus for the extra 5 years, Biologics Inc. will not provide storage or distribution. Juice Plus will be sent directly to the patient by the Juice Plus manufacturer.

## Concomitant Treatment

No concomitant cancer treatment (i.e., surgery, radiation therapy, or chemotherapy) or chemopreventive agents is acceptable. Study subjects will be instructed to maintain their usual dietary habit and lifestyle during the trial.

## Post-Treatment:

Patients will be given the option to continue taking **Juice Plus FREE** of charge for five years, following the completion of the 12-week study. Patients may contact the following individual to request that a 5-year supply be sent directly to their address free of charge:

Anita Boddie, RD, PhD  
Phone# 901-969-9051  
Fax# 901-541-1331

**\* Gift certificates for CCOP/ non CCOP sites are \$10.00 certificates after baseline visit and \$40.00 certificate after the 12 week visit. The gift certificates will be sent to the sites.**

## Blood Sampling for Biomarkers and Processing:

Each container or specimen should be labeled with patient's initials, date, and actual collection time and protocol number and documented on the completed *Biomarker/ Biopsy* Form.

### **BLOOD:**

#### **Blood collection:**

Collect 30 ml blood sample in:

- (4) 4.5 ml **light blue** top tube
- (1) 4 ml **purple** top tube (protect from **light**)
- (1) 4 ml **yellow** top tube (protect from **light**)

#### **Blood processing:**

**Yellow and Purple tops:**

- *Immediately* centrifuge (1) *yellow* top tube and (1) *purple* top tube at 2000 X g for 10 minutes (to separate the cellular elements from the serum/plasma).
- Keep sample cold and centrifuged at 0-4°C if possible.
- Transfer serum and plasma to **amber-colored** screw-capped polypropylene transfer tubes.
- Document on tubes: *serum* from *yellow* top; *plasma* from *purple* top.
- *Immediately* freeze both **amber-colored** screw-capped polypropylene transfer tubes.

**Light Blue Tops:**

- (4) *Light blue* tubes kept at *room temperature*.

### **ORAL BIOPSIES:**

#### **Oral Biopsies Collection and Processing:**

Collect 1 cm X 1mm oral biopsy from buccal mucosa:

- **Baseline** biopsy **left** side of buccal mucosa
- **12 week** biopsy from **right** side of buccal mucosa
- Divide biopsy into **4 sections**
- *Immediately* place (1) **section** in **10% buffered formalin**
- Place each remaining (3) **sections** in separate 0.4ml cryo vials - (**freeze immediately** on dry ice). **Do not add any saline or preservatives to the cryo vials.**

### **BLOOD and BIOPSIES SHIPMENT:**

#### **Frozen container:**

- (3) Frozen oral biopsy vials – each individually placed in separate 3 X 5 Ziploc bags.

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## Post Treatment

- (2) Frozen amber-colored screw-capped polypropylene transfer tubes - each individually placed in separate 3 X 5 Ziploc bags.
- Place all (5) frozen specimens in 7 X 11 IATA approved Therapak bag.

### **Room Temperature container:**

- (4) 4.5 ml light-blue citrate vacutainers. Each tube wrapped in paper towel, then placed in a 50 ml conical tube.
- (1) 7ml glass vial containing 10% buffered formalin.
- The glass formalin vial should be sealed tightly, and placed in a 50ml conical tube with vermiculite.

*Note: The shipment of human tissues to WFUHS must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any potential spill or leakage. The outer container must be puncture resistant (e.g. cardboard mail tube or corrugated cardboard box.)*

Note: A biohazard sticker must be affixed to both the inner and outer container.

1. Notify Andrea Rice at 336-716-2573 prior to shipment.
2. **Samples should be shipped overnight FedEx for AM delivery. They should not be sent to arrive on a Saturday, Sunday, or holiday.**
3. The frozen samples (serum/plasma and 3 biopsy specimens) are to be placed in an insulated container with enough dry ice to maintain them in a frozen state for two days.
4. Place 4 light blue top tubes and 1 formalin biopsy in the separate insulated container and ship at room temperature (50-80°F).
5. A copy of the **Biomarker/Biopsy Form** on the following page should be included in each shipment.
6. All specimens are to be shipped to: Attention: Andrea Rice CCCWFU Research Base Core Lab Wake Forest University Health Sciences Medical Center Boulevard Hanes Building, 4<sup>th</sup> Floor, Room 4012 Winston-Salem, NC 27157

**The kit** contains (2) double-insulated containers: (1) frozen specimens; (1) room temperature specimens.

### **Frozen insulated container contains: (Note- Sites must provide dry ice)**

- (3) amber storage tubes (1 for plasma, 1 for serum, 1 extra)
- (3) 0.4ml cryo vial storage vials for frozen biopsies
- (3) transfer pipettes (1 for plasma, 1 for serum, 1 extra)
- (5) 3 X 5 Ziploc bags (1 for plasma, 1 for serum, 3 for frozen biopsies)
- (1) 7 X 11 IATA approved Therapak bag ( for all 5 frozen specimens)
- 5 Cryo-babies specimen labels
- Absorbent materials to control any shock, leakage, or spills (bubble wrap, paper towels)
- (1) 4ml purple top tube
- (1) 4ml yellow top tube

### **Room temperature insulated container contains:**

- (4) 4.5ml light blue top tubes
- (4) 50ml conical centrifuge tubes (secondary containers for the light blue top tubes)
- 5 Cryo-babies specimen labels
- Absorbent materials to control any shock, leakage, or spills (bubble wrap, paper towels)
- (1) 7ml glass vial with 5ml 10% formalin with sealing tape
- Vermiculite in a 50 ml conical tube (secondary container for formalin vial)

### **Other items:**

- (1) 9 x 12 Ziploc bag for Biomarker/Biopsy Form
- (1) Dry ice label (for outer corrugated box)
- (1) Return shipping label for overnight shipping and FedEx account number
- (6) Biohazard stickers : (1) for outer corrugated box; (1) for 7 X 11 IATA approved Therapak bag, (4) for 50ml conical centrifuge tubes
- (1) Excepted quantities label for shipping formalin (for outer corrugated box)

**\*\*\* The CCOP/non CCOP site must contact Andrea Rice at 336-716-2573 immediately upon patient receiving Run-in placebo. This will insure Biomarker/Biopsy collection kits will be shipped to you prior to the patient's return visit.**

## Biomarkers and Biopsy Form

**INSTRUCTIONS:** This form is to be completed and submitted as required by protocol. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Submit a copy to the CCCWFU Protocol office and send original with samples to the laboratory. See protocol for required sample time points.

Patient's Last Initial, First Initial \_\_\_\_\_ CCCWFU ID # \_\_\_\_\_ Institution ID # \_\_\_\_\_

### BIOMARKERS Baseline (before any study drug)

Date and time of baseline blood sample:

M D Y

H m

### ORAL BIOPSY SPECIMAN Baseline (from LEFT Buccal Mucosa)

Date and time of baseline biopsy sample:

M D Y

H m

### BIOMARKERS 12 WEEK (after completion of study drug)

Date and time of 12 week blood sample:

M D Y

H m

### ORAL BIOPSY SPECIMEN 12 WEEK (from RIGHT buccal mucosa)

Date and time of 12 week biopsy specimen:

M D Y

H m

### Please look at special processing and shipping information requirements.

Name of person sending samples \_\_\_\_\_ Phone no. or pager no. \_\_\_\_\_

Institution name \_\_\_\_\_ Email address: \_\_\_\_\_

#### FOR LAB USE ONLY

Sample Receipt + Condition Information

Usable (1-no, 2- yes)

Tubes intact? (1-no, 2=yes)

Biopsies intact? (1-no, 2=yes)

Date of sample receipt \_\_\_\_/\_\_\_\_/\_\_\_\_

Name of analyst \_\_\_\_\_

#### Sample Analysis Information

Sample Time Points

Baseline biomarkers

Baseline biopsy

12 week biomarkers

12 week biopsy

 •  •  •



A Phase II Study of Single Agent Depsipeptide (FK228) in Metastatic or Unresectable Soft Tissue Sarcomas

Paul D. Savage, M.D.

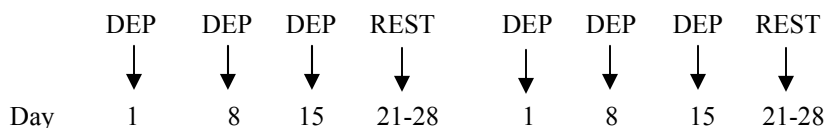
**\*Accrual Goal: 40 patients\***

## Objectives

- To estimate the response rates of metastatic or unresectable soft tissue sarcomas to single-agent depsipeptide.
- To estimate the time to progression of metastatic or unresectable soft tissue sarcomas to single-agent depsipeptide.
- To evaluate the scope and extent of acute toxicities associated with single-agent depsipeptide when given to patients with soft tissue sarcomas.

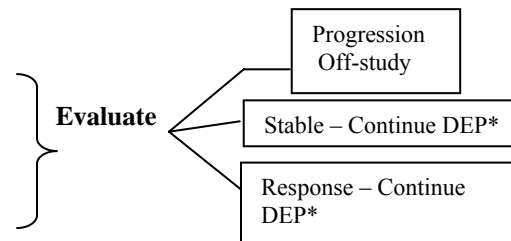
## Schema

### Cycle 1



DEP = Depsipeptide

### Cycle 2



Assessments after cycles 2, 4, 6 then every 3 cycles (cycle 9, 12,...)

Each cycle consists of 28 days.

DEP is administered at a dose of 13 mg/m<sup>2</sup> as a 4-hour intravenous infusion in the outpatient setting.

\*For patients who achieve a CR, 6 additional cycles of depsipeptide will be given; for patients who achieve a PR or stable disease, treatment will continue until an unacceptable toxicity or progression occurs.

Patients with stable disease and having received 12 cycles of depsipeptide treatment may elect to continue depsipeptide or discontinue depsipeptide and be followed expectantly. The decision is being left up to the patient and treating physician. If depsipeptide has been discontinued and progression occurs, depsipeptide may be restarted provided there has been no interim treatment.

## Eligibility Criteria

- Patients must have histologically or cytologically confirmed soft tissue sarcoma. Histologies typically associated with osseous primaries are acceptable provided it is established that the primary was extraskelatal (e.g. extraskelatal osteosarcoma, extraskelatal Ewing's sarcoma, etc. are acceptable). See Appendix D for further details regarding histologic subtypes
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm with conventional techniques or as  $\geq 10$  mm with spiral CT scan. See section 9.2 for the evaluation of measurable disease. Patients with strictly evaluable disease are not eligible.
- Prior therapy
- Patients may have received no more than 1 prior chemotherapeutic regimen for their sarcoma. For those patients who may have received adjuvant chemotherapy and have now relapsed, the adjuvant therapy counts as 1 prior regimen.
- Patients with gastrointestinal stromal tumors (GIST) must have received (and progressed on) Gleevec®. GIST patients may receive up to a total of 3 prior chemotherapeutic regimens consisting of treatment with Imatinib and/or Sutent, but no other chemotherapeutic agents are allowed. Similarly, patients with

other soft tissue subtypes for whom established, standard, curative therapies exist (e.g. Ewing's sarcoma, rhabdomyosarcomas, extraskelatal osteosarcoma) should have received the standard therapy prior to consideration of depsipeptide.

- Patients must have recovered from toxicities from all prior therapies received.
  - At least 4 weeks from prior chemotherapy; 6 weeks for nitrosoureas and mitomycin-C.
  - As depsipeptide has the potential to cause cardiac damage, patients must not have received more than 500 mg/m<sup>2</sup> doxorubicin; patients who received epirubicin will need to check with the principal investigator regarding maximal prior doses.
  - At least 4 weeks from prior radiation.
  - At least 4 weeks from prior surgery. Patients with incompletely healed surgical wounds must be cleared by their surgeon to begin chemotherapy.
- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of depsipeptide in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.
- Life expectancy of greater than 3 months.
- ECOG performance status ≤ 2 (Karnofsky ≥ 50%; see Appendix A).

Patients must have normal organ and marrow function as defined below:

- Leukocytes: ≥3,000/μL
  - absolute neutrophil count: ≥1,500/μL
  - platelets: ≥100,000/μL
  - total bilirubin: within normal institutional limits
  - AST(SGOT)/ALT(SGPT): ≤ 2.5X institutional upper limit of normal
  - Creatinine: ≤1.5X institutional limits of normal OR creatinine clearance: ≥60 mL/min/1.73 m<sup>2</sup> for patients with creatinine levels above institutional normal
  - Potassium: within normal institutional limits
  - Magnesium: within normal institutional limits
- The effects of depsipeptide on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, and because histone deacetylase inhibitors are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- Ability to understand and the willingness to sign a written informed consent document.

### **Exclusion Criteria**

- Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin-C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
- Patients *should not have had prior therapy with depsipeptide and* may not be receiving any other investigational agents *or drugs known to have HDI activity such as sodium valproate.*
- Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

- Patients can have no other invasive malignancies (other than non-melanoma skin cancer) during the past 5 years.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to depsipeptide.
- History of serious ventricular arrhythmia (VT or VF,  $\geq 3$  beats in a row), or QTc  $\geq 480$  msec.
- Patients may not take medications that cause QTc prolongation (see Appendix C).
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients with immune deficiency, either iatrogenic or secondary to an underlying disorder, are at increased risk of lethal infections when treated with myelosuppressive therapy. Therefore, HIV-positive patients receiving combination anti-retroviral therapy (e.g. HAART regimen), organ transplant recipients, and similar patients are excluded from this study.
- Pregnant women are excluded from this study because depsipeptide is a histone deacetylase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with depsipeptide, breastfeeding should be discontinued if the mother is treated with depsipeptide.
- Patients with known cardiac abnormalities such as Congenital long QT syndrome or QTc  $> 480$  milliseconds
- Patients who have a history of coronary artery disease (e.g. angina Canadian Class II – IV (Appendix M) or positive stress imaging study)
- Patients with an ECG recorded at screening showing evidence of cardiac ischemia (ST depression of  $> 2$  mm).
- Patients with congestive heart failure that meets New York Heart Association Class II to IV definitions (Appendix B)
- Patients with a history of sustained VT, VF, Torsades de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter defibrillator
- Patients with hypertrophic or restrictive cardiomyopathy from prior treatment or other causes and patients with significant left ventricular hypertrophy.
- Patients with uncontrolled hypertension (i.e.  $> 160/95$ )
- Patients with any cardiac arrhythmia requiring anti-arrhythmic medication other than a beta blocker or calcium channel blocker. Patients in whom digitalis cannot be discontinued are excluded from study.
- Patients with Mobitz II second degree block who do not have a pacemaker. Patients with first degree or Mobitz I second degree block, bradyarrhythmias or sick sinus syndrome require Holter monitoring and evaluation by cardiology.
- Patients with other cardiac disease may be excluded at the discretion of the PI following consultation with cardiology.

### **Treatment Plan**

All eligible patients will receive 2 cycles of depsipeptide as detailed below, after which an initial assessment of tumor response will be performed. All patients who have either stable or responding disease will continue to receive depsipeptide, with disease assessments performed every 2 cycles through cycle 6, and then every 3 cycles. Patients who achieve a complete remission will receive 6 cycles of depsipeptide beyond the establishment of complete remission, after which they will enter into observation. Those who achieve a partial remission followed by disease stability, or those whose disease remains stable (or have minor responses compared to baseline) will continue to receive depsipeptide provided there are no toxicities requiring discontinuation of depsipeptide, and there is no evidence of progression. Patients with stable disease and having received 12 cycles of depsipeptide treatment may elect to continue depsipeptide or discontinue depsipeptide and be followed expectantly. The decision is being left up to the patient and treating physician. If depsipeptide has been discontinued and progression occurs, depsipeptide may be restarted provided there has been no interim treatment.

## Study Parameters:

Baseline evaluations are to be conducted within 1 week prior to registration. Scans and x-rays must be done within 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	C1D1			C2D1				C3D1				Completion of 12 cycles (e)	Off Study (i)		
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10			Wk 11	Wk 12
Depsipeptide (a)		X	X	X		X	X	X		X	X	X			
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X-----X											X		
Physical exam	X	X				X				X				X	X
Vital signs	X	X	X	X	X	X	X	X	X	X		X		X	X
Height	X														
Weight	X	X	X	X		X	X	X		X		X		X	X
Performance status	X	X						X		X		X		X	X
LDH	X														
Phosphorus	X	X				X				X					
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry (b,c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/INR (f)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis only at baseline	X														
EKG (as indicated) (g)	X	X(h)	X	X										X	
Adverse event evaluation		X-----X												X	
Tumor measurements Palpable lesions	X	Tumor measurements are repeated every 4 weeks.											X	X (e) (i)	
Radiologic evaluation CXR, CT, MRI	X	<b>*Radiologic measurements should be performed every 8 weeks through cycle 6 then every 12 weeks.</b>											X (e)	X(e) (i)	
β-HCG (d)	X														

- a: Depsipeptide: Dose as assigned; as a 4-hour intravenous infusion on days 1, 8, and 15 of a 28-day cycle.
- b: Sodium, potassium, chloride, carbon dioxide, glucose, total protein, LDH, Bun, creatinine or creatinine clearance, phosphorus, albumin, calcium, alkaline phosphorus total bilirubin.
- c: Serum Creatinine <1.5 x institutional normal limits of Creatinine clearance  $\geq 60$  ml/min/1.73 m<sup>2</sup> for patients with Creatinine levels > 1.5 x institutional normal.
- d: Serum pregnancy test (women of childbearing potential) within seven days of registration.
- e: Off-study evaluation. Continued treatment after 12 cycles requires radiologic evaluation every 3 months. See section 4.0 for treatment continuation after 12 cycles.
- f: (If applicable). Patient on warfarin sodium due to possible drug interaction with depsipeptide (more frequently per doctor's discretion).
- g: EKG within 1 hour prior to start of Depsipeptide infusion and within 1 hour immediately following end of Depsipeptide infusion on C1D1; EKG within 1 hour prior to Depsipeptide infusion on C1D8 and C1D15.
- h Pre- and post-study
- i. Every 3 months for two years (years 1 and 2), then every 4 months for one year (year 3), then every 6 months for 2 years (years 4 and 5), then every year until 5 years are completed.

**Initial labs to be drawn at baseline:** CBC w/diff, plts, CMP, Mg<sup>++</sup>, Phosphorus, LDH, Serum Creatinine or creatinine clearance, UA, EKG, and if applicable PT/INR and BHCG.

**Study Medication: Provided free. Sites must order from NCI.**

## Depsipeptide Administration

- Depsipeptide will be administered on an outpatient basis at a dose of 13 mg/m<sup>2</sup> as a 4-hour infusion on days 1, 8, and 15 of each 28-day cycle. A treatment course of therapy will be defined as 28 days.
- Depsipeptide will be administered via a central venous catheter, PICC line (peripherally inserted central catheter) or peripheral IV line.
- Prophylactic antiemetics are mandatory (see Section 4.2).

- **First treatment cycle:** Patients must have a baseline EKG with a rhythm strip performed prior to administration of depsiptide (within 1 hour), immediately following the infusion (hour 4) and within 1 hour prior to administration of depsiptide on days 8 and 15 during the first cycle of treatment. If the EKG is normal it does not have to be reviewed immediately. In the case of abnormal EKG findings (QTc  $\geq$  480 msec, prolongation of QTc from baseline by 33%, new ST depressions of  $\geq$  2mm or new arrhythmia) a cardiology consultation will be obtained to determine whether further cardiac evaluation is necessary and whether treatment should be delayed or discontinued.
- **Subsequent cycles:** If no alerting findings during the first cycle were noted, no further monitoring is necessary. After the first cycle of Depsiptide, even if dose changes occurred, cardiac monitoring will be at the treating physician's discretion.
- Reported adverse events and potential risks are described in Section 6.
- Appropriate dose modifications of depsiptide are described in Section 5.
- No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

### Supportive Care Guidelines

- Antiemetics should be routinely administered in combination with depsiptide. Individualization is required, as some patients require no antiemetic therapy, while other patients require intensive antiemetic therapy. Recommended starting regimen: granisetron 1 mg IV or po 30 minutes before depsiptide and then every 12 hours for 24 – 48 hours following administration. Dexamethasone 8mg PO/IV needs to be given before each infusion of depsiptide. Other antiemetics found to be useful have included prochlorperazine, metoclopramide, lorazepam or diphenhydramine.
- Magnesium and potassium levels must be checked within four hours prior to administration of depsiptide. As a consequence of known QTc prolongation by depsiptide and reports of a few cases of sudden cardiac death in patients receiving depsiptide without other clear causes of death, serum potassium MUST be  $\geq$ 4.0 mmol/L and serum magnesium MUST be  $\geq$ 2.0 mg% before depsiptide can be given.

Potassium level must be $\geq$ 4.0 mmol/L before Depsiptide can be given		
<u>Potassium supplementation guidelines</u>		
Potassium $\geq$ 4.0 mmol/L	Requires no Potassium to be given	
< 4.0 and > 3.5 mmol/L	40 meq. Potassium po and/or IV routes	
< 3.5 mmol/L	80 meq. Potassium divided between po and IV routes. (40 meq. po and 40 meq. IV)	
Magnesium level must be $\geq$ 2.0 mg/dl (0.85 mmol/L) before Depsiptide can be given		
<u>Magnesium supplementation guidelines</u>		
Magnesium $\geq$ 2.0	0.85 mmol/L	Requires no Magnesium to be given
1.9	0.79 mmol/L	1 gram MgSO <sub>4</sub> IV (8.12 meq.)
1.8	0.75 mmol/L	2 grams MgSO <sub>4</sub> IV (16.24 meq.)
1.7	0.70 mmol/L	3 grams MgSO <sub>4</sub> IV (24.36 meq.)
< 1.6	0.70 mmol/L	4 grams MgSO <sub>4</sub> IV (32.48 meq.)

Maximum dose is 4 Grams of MgSO<sub>4</sub> (32.48 meq.)

- Each individual institution is cautioned to follow their own guidelines for administration of these electrolytes.
- Infusion must be completed before initiation of the Depsiptide infusion.
- Electrolyte levels must be rechecked and adequate levels achieved prior to Depsiptide administration.

If patient requires supplemental electrolytes during cycle 1, a repeat EKG needs to be done within 1 hour prior to administration of depsiptide.

- Prophylactic (oral) antibiotics and (oral) antifungal agents are permitted in neutropenic patients (ANC <1000).
- G-CSF (Neupogen ®) or pegylated G-CSF (Neulasta ®) use is allowed in patients with neutropenic fever according to ASCO guidelines ([www.asco.org](http://www.asco.org); [guidelines@asco.org](mailto:guidelines@asco.org)).

In general, other concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. Their use should be documented in the patient records and study specific flow sheets (this includes blood/platelet transfusions for patients with anemia and thrombocytopenia). The administration of other anti-neoplastic agents including chemotherapy, radiation therapy and biologic agents is not permitted on this study (except as described above). The use of other investigational agents is not allowed during this trial.

**\*Reduced dose is used for all subsequent depsipeptide infusions. No further dose adjustment is allowed. For any delay of treatment due to toxicity for more than 4 weeks, patient will be removed from study.**

### Availability

Depsipeptide is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Depsipeptide is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Gloucester Pharmaceuticals, Inc. and the DCTD, NCI (see Section 10.4).

### Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

### Pharmaceutical Information

#### Depsipeptide (NSC 630176)

*Chemical Name:* N-(3-hydroxy-7-mercapto-1-oxo-4-heptenyl)valylcysteinyl-2,3-didehydro-2-aminobutanoylvaline- $\gamma$ -lactone, cyclic-1 $\rightarrow$ 2-disulfide; (E)(1S,4S,10S,21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo [8,7,6]-tricos-16-ene-3,6,19,22-pentanone

*Other Names:* FR901228, FK228

*Classification:* HDAC inhibitor

*Molecular Formula:* C<sub>25</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> **M.W.:** 541

*Description:* Bicyclic peptide

*How Supplied:* Depsipeptide is supplied by the DCTD, NCI in a dual pack with special diluent.  
Active Drug: Sterile, single use vial containing 10 mg of lyophilized depsipeptide and 20 mg povidone, USP.  
Special Diluent: Sterile vial containing 2 mL of a solution of 20% ethanol USP, in propylene glycol, USP.

*Preparation:* Withdraw 2 mL of Special Diluent from the vial; add to the depsipeptide vial. Swirl until contents of the vial are free from visible particles. This provides a 5 mg/mL solution. Dilute further with 0.9% Sodium Chloride Injection, USP to a final drug concentration in the range of 0.02 to 0.1 mg/mL. The dilute solution is compatible with both glass bottles and PVC IV infusion bags and is chemically stable for at least 24 hours when stored at room temperature.

*Storage:* Store the dual pack in the refrigerator (2-8°C).

*Stability:* Formal shelf-life surveillance of the drug dual pack is on-going. Vials of formulated drug show no loss in potency up to twelve months when stored at 50°C.  
**CAUTION:** The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

*Route of Administration:* Intravenous.

A Phase III Randomized Study Comparing the Effects of Oxandrolone (Oxandrin)<sup>®</sup> and Megestrol Acetate (Megace)<sup>®</sup> On Lean Body Mass, Weight, Body Fat, and Quality Of Life in Patients with ***Solid Tumors and Weight Loss Receiving Chemotherapy***

Glenn J. Lesser, M.D.

**\*Accrual Goal: 155 patients\***

**Study Design**

This is a randomized study in patients with solid tumors and weight loss who are receiving chemotherapy. Patients will be randomized at the time of study entry to **Oxandrin 20 mg/day or Megestrol acetate 800 mg/day for a total treatment period of 3 months (12 weeks)**. Measurements of weight, body composition, laboratory studies and health-related quality of life will be obtained at baseline, at one, two and three months during the treatment phase of the study, and at the one-month post-treatment follow-up visit.

- **Oxandrin and Megace are both provided to the patient FREE of charge.**

SCHEMA

<b>Stratify:</b>		
1) Stage I-III vs Stage IV (Metastatic)	<b>R A N D O M I Z E</b>	1. <b>Arm 1:</b> Oxandrolone (Oxandrin <sup>®</sup> ) 20mg (10 mg BID) daily for a total of 12 weeks with 4 additional weeks of follow-up
2) Concurrent Radiotherapy vs None		2. <b>Arm 2:</b> Megestrol acetate 800 mg daily for a total of 12 weeks with 4 additional weeks of follow-up
3) Gender		

**Objectives**

- To compare the effects of Oxandrin and Megestrol acetate on the lean body mass and weight of patients with solid tumors and weight loss receiving chemotherapy.
- To compare the impact of Oxandrin and Megestrol acetate on health-related quality of life in patients with solid tumors and weight loss receiving chemotherapy.

**Eligibility**

- Age  $\geq 18$  years with no pre-existing or uncontrolled medical or psychological illness that would impair a patient's ability to provide informed consent or to complete protocol therapy or quality of life questionnaires.
- A minimum of one month planned chemotherapy remaining at the time Oxandrin or Megestrol acetate is begun. Oral chemotherapy medications, biologicals, and monoclonal antibodies are included in eligibility criteria.
- Histologically confirmed solid tumor (see exceptions in ineligibility list).
- Female patients with a history of breast cancer, gynecologic cancer, and hormonally responsive germ cell tumors must be disease free  $\geq 5$  years to be eligible for this study.
- Patients with non-melanoma skin cancers and carcinoma in situ of the cervix are eligible.
- History of weight loss of: (MUST ONLY MEET ONE OF THE FOLLOWING CRITERIA)
  - a.  $\geq 5\%$  total body weight during the previous 6 months OR
  - b.  $\geq 3\%$  in previous month OR
  - c. Progressive weight loss on 2 consecutive visits despite attempts at dietary, behavioral, or pharmacologic intervention.
- ECOG Performance Status of 0-2
- Life expectancy  $\geq 6$  months
- Serum creatinine  $\leq 2.5$ mg/dl, SGOT and SGPT  $\leq 2$  times upper limit of normal, total bilirubin  $\leq 2.5$  mg/dl
- **Patients must be able to swallow 1 tablet twice a day or 20 cc of liquid each day**
- Patients must be able to meet their nutritional requirements via the oral route with food and/or oral supplements or via enteral tube feedings. However, Oxandrin pills must be administered orally.
- Use of oral anticoagulants (warfarin) for maintenance of central venous catheter patency is allowed. The patient will be eligible if the INR  $\leq 1.2$ . Because of the interaction between warfarin and Oxandrin, the maintenance dose of warfarin should be halved to keep the INR at 1-1.2. For example, if a patient is taking 1 mg of warfarin at study entry, it is recommended that the dose be decreased to 0.5 mg per day during the treatment phase of this study. If a patient is taking 0.5 mg per day, their dose should be decreased to every other day, every third day, etc. to keep the INR at  $\leq 1.2$ . INR must be checked weekly until stable at  $\leq 1.2$ . (See systemic anticoagulation under ineligibility for patient's that develop thrombolytic event while taking study medication.)
- Patients can be receiving concurrent RT.

**Ineligibility**

- Ongoing or planned treatment with corticosteroid medications, estrogens, progestins (including Megestrol acetate) or any other steroid hormone during the study period. Patients who receive intermittent corticosteroids as part of a pre-chemotherapy antiemetic regimen are eligible for this study. Patients treated with Oxandrin or Megestrol acetate  $\leq 3$  months before study entry are not eligible. Patients taking dronabinol or any other appetite stimulant must be off medication for a minimum of 3 days prior to start of study medication.
- Patients who have had the following are ineligible: Prostate cancer, Male breast cancer, Female breast, gynecologic, or hormonally responsive germ cell tumors in the last 5 years, Primary or metastatic malignant brain tumors that have not been stable or demonstrate progressive disease in the last 6 months.

- Men  $\geq 40$  years of age should have a prostate-specific antigen (PSA) level checked if not monitored in the past year. Those patients with PSA  $> 4$  ng/mL will be excluded from participation in the study.
- If required, the PSA should be done within 2 weeks prior to registration.
- Patients with hypercalcemia, nephrosis or the nephrotic phase of nephritis or uncontrolled hypertension, congestive heart failure, pulmonary edema, unstable angina or Cushing's syndrome.
- Patients with recent (within 6 months) active thromboembolic disease or recent myocardial infarction (within 3 months of study entry).
- **Systemic anticoagulation:** Patients currently on oral anticoagulants (warfarin) are not eligible unless they are taking low doses of warfarin for catheter patency. **If a patient develops thromboembolic disease while on treatment,** they may remain on study. It is recommended that they receive a standard loading dose of coumadin on day 1. Because of the interaction between Oxandrin and Coumadin (Oxandrin elevates the INR), patients will subsequently require a much lower dose of Coumadin. The effect of these combined medications should develop within 24 to 48 hours. The recommended Coumadin dose should be decreased to 20% of what is normally required for sufficient anticoagulation. (Example: If patient would normally receive 5 mg every day, they should only receive 1 mg every day.) PT/INR results should be monitored frequently with dosage adjustment as needed.
- Significant ascites, pleural effusions or edema which may inhibit oral food intake or invalidate weight determinations.
- Diabetic medications are allowed, however patients taking sulfonyureas are ineligible. Below is a list of commonly used sulfonyureas (Note: This is a helpful guide, not a complete list.): Glimepiride (Amaryl®), glyburide (DiaBeta®), chlorpropamide (Diabinese®), glipizide (Glucator®), combined glyburide and metformin (Glucovance®) and orinase (Tolbutamide®).
  - There is no contraindication for concomitant use of insulin and oxandrolone (Oxandrin®) if required by the patient. Any patient on insulin or other oral hypoglycemics should self-monitor to prevent hypo & hyperglycemia.
- Patients who are pregnant or nursing.
- Patients with history of priapism (persistent erections) and sickle cell anemia.
- Patients with a BMI (Body Mass Index)  $\geq 35$

### **Drug Interactions**

**Anticoagulants:** - Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

**Oral Hypoglycemic Agents:** - Oxandrin may inhibit the metabolism of the oral hypoglycemic category sulfonyureas. There is no contraindication for concomitant use of insulin and oxandrolone. Any patient on insulin or oral hypoglycemics should self-monitor to prevent hypo & hyperglycemia. Therefore, these medications are not allowed. All other hypoglycemic medications are allowed.

**Adrenal Steroids or ACTH:** - In patients with edema, concomitant administration of Oxandrin with adrenal cortical steroids or ACTH may increase the edema.

**Drug/Laboratory Test Interactions:** - Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total  $T_4$  serum levels and increased resin uptake of  $T_3$  and  $T_4$ . Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

**Study Parameter Table**

**Study entry lab work and assessments must be performed within 14 days prior to registration.**

<b>PARAMETER</b>	<b>STUDY ENTRY</b>	<b>ONE, TWO and THREE MONTH VISITS</b>	<b>ONE MONTH POST-TREATMENT VISIT</b>
Signed Informed Consent	X		
Pregnancy Test (1)	X		
PSA (2)	X		
Body Mass Index (<35)	X	X	X
Physical Examination	X	X	X
Weight	X	X	X
ECOG Performance Status	X	X	X
Body Composition (BIA) (3)*	X	X	X
QOL Questionnaire (4)	X	X	X
PG-SGA (Nutritional Assessment - Appendix XII)	X	X	X
Patient Medication Diary	X	X	
CBC with differential, platelets	X	X	X
Serum Chemistry (including electrolytes, glucose, BUN, Creatinine, SGOT, SGPT, Total Bilirubin, Calcium, Albumin)	X	X	X
PT (5)	X	X	X
Transferrin (6)	X	X	

- (1) Pregnancy test is required at least 10 days prior to registration in women of childbearing potential.
- (2) Only in men ≥ 40 years of age if not monitored in the past year. Those patients with PSA > 4 ng/mL will be excluded from participation in the study. If required, the PSA should be done within 2 weeks prior to study registration.
- (3) \*BIA – Baseline and 12 week BIA must be performed at specified times. One, two and four month BIAs may be done within one week prior to or one week after specified times, depending on patient’s chemotherapy schedule. BIA information should be entered into R>JL system in computer. ([www.rjlsystems.com/cyprus/download/cyprus\\_27b8.exe](http://www.rjlsystems.com/cyprus/download/cyprus_27b8.exe)) Complete the body composition report. The report should be printed and submitted to data managers.
- (4) Each patient will complete a quality of life assessment questionnaire consisting of the FACT-G and subscales for anorexia/cachexia and fatigue. This will be completed by the patient, with or without assistance from a health care professional.
- (5) PT: IF a patient is taking Coumadin (Warfarin) for central venous catheter maintenance. Patient should be monitored per guidelines in section 3.1.10 with weekly PT’s, until INR is stable (≤ 1.2).
- (6) Transferrin is drawn at baseline and at second follow-up visit only.

**Initial labs to be drawn: CBC w/diff,plts, CMP, SGOT, SGPT, and Tranferrin**

**If applicable: PT/ INR, PSA, and serum pregnancy tests**

**\*Study medication is provided free of charge. Upon patient registration Biologics will receive notification to initiate shipment of study medication. Site must fax prescription to Biologics for Oxandrin. No prescription is required for Megace.**

**Drug Ordering and Destruction**

Oxandrin will be supplied by Savient Pharmaceuticals Inc. for patients on this trial randomized to the Oxandrin arm. Distribution of the Oxandrin will be performed by Biologics, Inc. When the patient is registered in the Comprehensive Cancer Center of Wake Forest University CCOP Research Base data base, Biologics will automatically be notified of the registration and Biologics will arrange for a 12 week supply of Oxandrin to be distributed to the participating institution.

Because Oxandrin is a Class III drug, a written prescription will need to be obtained. This should read "Oxandrin 10 mg, instructions and supply per CCCWFU Protocol 97102." Immediately fax a copy of the prescription to Biologics, Inc. at 919-546-9816. Second, promptly mail original prescription to Biologics, Inc. (see address below). If you need to speak to someone at Biologics by phone, please call 1-800-850-4306. The prescription must include the following information: 1) complete name and address and DEA# of the physician writing the prescription 2) complete name and address of the patient who will receive the drug.

Biologics, Inc.  
625 Oberlin Road  
P. O. Box 10568  
Raleigh, NC 27605

All unused drug must be destroyed on site following DEA/State Regulatory regulations for CIII substances (i.e., indicate the following in the patient's medical record: dose, # pills, method of destruction, and names/signatures of two witnesses). A State Drug Regulatory agent may need to witness drug destruction if your pharmacy is not overseeing drug inventory. Follow controlled substance regulations appropriate for your site.

Megestrol Acetate will be supplied by Savient for patients participating in this trial and randomized to the Megace arm. Distribution of the Megestrol acetate will be performed by Biologics, Inc. Any unused drug remaining at the conclusion of the patient's participation in this trial should be inventoried and disposed of by the treating institution's research nurse, study coordinator, or principal investigator. A prescription of the Megestrol Acetate does not need to be faxed or mailed to Biologics.

The patient is to be weighed and measured while dressed in underwear and a hospital gown without shoes.

**BIA Equipment Supply and Instruction**

Each site will be supplied with a BIA apparatus upon local protocol activation. The BIA equipment used in this study will be obtained on loan from Savient Pharmaceutical Inc, the manufacturer of Oxandrin.

Calibration of BIA

Resistance Value: (between 495 and 505)

Reactance Value: (between -003 and 003)

BIA patient readings

Resistance readings are 3 digits usually ranging from 250-850.

Reactance readings are 2 digits usually ranging from 30-80.

**A Phase III Randomized Double-Blind Placebo-Controlled Study of Oral Coenzyme Q10 to Relieve Self-Reported Cancer Treatment Related Fatigue in *Breast Cancer***

***Patients***

Glenn Lesser, MD

**\*Accrual Goal: 202\***

**Schema**

**Randomize**

**Recruit and Consent**

202 female breast cancer patients  
Prior to initiation of adjuvant chemotherapy treatment  
(Recruitment expected to take 6mos. - one year)

Placebo-Vit E  
100mg /day in 3  
doses

CoQ10 100 mg +  
Vit E 100 mg /day  
in 3 doses



**Baseline Screening (*week one*)**

CBC, Platelet, Diff, Total cholesterol, Weight

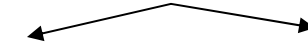


**Remaining Baseline (*week one*)**

Serum Co Q10, Serum alpha tocopherol  
Liver function tests: bilirubin, SGOT, SGPT  
POMS-F, FACT-B with FACIT-F subscale, Patient  
Self-Rating of Fatigue Visual Analogue Scale (VAS),  
CES-D Short-Form, MOS Social Support Scale,



**Stratify by type of chemotherapy anthracycline vs  
non anthracycline**  
**Stratify by radiation vs no radiation**



**Interim Measures (*wks 8, 16*)**

Serum Co Q10, Serum alpha tocopherol  
Liver function tests: bilirubin, SGOT, SGPT  
POMS-F, FACT-B with FACIT-F subscale, Patient  
Self-Rating of Fatigue Visual Analogue Scale (VAS),  
CES-D Short-Form, MOS Social Support Scale



**Outcome Measures (*week 24*)**

(At the completion of 24 wks of study medication.)  
Primary: POMS-F  
Secondary: Serum Co Q10, Serum alpha tocopherol  
Liver function tests: bilirubin, SGOT, SGPT  
FACT-B with FACIT-F subscale, Patient  
Self-Rating of Fatigue Visual Analogue Scale (VAS),  
CES-D Short-Form, MOS Social Support Scale

*The overall goal of this study is to determine the efficacy of administering oral Co Q10 combined with Vitamin E to relieve self-reported cancer treatment-related fatigue in female breast cancer patients receiving chemotherapy. Specifically, the primary study aim is to: Assess the effect of Co Q10 on cancer treatment-related fatigue. Secondary study aims are to: Assess the effect of Co Q10 on overall Quality of Life and Assess the effect of Co Q10 on depression*

**Eligibility**

- Signed Consent
- Hgb  $\geq$  11g/dl; (erythropoietin, transfusion, iron therapy should be utilized to assist with maintaining Hgb levels)
- Total cholesterol  $\geq$  160mg/dL.
- Female with primary cancer diagnosis (breast)
- Planned adjuvant chemotherapy
- KPS  $\geq$  60
- Bilirubin  $\leq$  1.5 x ULN
- SGOT  $\leq$  2.5 x ULN
- SGPT  $\leq$  2.5 x ULN

**Ineligibility**

- Recent involuntary weight loss (> 5% of body weight in the past 3 months)
- Statin therapy - current or planned during study. Below is a list of some commonly used statin drugs.

(Note: This is a helpful guide, not a complete list.)

- Atorvastatin (Lipitor)
- Cerivastatin
- Fluvastatin (Lescol)
- Lovastatin (Mevacor, Altacor, Advicor)
- Mevastatin
- Pravastatin (Pravachol)
- Rosuvastatin
- Simvastatin (Zocor)
- Current or planned use of the following medications for fatigue (See Section 4.4):
  - Corticosteroids (intermittent use as part of chemotherapy regimen is allowed)
  - Amphetamines or other stimulants including methylphenidate (Ritalin) or modafinil (Provigil)
- Patients diagnosed with uncontrolled hypertension
- *Breast cancer patients who are male*
- Pregnant women are excluded from participation in this study. A Serum pregnancy test is required within 1 week of registration if the patient is a woman of childbearing potential.
- Anticoagulant therapy – current or planned during study (except for maintenance of catheter patency)
- Patients with uncontrolled thyroid dysfunction

**Treatment Schedule**

**Supplements will be taken for 24 weeks beginning on the day of the first chemotherapy treatment. Patients must start taking supplements no later than 4 days after chemotherapy treatment.** Interim measures will be obtained at 8 and 16 weeks. At the completion of 24 weeks, the supplements will be discontinued and outcome measures obtained.

Assessments of fatigue will be conducted at the specified intervals just prior to initiation of the subsequent chemotherapy cycle. The type and frequency of chemotherapy is expected to vary among participants. Therefore, this information will be recorded at each assessment to note the date of last chemotherapy treatment in relation to assessment of fatigue. Every effort will be made to assess fatigue in each participant just prior to the next chemotherapy cycle.

**Study Parameters**

**NOTE: Baseline lab work must be drawn within one week prior to registration**

Assessment	Screening Baseline	Remaining Baseline	Week 8	Week 16	Week 24
CBC, platelet, DIFF (e)	X		X	X	X
Total Cholesterol	X				
Serum Co Q10 (b)(c)		X	X	X	X
Serum alpha tocopherol (b) (c)		X	X	X	X
Liver Function (f): (Bilirubin, SGOT, SGPT,) Creatinine (d)	X		X	X	X
Pregnancy Test (a) (serum)	X				
KPS $\geq$ 60	X		X	X	X
Weight	X		X	X	X
CES-D Short Form		X	X	X	X
Patient Self-Rating Fatigue Scale (VAS)		X	X	X	X
POMS - F		X	X	X	X
FACIT - F		X	X	X	X
FACT - B		X	X	X	X
MOS Social Support		X	X	X	X
Pill Count			X	X	X

(a) A serum pregnancy test is required within one week prior to registration if the patient is a woman of childbearing potential.

(b) Baseline and 24 week CoQ10 and alpha tocopherol levels must be drawn at specified times. 24 week labs are drawn after the completion of 24 weeks of study medication.). 8 week and 16 week levels may be drawn within 1 week pre- or post- specified time due to chemotherapy schedule (every 3 or every 4 weeks).

(c) Serum CoQ10 and alpha tocopherol levels do not have to be drawn prior to registration but must be drawn prior to first chemotherapy treatment.

(d) Due to delay in lab results, patient may be registered within 24 hours of first chemotherapy treatment if labs were drawn prior to treatment.

(e) It is recommended that standard care during chemotherapy include regular assessment of CBC with platelet and differential.

(f) It is recommended that standard care during chemotherapy include assessment of liver function prior to each cycle of chemotherapy.

- \* **Initial labs to be drawn at screening/baseline:** CBC w/diff, plts, Cholesterol, Liver function (to include: Bilirubin, SGOT, SGPT, creatinine, and pregnancy test if applicable.)
- \* **Remaining Baseline:** Serum CoQ10 and serum Alpha tocopherol. See lab instructions.
- \* **Study medication is provided free of charge. Upon patient registration, Biologics will be notified to initiate shipment.**

### **Blood Specimen Collection and Processing (CCOPS/Non CCOP Sites)**

#### **For Alpha Tocopherol and CoQ10:**

1. Approximately 10 ml venous blood sample should be collected into a purple top Vacutainer tube after study registration but before starting any study therapy, and then **before taking the daily dose of study drug at weeks 8, 16, and 24.** (24 week blood sample should be drawn at the completion of 24 weeks of study medication.)
2. The date and *actual collection time* for each specimen should be recorded on the Pharmacology Form. The patient's first and last initials, patient's protocol ID#, and the date and time of the last administration of study drug should be documented on the form.
3. Immediately after collection, each blood sample should be gently inverted several times to ensure good mixing of anticoagulant and blood; the tube should then be placed on ice and protected from light.
4. Within 30 minutes after collection, each sample should be centrifuged (under refrigeration (0-4°C) if available) at 1000x g for 10 minutes to separate the cellular elements from the plasma. Plasma is then transferred into **two** amber colored screw-capped polypropylene transfer tubes in equal amounts and the tubes indelibly labeled with the patient's first and last initials, protocol ID #, and date and actual collection time of blood sample
5. Plasma samples should be stored at -20°C or colder. **All frozen study samples for any one patient should be shipped as a single batch** to Dr. Miler's analytical laboratory on dry ice (see below).

#### **Shipment of Plasma Samples for Alpha Tocopherol and CoQ10 Measurements**

1. The shipment of human blood samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g., cardboard mail tube, corrugated cardboard box).

A biohazard sticker must be affixed to both the inner and outer containers.

2. Samples for CoQ10 and alpha tocopherol analysis should be shipped by overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state for 3 days. A copy of the Pharmacology Form on the following page for each individual patient should be included in the shipment.

**Pharmacology Form**

**INSTRUCTIONS:** This form is to be completed and submitted as required by protocol. Do not leave any entries blank. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Submit a copy to the CCCWFU Protocol office and send original with samples to the laboratory. See protocol for required sample time points. Use military time.

Patient Initials:	Protocol ID #:
Site Name:	Patient institutional ID#:

**Baseline Week 1 Sample**

(Before any study drug)

Date and time of baseline blood sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

**Week 8 Sample**

Date and time of last study drug administration before sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

Date and time of 8 week blood sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

**Week 16 Sample**

Date and time of last study drug administration before sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

Date and time of 16 week blood sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

**Week 24 Sample**

Date and time of last study drug administration before sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

Date and time of 24 week blood sample:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
M	D	Y			H	m	

\*Blood sample should be drawn at completion of 24 weeks of study medication.

Name of person sending samples \_\_\_\_\_ Phone no. or pager no. \_\_\_\_\_

Site name \_\_\_\_\_ Email address \_\_\_\_\_

**FOR LAB USE ONLY**

**Sample Analysis Information**

Sample Receipt + Condition Information

Sample Time Points

Tocopherol

CoQ10 Concentration

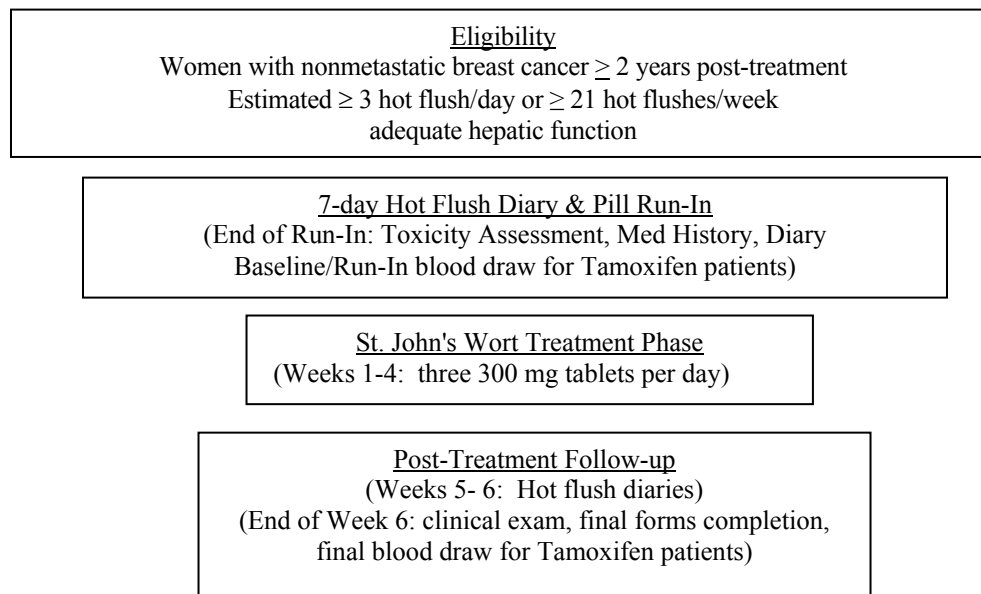
- Usable (1-no, 2- yes)
- Tubes intact? (1-no, 2-yes)
- Biopsies intact? (1-no, 2-yes)

- Baseline
- Week 8
- Week 16
- Week 24

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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A Phase II Study of St. John's Wort for the Treatment of Hot Flushes in Women with a History of **Breast Cancer**  
Michelle Naughton, PhD  
**\*Accrual Goal: 39 patients\***

## Schema



## Objectives

### **Primary Protocol Objectives**

- To determine the effect of St. John's Wort on the alleviation of mild to moderate hot flushes in breast cancer survivors over a 4 week period. Treatment response or efficacy for this Phase II study will be quantitated by the:
  - change in the frequency of hot flushes from baseline to 4 weeks
  - change in the severity of hot flushes from baseline to 4 weeks

### **Secondary Protocol Objectives**

- To evaluate changes in average weekly hot flush scores and duration over the course of the study.
- To evaluate the toxicity of St. John's Wort in breast cancer survivors who experience hot flushes.
- To determine the effect of St. John's Wort on serum Tamoxifen levels in women receiving Tamoxifen therapy.
- To determine the effect of St. John's Wort on general health-related quality of life and mood at 2 and 4 weeks relative to baseline, and during the 2 week post-treatment phase.

## Eligibility Criteria

- noninvasive (ductal carcinoma *in situ*, DCIS), localized breast cancer (includes stage 0-IIIB) or locally recurrent disease if post-treatment and disease-free for  $\geq 2$  years
- treatment with tamoxifen is allowed as long as treatment is planned to continue through the duration of the study (6 weeks). Treatment with other selective estrogen receptor modulators or aromatase inhibitors (such as anastrozole, letrozole, or exemestane) is not permitted while on study.
- age  $\geq 18$  years
- minimum of three hot flushes daily (or  $\geq 21$ /week), as defined by, sweating, flushing, sensation of warmth, night sweats and or rapid heart beat of sufficient severity that the patient desires therapeutic intervention

- adequate hepatic function (total bilirubin  $<2$ ; AST (SGOT)  $\leq 2$  x normal)
- post-menopausal (no periods  $\geq 12$  months; surgical menopause)
- documentation of a normal mammogram in the past 10 months. Patients who are overdue for a mammogram or who are due for a mammogram in the next 2 months will be required to have a normal mammogram prior to study enrollment.
- signed protocol-specific informed consent and authorization form prior to registration.

### Exclusion Criteria

- concurrent therapy with estrogen, progestational agents, corticosteroids, androgens, or other medications directed at alleviating hot flushes (such as clonidine, bellamine, etc.)
- concurrent antidepressant therapies
- history of intolerance St. Johns wort
- recent (within 14 days) use of St. John's wort, monoamine oxidase inhibitor, SSRI (selective serotonin reuptake inhibitor, such as sertraline, paroxetine, fluoxetine, etc), or SNRI (selective norepinephrine reuptake inhibitor, such as venlafaxine).
- Current or planned use of theophylline, warfarin (except for central line prophylaxis), protease inhibitors used to treat AIDS, digoxin, cyclosporin, benzodiazepines (such as diazepam, alprazolam, etc), calcium-channel blockers (such as diltiazem, nifedipine, etc), coenzyme A reductase inhibitors (cholesterol lowering agents), macrolide antibiotics (such as azithromycin, erythromycin, clarithromycin, etc), griseofulvin, phenobarbital, phenytoin, rifampin, rifabutin, ketoconazole, fluconazole, itraconazole, corticosteroids, grapefruit juice. (Call study chairperson with questions about this criterion).
- Current or planned use of cytotoxic chemotherapy.

### Treatment Schedule

Study treatment will consist of St. John's Wort. The St. John's Wort will be dispensed as 300 mg tablets. The dosage for the 4 week treatment phase will be 900 mg or three tablets each morning.

### Treatment Plan

The research PI or designee at each CCCWFU CCOP Research Base, which may include the clinic physician, resident, research nurse or research assistant, will review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified using these methods will be asked to join the study during their next clinic visit or consult. Patients not scheduled for a clinic visit within the next 6 weeks will be sent a letter from their physician informing them about the study, and indicating that a research nurse/assistant will be calling them within the next 10 days to tell them more about the study and to see if they are eligible to participate.

Blood tests for bilirubin and SGOT (AST), a medical history and physical examination (including breast exam) will be completed at baseline. All patients must also be current with their annual mammograms in order to be eligible for the study. In addition, patients currently taking tamoxifen will have an additional blood test to measure tamoxifen levels prior to the initiation of St. John's Wort treatment.

Patients meeting initial eligibility criteria and who agree to participate in the study will sign informed consent, complete the quality of life instruments, and will be given a 7 day "run-in" period to determine if the patients can take one 300 mg St. John's wort tablet each day and complete the hot flush diary as directed. At the end of the 7 day period, patients who experienced no major side effects to St. John's wort and who could complete the hot flush diary as directed will begin the 4 week treatment phase.

**Patients will be told to begin their study pills on a Sunday**, in order to make it easier for participants to complete the diaries. During all four weeks of the treatment phase, patients will take three 300 mg St. John's Wort tablets each morning, and complete the hot flush diaries. Participants will stop taking the SJW

at week 4, but will complete the hot flush diaries through the end of week 6 to ascertain changes in daily hot flushes following the completion of the SJW treatment. Similarly, quality of life assessments will also be completed at week 6 to assess any changes in daily functioning and mood following the completion of therapy.

At weeks 2 and 4, patients will return to the clinic to hand in their completed hot flush diaries, to complete the SF-12 and the Profile of Mood States (POMS) forms, and for the assessment of toxicities and current medications. At week 4 (treatment phase end), patients will be requested to bring in their remaining SJW pills, and will be given two hot flush diaries to complete during weeks 5 and 6. At the end of week 6, patients will return to the clinic for the final visit to hand in their remaining hot flush diaries, complete study forms, and undergo a physical exam.

For patient receiving tamoxifen, blood tests to measure tamoxifen levels will also be required at screening, run-in / baseline, and at weeks 2, 4, and 6.

## 11.0 STUDY PARAMATERS

### STUDY PARAMATERS

	Screening	Baseline/ Run-In (7 days)	Treatment (Weeks 1-4)	Post-Treatment Follow-up (Week 6)
Medical History and Physical Exam (including breast exam)	X			X
Informed consent and authorization	X			
Total Bilirubin <sup>A</sup>	X			
SGOT (AST) <sup>A</sup>	X			
Tamoxifen Levels <sup>C</sup>	X	X	X (weeks 2 and 4)	X
Mammogram	X <sup>B</sup>			X <sup>B</sup>
Hot Flush Diaries		X	X (weeks 1 - 4)	X (weeks 5-6)
SF-12	X		X (weeks 2 and 4)	X (week 6)
POMS Short Form	X		X (weeks 2 and 4)	X (week 6)
Toxicity Assessments	X	X	X (weeks 2 and 4)	X (week 6)
Medication History Updates	X	X	X (weeks 2 and 4)	X (week 6)
Information Form	X			X (verification only)

A - LFT's (Total Bilirubin and SGOT (AST)) are required within six months of study entry.

B- A normal mammogram is required within the last 10 months prior to registration. Mammogram at week 6 as clinically indicated.

C - Tamoxifen levels will be assessed only on those participants taking Tamoxifen while on study.

## **Initial Labs to be drawn:**

**Baseline:** Liver function test to include total bilirubin and SGOT (within last 6 months), Tamoxifen level if applicable.

**Mammogram required within last 10 months.**

**St. John's Wort will be provided free of charge for the study.**

## **Blood Specimen Collection and Processing (CCOPS/Non CCOP Sites)**

### **For Tamoxifen Level:**

1. (1) 7 ml venous blood sample collected into a EDTA purple top Vacutainer tube should be drawn at protocol registration before starting any study medication, 7 day run in / Baseline and then at 2, 4 and 6 weeks.
2. Immediately after collection, each blood sample should be gently inverted several times to ensure good mixing of anticoagulant and blood; the tube should then be placed on ice and protected from light.
3. Within 30 minutes after collection, each sample should be centrifuged (under refrigeration (0-4°C) if available) at 1000x g for 10 minutes to separate the cellular elements from the plasma. Plasma is then transferred into **two** amber colored screw-capped polypropylene transfer tubes in equal amounts and the tubes indelibly labeled with the patient's first and last initials, protocol ID #, and date and actual collection time of blood sample.
4. Plasma samples should be stored at -20°C or colder. **All frozen study samples for any one patient should be shipped as a single batch** at the completion of the study to Dr. Miller's analytical laboratory on dry ice (see below).

### **Shipment of Plasma Samples for Tamoxifen level:**

1. The shipment of human blood samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g.-corrugated cardboard box). A biohazard sticker must be affixed to both the inner secondary and outer containers.
2. Samples for Tamoxifen analysis should be shipped by overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state for 3 days. The samples should not be sent to arrive on Saturdays, Sundays or holidays.
3. The date and *actual collection time* for each specimen should be recorded on the Pharmacology Form. The patient's first and last initials, and patient's protocol ID #, should be documented on the form. A copy of the Pharmacology Form on the following page for each individual patient should be included in the shipment.

4. Prior to patient registration, a completed Form 310 or IRB approval letters must be submitted to the CCCWFU CCOP Research Base Data Management Center at the following address:

Attn: CCCWFU CCOP Research Base Data Management Center  
Wake Forest University School of Medicine  
Department of Radiation Oncology  
Medical Center Boulevard  
Winston Salem, NC 27157-1030

After receiving the Form 310, or IRB approval letter, the CCCWFU CCOP Research Base Core Laboratory will send each site Patient Specimen Collection/Shipping Kits. These kits comply with the appropriate regulations for the shipment of human tissues as specified by the carrier.

Each kit contains the following:

1 insulated shipper  
10 -2ml amber vials with tape  
10 vial labels  
5 - 7ml KEDTA vacutainers  
5- 3x5" amber bags (use these inside your own biohazard transport bag to protect sample from light)  
5 -transfer pipettes  
Dry Ice Hazard Label  
Biohazard Label  
UN 3373 Diagnostic Specimen Label  
IATA Approved 95kp secondary shipping receptacle  
3x5" secondary receptacle  
Absorbent Material  
Bubble wrap

5. All samples should be shipped overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state. A copy of the Hyperforin Pharmacology Form on the following page for each individual patient should be included in the shipment.
6. All pharmacokinetic plasma specimens are to be shipped to:

Attn: Andrea Rice  
CCCWFU CCOP Research Base Core Laboratory  
Wake Forest University School of Medicine  
Medical Center Boulevard  
Hanes Building, 4<sup>th</sup> floor, Room 4012  
Winston Salem, NC 27157

Please notify Andrea Rice by telephone (336) 716-2573 or by fax (336) 716-0255 at least 24 hours prior to shipment. Samples should be shipped to arrive Tuesday, Wednesday, Thursday or Friday. **Samples must not be sent to arrive on the week-end or holidays.**



**Randomized Study of Soy Protein and Effexor™ on Vasomotor Symptoms of Men with Prostate Cancer**

Recruit, Screening, and Consent  
Men receiving hormonal manipulation treatment for prostate cancer

↓  
Determine Eligibility-Pre Study period  
Seven days symptom recording

**Baseline Assessment**

Total Bilirubin/SGOT      Blood pressure  
Height and weight          Fact-P  
Soy food questionnaire    Medications and Supplement form  
↓ Toxicity Assessment Sheet

Enroll in study [stratified: disease severity (metastatic vs non-metastatic) and baseline severity of hot flashes] and randomized: 2 x 2 factorial design

**Arm A**

↓  
Soy protein powder (20gm)  
+ Placebo pill

**Arm B**

↓  
Casein powder  
+ EffexorXR™-75mg

**Arm C**

↓  
Soy protein powder-(20gm)  
+ EffexorXR™-75 mg

**Arm D**

↓  
Casein protein powder  
+ Placebo pill

**2 week Clinic visit**

Hot Flash Symptom and Adherence Diary  
Medications and supplement form  
Blood pressure      ↓ Toxicity Assessment Sheet, Other

**4 week contact (telephone)**

Hot Flash Symptom and Adherence Diary  
Medications and Supplement Form  
Toxicity Assessment Sheet

**8 week contact (telephone)**

Hot Flash Symptom and Adherence Diary  
Medications and Supplement Form  
Toxicity Assessment Sheet

**12 week clinic visit**

Blood pressure  
Weight  
Fact-P  
Medications and Supplement Form  
Hot Flash Symptom and Adherence Diary  
Instruction for how to taper Effexor XR™, other

**Sample Size: A maximum of 176 men**

**Time on study: 7 day pre-screening symptom recording and 12 weeks on “treatment”**

## **OBJECTIVES**

### **Primary Protocol Objective**

Assess the effect of soy and Venlafaxine (EffexorXR™) on the hot flash symptom severity score in men receiving hormonal manipulation treatment for prostate cancer

### **Secondary Protocol Objective**

Assess the effect of soy and EffexorXR™ on quality of life in men receiving hormonal manipulation treatment for prostate cancer  
Monitor and assess participant drop out rate

## **Eligibility**

- Histologic documentation of prostate cancer, any stage
- Life expectancy of  $\geq$  nine months
- Currently undergoing hormonal manipulation for treatment or control of prostate cancer to include orchiectomy or LHRH agonist, with or without antiandrogen therapy. PATIENTS MAY UNDERGO CONCURRENT RADIATION THERAPY TO THE PROSTATE, PROSTATE + SEMINAL VESICLES, AND/OR PELVIS.
- Participant report of hot flash frequency of an average of four or more per day, as defined by sweating, flushing, sensation of warmth, night sweats
- Participants report of overall hot flash severity as moderate to severe
- Age  $\geq$ 21
- No allergies to soy or dairy products
- No current use of SSRIs, MAOIs
- No preexisting hypertension or greater than Class I American Heart Association functional capacity
- No history of mania, hypomania, bipolar disorder, or anorexia nervosa
- No history of seizures
- Adequate hepatic function (total bilirubin  $<$ 2; AST (SGOT)  $\leq$ 2 x institutional ULN)
- Must have a telephone
- Signed protocol-specific Informed Consent
- Participant must be willing to discontinue and/or avoid consuming soy foods or soy based supplements during study participation

## **Exclusion**

- Concurrent therapy with estrogen, progestational agents, corticosteroids, androgens, or other medications directed at alleviating hot flashes (such as clonidine, bellamine, etc.)
- Anticipated changes in hormone treatment regimen, currently receiving chemotherapy or anticipating surgery
- Concurrent antidepressant therapy
- History of intolerance to venlafaxine
- Recent (within 14 days) use of venlafaxine (Effexor™), monoamine oxidase inhibitor, SSRI (selective serotonin reuptake inhibitor), or SNRI (selective norepinephrine reuptake inhibitor)
- History of seizure disorder

### **Treatment Schedule**

**Pre-study period (7 days)** Candidates who are screened during a clinic visit and are eligible and willing to participate in the study, will be asked to complete the informed consent form at that visit, if possible. Patients signing the informed consent form will be asked to complete a vasomotor symptom diary for the next 7 days to document their baseline level of hot flashes. This week long period will also enable study personnel to determine if the patient is able to comply with completing the diary correctly during the entire 7 day period. Candidates experiencing difficulty in completing the diary correctly and/or completely will be counseled again in correct diary completion, and will be asked to complete a second 7 day vasomotor symptom diary to see if their recording of vasomotor symptoms improves. At the end of the second 7 day period, if the patient still has not completed the diary correctly and/or completely, the candidate will not progress to the study intervention phase of the study and will be dropped.

**The candidate must have an average of four or more hot flashes per day (i.e., 28 or more hot flashes for the week) and must report that his symptoms were moderate to severe. Candidates reporting fewer flushes will be deemed ineligible.**

**Baseline** After the 7 day baseline record of hot flashes, participants are randomly assigned, in a blinded fashion, to (1) Effexor XR™ 75mg po qAM and casein powder (20 gms) 1 packet/day; or (2) placebo pill po qAM and soy protein powder (20 gms with 160 mg isoflavones) 1 packet/day; or (3) Effexor XR™ 75mg po qAM and soy protein powder (20 gms with 160 mg isoflavones) 1 packet/day; or (4) placebo pill po qAM and casein powder placebo (20 gms) 1 packet/day.

The participant will be issued a one month supply of study powder, pills and vasomotor symptom diaries. During the study period, participants will take one pill and consume one packet of study powder each day. Participants will be instructed to begin their study treatments on a **Sunday**, in order to make it easier to complete the symptom diaries. Participants will be instructed to document symptoms in the diary each day and to indicate if they took their pill and study powder each day.

**Week 2** A clinic visit will be made during the second week of the study to measure the participant's blood pressure and evaluate how he is doing in completing the diaries, and to see if he has any questions about the study powder and pills, and to encourage compliance.

**Week 4** The participant will be contacted by telephone to complete forms and check compliance. Patients will also be asked to return their 4 week Hot Flash Symptom and Adherence Diaries to the study coordinators in the same envelope. Patients will be sent the next month's pills by the study site.

**Week 8** the participant will be contacted by telephone to complete forms and check compliance. Participants will also be asked to return their 8 week Hot Flash symptom and Adherence Diaries to the study coordinators in the same envelope. Patients will be sent the next month's pills by the study site.

**Week 12** Patients will come to the clinic to be weighed and have their blood pressure Measures. They will be asked to return their remaining powders, pill bottle, pills, and all of their remaining symptom diaries. They should be provided with enough pills to complete the taper during week 13.

\*\*\* **Week 13** Patients will be instructed to taper their pills to one every other day for 1 week.\*\*\*

**Agent Ordering and Distribution**

Following patient registration, Biologics, Inc will be notified through the On- line registration process. Biologics will contact the site directly to obtain specific shipping information. All treatment required for the participant complete the study will be delivered to the site in one shipment.

**Administration**

Effexor XR is a tablet to be taken by mouth every morning through week 12.

**Effexor/Placebo will be tapered to one pill every other day for week 13.**

**STUDY PARAMETERS**

**Lab tests required within four weeks of registration**

Study Measure	Pre-study Period (7 days)	Baseline	Week 2 Clinic contact	Week 4 Telephone contact	Week 8 Telephone contact	Week 12 Clinic contact
Hot Flash Symptom Diary (Appendix A)	X					
Hot Flash Symptom and Adherence Diary (Appendix B)		X	X	X	X	X
Soy Food Questionnaire		X				
Toxicity Assessment Sheet		X	X	X	X	X
Fact-P		X				X
Medications & Supplement Form		X	X	X	X	X
Total Bilirubin (flowsheet)		X				
SGOT (AST) (flowsheet)		X				
Height (flowsheet)		X				
Weight (flowsheet)		X	X			X
Blood Pressure (flowsheet)		X	X			X

- \* **Initial labs to be drawn at baseline:** Total Bilirubin, SGOT
- \* **Study medication is provided free of charge.**
- \* **Upon patient registration, Biologics will receive notification to initiate shipment of study drug.**