Title: A Single Arm Phase II Study of Oral Vitamin B12 for the Treatment of Aromatase Inhibitors (AI)-Associated Musculoskeletal Symptoms (AIMSS) in Women with Early Stage Breast Cancer

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SUMMARY

Significant aromatase inhibitor (AI)-associated toxicity, affects as many as 50% of patients with breast cancer leading to early discontinuation of this life-saving cancer treatment. No effective pharmacologic therapy has yet been identified for management of these symptoms, as many patients do not experience relief of symptoms with analgesic therapy. Improvement in treatment-related symptoms is needed and may improve compliance with AI therapy, and thereby lead to improved breast cancer outcomes. Vitamin B12, whether as injection or oral forms, has been used as a naturopathic product to provide relief for joint pain caused by arthritis. Vitamin B12, in addition to its neurological and hematological functions, suppresses the cytokine production of T lymphocytes at articulation lesion sites which might explain, in part, its reported benefit in arthritis. This effect has not been studied in the setting of Aromatase Inhibitor-associated Musculoskeletal Symptoms (AIMSS). However, patients who use vitamin B12 report anecdotally that they feel relief from AIMSS. We are proposing a Phase II open label, single arm clinical trial of Vitamin B12 2500 mcg daily to evaluate the benefit of vitamin B12 for management of (AIMSS) and other related symptoms that can impact quality of life. We will also perform exploratory correlative studies for hypothesis generation.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below. Aromatase inhibitors are not used in men with breast cancer; therefore, men will not be included in this study.

Ethnic Category			
	Females	**Males**	**Total**
Hispanic or Latino	30	0	30
Not Hispanic or Latino	5	0	5
Total Ethnic	35	0	35

SCHEMA

Enrollment/Informed Consent obtained

Women with hormone receptor-positive breast cancer who are receiving AIs and report average pain of at least 4 (out of 10) on the BPI-SF that has started or increased since initiation of AI treatment

Days 0, 45, AND 90:
Staff administered assessments and patient-completed questionnaires via an iPad or if unavailable via paper copies
(FACT-ES, BPI-SF, Assessment of AI Adherence, Demographics, and Supplemental Agents Reporting Form, AE assessment at day 45 and 90)

Days 0, 45, AND 90:
Blood collection to test CRP, Vitamin B12, MMA, and homocysteine levels before protocol treatment, at day 45, and at day 90

Oral Intake of Vitamin B12 Daily X 90 days

Day 90 (at 12 weeks):
COMPLETION OF STUDY TREATMENT

1.0 OBJECTIVES

1.1 Primary Objective

To assess whether daily oral Vitamin B12 decreases average joint pain in women with Aromatase Inhibitor-Associated Musculoskeletal Symptoms (AIMSS), as measured at baseline, day 45 (+/- 10 days) and day 90 (+/- 10 days) by the modified Brief Pain Inventory Short Form (BPI-SF).

1.2 Secondary Objectives

a. To investigate whether daily vitamin B12 improves functional quality of life as measured at baseline, at day 45 (+/- 10 days), and at day 90 (+/-10 days) by the Functional Assessment of Cancer Therapy-Endocrine Scale (FACT-ES);

b. To explore the impact of treatment on serum inflammatory cytokine levels (C-REACTIVE PROTEIN) between baseline, day 45 (+/-10 days), and day 90 (+/- 10 days) of treatment.

2.0 BACKGROUND

Almost 180,000 women are diagnosed with breast cancer each year in the United States (1). The incidence of breast cancer increases with age; approximately 75% of patients are postmenopausal at the time of diagnosis. In addition, hormone receptors (HR) are over expressed on 80% of breast cancer tumors in postmenopausal women. Therefore, more than 100,000 postmenopausal women who are diagnosed with breast cancer each year in this country are potential candidates for anti-endocrine breast cancer therapy.

Two classes of anti-endocrine therapies are used for treatment of HR-positive breast cancer: tamoxifen and the aromatase inhibitors (AIs). AIs can only be used to treat postmenopausal women because they are ineffective in women with functional ovaries. Because of their superior efficacy, AIs are increasingly used for adjuvant treatment of

postmenopausal women with HR- positive breast cancer. Based on currently available data, women are treated with either tamoxifen or AI therapy for 5 years, although studies are underway to determine if treatment should be continued for a longer period of time.

AI-associated Musculoskeletal Symptoms (AIMSS)

It has been increasingly recognized that arthralgias are a significant AI-associated toxicity, affecting as many as 50% of patients (2, 3). No factors associated with breast cancer treatment (such as chemotherapy) or co-morbid conditions (such as diabetes or body mass index) have been clearly shown to be predictive of the development of arthralgias (3). The etiology of AI-associated musculoskeletal symptoms remains elusive. The hypotheses include direct effects of estrogen deprivation on bone, neurohormonal changes which result in change of pain sensitivity, and immune system changes resulting in alteration of circulating or local inflammatory cytokine concentrations.

A greater than 20% treatment discontinuation rate due to AI-associated arthralgias in a prospective trial of AI therapy was reported (4, 5). Based on the number of patients treated with aromatase inhibitor therapy and the incidence of musculoskeletal symptoms that occur with therapy, as many as 40,000 women are affected by this toxicity in the United States annually. More importantly, up to 20,000 women discontinue these potentially life-saving medications because of intolerable arthralgias and myalgias.

No effective pharmacologic therapy has yet been identified for management of these symptoms, as many patients do not experience relief of symptoms with analgesic therapy. The current treatment for AIMSS is limited to oral analgesics and exercise, however, neither intervention has optimal effect, and long term use of oral analgesics is problematic.

Currently a phase III trial is ongoing nationwide S1202, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Our site at Texas Tech University Health Sciences Center El Paso (TTUHSC-EP) is participating in this study. However, it is limited to English speaking patients only; therefore the majority of our breast cancer patients are not able to participate in this clinical trial. Also, those who qualify have been reluctant to participate due to the significant and serious side effects listed for Duloxetine, including death.

Testing Vitamin B12 for the treatment of AIMSS

We are proposing to study the effect of Oral Vitamin B12 on reducing the symptoms of AIMSS. Vitamin B12, whether as injection or oral forms, has been used as a naturopathic product to provide relief for joint pain caused by arthritis (6). Preclinical data suggests that in vitro, Vitamin B12 suppresses the cytokine production of T lymphocytes which are expressed also in vivo in patients with rheumatoid arthritis, especially at articulation lesion sites (7). This might explain the anecdotal benefit reported in patients with arthritis. **We are proposing a Phase II open-label clinical trial of Vitamin B12 2500 micrograms per day over the course of 90 days (+/- 10 days) to assess the impact on postmenopausal women who have been treated with AI therapy for at least 2 weeks and who have developed new or worsening pain after starting AI therapy (details below).** Although there are minimal data to suggest that women with AIMSS have altered levels of circulating inflammatory markers prior to therapy, we would explore whether it is possible that treatment with vitamin B12 could impact serum concentrations of pro- or anti-inflammatory factors, such as C-Reactive Protein (CRP) or that subsets of women who have altered levels prior to treatment initiation could be more likely to benefit.

One of the reasons for our decision to explore the possible beneficial effect of vitamin B12 to treat AIMSS is our experience at the TTUHSC-EP Garbar Breast Care Center, where we conducted a pilot study to evaluate quality of life (QOL) in breast cancer survivors. Our findings support that QOL levels appear to be lower in women taking AIs. The study included patients with breast cancer who were within the first 5 years post-diagnosis after having completed surgery/chemotherapy/radiation therapy **(Figure 1).** We assessed their quality of life (QOL) using a multi-purpose health related QOL questionnaire, the SF-36. The SF-36 scores were analyzed as two summary scales—one for physical health called the SF-36 Physical Component Summary (PCS) and a second for mental health called the Mental Component Summary (MCS). We noted the following: 60% of breast cancer survivors are receiving or have received anti-endocrine "hormonal therapy" and all patients had a low mean PCS at 40.4 and a mean MCS at 47.8, both lower than U.S. norm and values in other breast cancer survivors. Also, there was a lower Mental QOL in patients receiving or who have received hormonal therapy. The difference in the means for MCS was found to be statistically significantly lower

according to hormonal therapy status, 45.48 versus 51.5, p=0.006 (manuscript submitted under peer review).

Figure 1. Patient Characteristics in the Pilot study conducted at the Garbar Breast Care Center-TTUHSC-EP (Manuscript in peer review)

Variable	N (%)
Age [mean (SD) years]	57.75 (10.03)
Duration of diagnosis [median (IQR) years]	2.00 (1, 4)
Stage	
I	33 (32.35)
II	47 (46.08)
III	22 (21.57)
Chemotherapy received	
Yes	69 (67.65)
No	33 (32.35)
Hormonal therapy received	
Yes	61 (60.40)
No	40 (39.60)
Language	
English	23 (22.55)
Spanish	79 (77.45)

3.0 DRUG INFORMATION

Vitamin B-12 (or cobalamin) is one of multiple vitamins that belong to a family of vitamins known as the B vitamins. Vitamin B12 is water soluble and can't be made in the body, therefore, it must be obtained by food or supplements. Dietary sources are found primarily in animal-derived foods such as dairy, eggs, meat, poultry and fish. Vitamin B-12 plays an essential role in a variety of bodily processes such as development and maintenance of red blood cells, nerve

cells, normal covering (myelination) of nerve cells, cellular metabolism, DNA and RNA synthesis and energy production.

Deficiencies in Cobalamin (Cbl) can lead to altered neurological and hematological functioning. Neurological deficiencies may affect the central and peripheral nervous systems and may manifest in the body as depression, cognitive difficulties, memory loss, paranoia, peripheral neuropathy and decreased sensation in peripheral nerves (8). Other symptoms include weakness and fatigue. Interestingly, 7-30% people over the age of 60 have vitamin B12 deficiency, yet their presentation is 'subclinical' also known as 'functional cobalamin deficiency' (9, 10). That is, though blood analysis may reflect that levels of vitamin B12 that are in the low normal range, levels of cobalamin metabolites such as methylmalonic acid (MMA) or homocysteine are elevated and may be the first sign of deficiency (10).

Risk factors in developing Vitamin B12 deficiency include: strictly vegetarian or vegan diets, excessive alcohol intake, atrophic gastritis, Helicobacter pylori infections, intestinal pathology and certain medications. Older adults are at risk for developing deficiency due to atrophic gastritis which decrease the production of gastric acids that are essential in the digestion of meat derived foods and subsequent absorption of the vitamin. Vitamin B12 is absorbed in the small intestine therefore illness or surgery of the small intestine, bariatric surgery or gastrectomy may also lead to deficiency (11). Defining deficiency is another task for the clinician as there are various interpretations of lab results. Serum Vitamin B12 concentrations of 150-160 pmol/L are indicative of overt deficiency (11).

There is no consensus regarding how best to measure vitamin B12 deficiency as some studies use only serum Vitamin B-12 levels, while other studies use serum B12 levels in conjunction with methylmalonic acid (MMA) levels. Methylmalonic acid is considered highly sensitive and specific marker to determine vitamin B12 deficiency. As previously mentioned, many patients are identified with subclinical vitamin B12 deficiency which can be found in patients with cobalamin levels <200 ng/L (12). Supplementation of Vitamin B12 is a low risk endeavor since there is no Tolerable Upper Intake Level (UL) (11).

Vitamin B12 comes in a variety of forms including: Cyanocobalamin, Methylcobalamin, hydroxocobalamin and adenosylcobalamin. When ingested, cyanocobalamin is converted to

other forms of the vitamins in the liver. The conversion starts with hydroxocobalamin then into methylcobalamin and adenosylcobalamin which are stored in the liver. All forms of vitamin B12 are deemed safe as the risk of toxicity with the vitamin is very low because it is water-soluble and so easily removed from the body. The vitamin B12 form known as cyanocobalamin is inexpensive and readily available at pharmacies, health food stores or grocery stores.

The dose of Vitamin B12 as recommended by RDA is 2.4 mcg/dl for the general population 51 years and older (13). One often used method of vitamin B12 replacement in deficient patients is parenteral injection of the vitamin, in spite of the fact that oral Vitamin B12 is available. One review of the literature cited two randomized controlled trials that compared oral versus parenteral vitamin B12 administration. Though the number was small, the outcomes of both studies indicate that oral Vitamin B12 in doses ranging from 1000-2000 mcg is as effective as parenteral Vitamin B12 (14).

How supplied?

- We will use 1 tablet of vitamin B-12 2500 mcg for sublingual (SL) consumption.
- This product is usually stored at room temperature between 59-86 degrees F (15-30 degrees C) away from light and moisture.
- Certain medications can decrease the absorption of vitamin B12, including: colchicine, metformin, extended-release potassium products, antibiotics (such as gentamicin, neomycin, tobramycin), anti-seizure medications (such as phenobarbital, phenytoin, primidone), medications to treat heartburn (such as H2 blockers including cimetidine/famotidine, proton pump inhibitors such as omeprazole/lansoprazole). The vitamin B12 tablet will be taken sublingually, 1 hour after meals in AM, daily for 90 days (+/- 10days).

4.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for participation.

A. Disease Related Criteria

1. Patients must be women with histologically confirmed estrogen receptor (ER) and/or progesterone receptor (PgR) positive invasive carcinoma of the breast (Stage I-III) with no evidence of metastatic disease (M0).
2. Patients must have completed mastectomy or breast sparing surgery, and must have recovered from all side effects of the surgery. Patients should have recovered from all Grade 2 or higher side effects of chemotherapy and/or radiation therapy with the exception of alopecia and peripheral neuropathy. Concurrent bisphosphonate and trastuzumab therapies are allowed.

B. Clinical/Laboratory Criteria

1. Patients must be post-menopausal, as defined by at least one of the following:
   a. ≥ 12 months since the last menstrual period OR
   b. Prior bilateral oophorectomy OR
   c. Previous hysterectomy with one or both ovaries left in place (or previous hysterectomy in which documentation of bilateral oophorectomy is unavailable) AND (unless ≥ 60 years of age) FSH values consistent with the institutional normal values for the post-menopausal state.

2. Patients must currently be taking one of the following aromatase inhibitor (AI) doses for at least 14 days prior to registration and plan to continue for at least an additional 180 days after registration:
   a. Anastrozole (Arimidex®) 1 mg daily OR
   b. Letrozole (Femara®) 2.5 mg daily OR
   c. Exemestane (Aromasin®) 25 mg daily

3. Patients must have aromatase inhibitor (AI) associated musculoskeletal symptoms that began or increased after starting AI therapy. New musculoskeletal pain must not be due specifically to fracture or traumatic injury.

4. Patients must have completed the Brief Pain Inventory-Short Form (BPI- SF) via an iPad or if unavailable or due to technical

difficulties via paper copies within 7 days after enrollment. Patients must have an "average pain" of at least 4 on the BPI-SF (item #5).

5. Patients must have Zubrod performance status of 0-2.

6. Patients must have no known allergy or hypersensitivity to vitamin B12.

7. Patients must not have any contraindicated concurrent illnesses including:
   a. History of alcohol or other substance abuse or dependence within 365 days prior to enrollment.
   b. Chronic liver disease.
   c. End stage renal disease.

8. Patients who are receiving treatment with narcotics, tramadol, gabapentin, and/or pregabalin must have been taking a stable dose for at least 30 days prior to registration.

9. Patients must be able to complete study questionnaires in English or Spanish, which will be given via an iPad or if unavailable or due to technical difficulties via paper copies.

10. Patients who are currently taking vitamin B12 or a multivitamin containing vitamin B12 will be able to participate in the study after having stopped taking the vitamin B12 or the multivitamin containing the B12 for two weeks.

C. Specimen Submission Criteria

1. Patients must be willing to submit blood samples for laboratory testing [to test for Serum Vitamin B12, C-Reactive Protein (CRP), homocysteine level, and Methyl Malonic Acid (MMA)]. Baseline samples must be obtained prior to beginning protocol treatment.

D. Regulatory Criteria

1. All patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.0 TREATMENT PLAN

This is a single arm study; therefore, all patients enrolled will take 1 tablet of Vitamin B12 2500 mcg, 1 hour after meals in AM, daily for 90 days (+/- 10 days). As it is a single arm study, there will be no control group. Patients will be provided with a calendar to keep track of their intake. Each patient will receive 2 bottles (each containing 60 tablets) total over the course of 90 days.

5.1 Study Plan

Breast cancer patients seen at the Garbar Breast Care Center during their routine follow-up visits with their medical oncologist will be screened and referred to the clinical research coordinator. Patients will have a general physical exam (including a record of their height and weight). The study coordinator will explain the study to the patient, answer their questions related to the study and obtain written consent and enroll them into the study. Consented patients will then be required to complete the Brief Pain Inventory Short Form questionnaire, which will be administered via an iPad or if the iPad is unavailable, it will be administered via paper copies. The referring medical oncologist will then verify that the patient had an "average pain" score of at least 4 on the BPI-SF to confirm eligibility criteria. Once this information has been confirmed, the clinical research coordinator will proceed administering the remaining questionnaires via an iPad but if the iPad is unavailable or due to technical difficulties, they will be administered via paper copies, the FACT-ES questionnaire, the AI Adherence Assessment, and the Demographics questionnaires. Additionally, with the patient's assistance, the study coordinator will fill out the Agent Reporting Questionnaire also via an iPad or if unavailable via paper copies.

<u>Initial Visit</u>

Within 10 days of signing the consent form, the patient will be scheduled for their Initial/baseline visit, which will include the following:

1. Blood collection for laboratory testing:

a. Serum B12 levels
b. C-Reactive Protein (CRP)
c. Homocysteine level
d. Methylmalonic Acid (MMA)

2. Administration of questionnaires via iPad or if unavailable via paper copies, which will include the following:
   a. Brief Pain Inventory – Short Form survey
   b. FACT-ES Trial Outcome Index (Version 4)
   c. "Questionnaire to Assess Adherence to Aromatase Inhibitors" (AI).
   d. Demographics Questionnaire
   e. Supplemental Agents Reporting Form (to be filled out by the clinical research coordinator)

   It should take approximately 20-25 minutes to complete the questionnaires.

3. Dispensing of Vitamin B12 - The patient will be provided with a bottle containing 60 tablets of vitamin B12 2500 mcg and instructed to take 1 tablet sublingually, 1 hour after their morning meal for the next 45 days (+/- 10 days)

4. Intake Calendar for Vitamin B12 - The patient will be provided with a vitamin B12 intake calendar and instructed to record on the calendar the days that they take the vitamin B12 tablet.

5. Intake Calendar for AI - The patient will be provided with an AI intake calendar and instructed to record on the calendar the days that they take the AI tablet.

6. Instructions for Follow-Up Visit - The patient will be instructed to bring their vitamin B12 bottle and both of their intake calendars to their follow-up visit on day 45 (+/- 10 days).

<u>Follow-up Visits</u>

The patient will be asked to return for follow-up visits on day 45 (+/- 10 days) and on day 90 (+/- 10 days). Follow-up visits will consist of the following:

1. Blood collection for laboratory testing which will be performed at the University Medical Center Outpatient Laboratory:
    a. Serum B12 levels
    b. C-Reactive Protein (CRP)
    c. Homocysteine level
    d. Methylmalonic Acid (MMA)

2. Administration of questionnaires via iPad or if unavailable via paper copies, which will include the following:
    a. FACT-ES Trial Outcome Index (Version 4)
    b. (BPI-SF) questionnaire
    c. "Questionnaire to Assess Adherence to Aromatase Inhibitors" (AI) (Administered only at baseline and on Day 90 +/- 10 days, not to be administered at Day 45)
    d. Supplemental Agents Reporting Form (to be filled out by the clinical research coordinator with assistance from the patient)
    e. The Adverse event summary form will be also administered on days 45 and 90 (+/-10 days) (to be filled out by the clinical research coordinator with assistance from the patient)

    It should take approximately 20-25 minutes to complete the questionnaires.

3. Vitamin B12, Intake Calendars, and Swift Pay Card - On day 45 (+/- 10 days), the study coordinator will give the patient a new bottle of Vitamin B12, two new intake calendars, one for the Vitamin B12 and another for the aromatase Inhibitor, and a $25 Swift Pay card.

4. Pill Count - The study coordinator will collect the bottles of Vitamin B12 from the patient, perform a pill count, and record the information on the Investigational Agent Accountability Record on day 45 (+/- 10 days) and day 90 (+/- 10 days).

5. Intake Calendars - The study coordinator will collect the Vitamin B12 intake calendar and the AI intake calendar on days 45 (+/- 10 days) and 90 (+/- 10 days).

6.0 DOCUMENTATION

Drug compliance will be recorded by patients in the Intake Calendar. The clinical research coordinator will review and ascertain patient adherence with protocol therapy at the end of treatment for each visit. Note that the Vitamin B12 and AI Intake Calendars will be provided only as a tool for tracking patient compliance. Counts of tablets remaining in the Vitamin B12 bottles will be recorded on the Investigational Agent Accountability Record. Adverse events will be assessed and recorded on the Adverse Event Summary Form during each study visit. Use of pain medications, steroids, physical therapy, and acupuncture will be recorded on the Supplemental Agents Reporting Form.

The clinical research coordinator will also complete the Cover Sheet for Patient-Completed Questionnaires at each visit to indicate whether or not the patient completed the questionnaires, if the patient required assistance and the method for completing the questionnaires. If one or more of the questionnaires was not completed, an overall reason will be indicated on the Cover Sheet.

7.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

1 NCI Common Terminology Criteria for Adverse Events

The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of the CTCAE.

2 General Considerations

Patients who are taking narcotics, tramadol, gabapentin, and/or pregabalin at study enrollment should continue to take a stable dose of medication. Dose increases for these medications should be discouraged.

Patients who need additional analgesic medication during study participation are requested to take acetaminophen. Patients should not undergo therapy with other treatment modalities such as physical therapy, acupuncture, systemic steroids, or intra- articular steroid injections during study participation unless medically necessary. Usage of all medications and other therapies for treatment of pain should be documented.

3 Dose Modifications

No dose modifications of Vitamin B12 are allowed. Follow-up will be conducted at the intervals specified in the protocol.

8.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

1 **Primary Outcome**

Reduction in average joint pain according to the Brief Pain Inventory – Short Form (BPI- SF) average pain score. This item has a scale of 0 to 10 with 0 indicating "No pain" and 10 indicating "Pain as bad as you can imagine" [assessed within 10 days prior to study enrollment, at Days 45 (+/- 10 days) and at Day 90 (+/- 10 days)].

2 **Main Secondary Outcome**

Reduction in worst joint pain according to the BPI-SF worst (maximum) pain score at day 90 (+/- 10 days). This item has a scale of 0 to 10 with 0 indicating "No pain" and 10 indicating "Pain as bad as you can imagine".

3 **Performance Status**

Participants will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

9.0 STATISTICAL CONSIDERATIONS

1.0 Primary Endpoint

The primary endpoint is improvement in the BPI-SF scale. Joint pain will be assessed using "average pain" according to the BPI-SF. Enrollees must currently be taking AIs and must exhibit joint pain with a minimum BPI-SF average pain score of 4; scores of 4 to 10 are considered to reflect moderate to severe pain. (15)

2.0 Secondary Endpoints

The following secondary analyses will be conducted:

a. Improves functional quality of life as measured by the Functional Assessment of Cancer Therapy-Endocrine Scale (FACT-ES).(16,17)

b. Decreases the use of supplemental agents.

A. Sample Size: The improvement in BPI-SF worst pain scores and pain severity scores were observed in between 70% to 90% in a study of comparing the effect of acupuncture for the management of Aromatase Inhibitor–Associated Joint Symptoms in women with early-stage breast cancer (18). We expect at least 20% improvement in BPI-SF pain scores (less than half of the estimated effect with acupuncture) with a common standard deviation of 30% (a conservative estimate based on a published study). Using this information, we need at least a total of 30 patients to achieve more than 85% power to detect the differences in BPI-SF pain scores relative to baseline using a two tailed paired t-test with 5% level of significance. After accounting for 15% dropouts, we estimated to include at least 35 patients in the study. The sample size estimate was calculated using PASS 12 (19).

B. Data Analysis: Data will be described using appropriate summary measures. The difference in mean pain scores between pre and post treatment with 95% confidence interval (CI) will be estimated. A paired t-test will be used to determine the significant effect of Vitamin B12 on pain scores and quality of life scores. Further, the pain scores will be categorized and compared from the baseline using Mc Nemar's test. Pearson's correlation analysis will be carried out between quality of life scores and pain scores. Heterogeneity effect of the treatment on the pain scores will be examined using cluster analysis. P-values less than 5% will be considered significant results. All statistical analyses will be carried out using SAS 9.3.

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APPENDIX

I. Study Calendar

II. Brief Pain Inventory – Short Form Questionnaire

III. Demographics Questionnaire

IV. FACT-ES Questionnaire (Version 4)

V. Aromatase Inhibitor Adherence Questionnaire

VI. Supplemental Agents Reporting Form

VII. Vitamin B12 Intake Calendar

VIII. Aromatase Inhibitor Intake Calendar

IX. Investigational Agent Accountability Record

X. Coversheet for Patient Completed Questionnaires

XI. Adverse Event Summary Form

XII. Eligibility Criteria Checklist

XIII. Laboratory Results Form

I. Study Calendar

		α						π						√
		Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk
		0	1	2	3	4	5	6	7	8	9	10	11	12
REQUIRED STUDIES	PRE	D	D	D	D	D	D	D	D	D	D	D	D	D
	STUDY	1	8	15	22	29	36	45(+/- 10 DAYS)	50	57	64	71	78	90 (+/- 10 DAYS)
Informed Consent Signed*	X													
PATIENT COMPLETED QUESTIONNAIRES														
Brief Pain Inventory-Short Form (BPI- SF)	X ~							X						X
Demographics Questionnaire	X													
FACT-ES Questionnaire (Version 4)		X						X						X
Aromatase Inhibitor Adherence Questionnaire		X												X
Supplemental Agents Reporting Form Φ		X						X						X
LABORATORY														
Serum vitamin B12		X						X						X
C-reactive Protein (CRP)		X						X						X
Homocysteine		X						X						X
Methyl Malonic Acid (MMA)		X						X						X
TREATMENT														
Dispense one bottle of 60 tablets of Vitamin B12 2,400 mcgº		X						X						
Collect bottle of vitamin B12								X						X
Investigational Agent Accountability Record Φ								X						X
Adverse Event Summary Form Φ								X						X
INTAKE CALENDARS														
Provide patient with Vitamin B12 and AI intake calendars		X						X						
Collect Vitamin B12 and AI intake calendars								X						X

Study Calendar Footnotes

α Baseline questionnaires and blood draw must be completed prior to starting the vitamin B12.
π Assessments must be completed during Day 35-55.
√ Assessments must be completed during Day 80-100.
* A statement that arthralgias started or worsened since initiation of adjuvant AI therapy must be documented in the patient's medical record at pre-study and prior to signing consent form.
~ Must be performed within 7 days prior to enrollment.
º Patient is to take study drug daily.
Φ Form to be filled out by Clinical Research Coordinator

II. Brief Pain Inventory (Short Form)

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

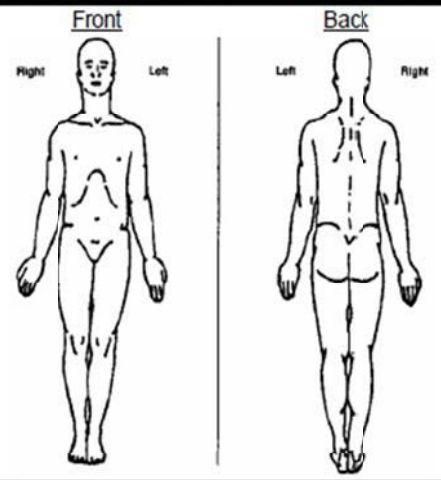
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

II. Brief Pain Inventory (Short Form) – Continued

1903

Date: (month) / (day) / (year)

Subject's Initials: _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

B. Mood

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

C. Walking ability

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

E. Relations with other people

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

F. Sleep

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

G. Enjoyment of life

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

Page 2 of 2

III. Demographics Questionnaire

Questionnaire

Today's date: __ __/__ __/__ __ __ __ Patient's initials _____
Study ID number _____

1. What is your total yearly household income?		
☐ Less than $15,000 (1)	☐ $25,000-$35,000 (4)	☐ $70,000-$90,000 (7)
☐ $15,000-$20,000 (2)	☐ $35,000-$50,000 (5)	☐ greater than $90,000 (8)
☐ $20,000-$25,000 (3)	☐ $50,000-$70,000 (6)	☐ Don't Know (9)
2. How many people are supported by this income? _____		

3. What country were you born in? _____	
4. What languages do you speak?	☐ English
	☐ Spanish
	☐ Other _____
	☐ Other _____

5. What is your current marital status?	
☐ Married (1)	☐ Living with someone (4)
☐ Separated (2)	☐ Never Married (5)
☐ Divorced (3)	
6. What is the highest level of education you have completed?	
☐ Eighth grade or less (1)	☐ Bachelor's Degree (4)
☐ High School Diploma/GED (2)	☐ Master's Degree (5)
☐ Associate's Degree (3)	☐ MD or PhD (6)

7. How many full sisters do you have, either living or deceased? _____
8. How many full brothers do you have, either living or deceased? _____
9. How many daughters and sons do you have? Do not include adopted, step or foster children. Daughters_____ Sons_____

10. How old were you were you when you had your first mammogram? _____

Version 1.1
Revised 10.19.15

IV. FACT-ES Questionnaire (Version 4) - Page 1 of 3

FACT-ES (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to sperd time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

IV. FACT-ES Questionnaire (Page 2 of 3)

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-ES Questionnaire (Page 3 of 3)

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
ES1	I have hot flashes	0	1	2	3	4
ES2	I have cold sweats	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
ES4	I have vaginal discharge	0	1	2	3	4
ES5	I have vaginal itching/irritation	0	1	2	3	4
ES6	I have vaginal bleeding or spotting	0	1	2	3	4
ES7	I have vaginal dryness	0	1	2	3	4
ES8	I have pain or discomfort with intercourse	0	1	2	3	4
ES9	I have lost interest in sex	0	1	2	3	4
ES10	I have gained weight	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
ES11	I have breast sensitivity/tenderness	0	1	2	3	4
ES12	I have mood swings	0	1	2	3	4
ES13	I am irritable	0	1	2	3	4
BRM1	I have pain in my joints	0	1	2	3	4

V. Questionnaire to Assess Adherence to Aromatase Inhibitors (AI)

Patient #:_____ **Patient's Initials #:**_____ **Study Number:**_____

Date:___/____/____ **Time:**_____

Questionnaire to Assess Adherence to Aromatase Inhibitors (AI)

You have been prescribed a pill for breast cancer to take orally for a minimum of 5 years. We know this could be challenging even for highly committed patients. Please answer the following questions by circling the best response in order to help us better understand your needs.

1. Do you remember missing doses of your AI (cancer pill) during the past 6 month's period?

   Yes No

2. Have you not taken the pill for 2 or more consecutive days in the past 3 months?

   Yes No

3. Do you miss a dose one or more times a week?

   Yes No

4. Why do you not take the pill sometimes? (Please circle all that apply).

   a. Side effects (Please describe the reasons in the space below).

   _____
   _____
   _____
   _____

   b. I forget.

   c. It is expensive and I am trying to save money.

   d. Other reasons (Please describe the reasons in the space below).

   _____
   _____
   _____
   _____

Created: 10/20/15 by CO
Version date: 02/04/2016 Page 1 of 1 Vitamin B12 Protocol

VI. Supplemental Agents Reporting Form

SUPPLEMENTAL AGENTS REPORTING FORM
(to be filled out by Clinical Research Coordinator)

Patient ID _____ Patient Initials (L, F, M) _____

Today's Date: _____ Day _____ Week _____ of Study

Instructions: Please complete this form at Day 1 and at 45 days (+/- 10 days) and 90 days (+/- 10 days) post-registration. Document supplemental agent usage information during the reporting period marked above. All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Comments section.

Reporting period start date: ☐☐ / ☐☐ / ☐☐☐☐

Reporting period stop date: ☐☐ / ☐☐ / ☐☐☐☐

Pain Medications:

Please ask patient to list all pain medications they have taken during the reporting period for joint pain or musculoskeletal pain. If "other", specify type and dose units. If more than two "other" medications were taken, explain in comments section. If medications were not taken in pill form, explain in comments.

Medication	Dosage per pill	Number of pills	
☐ Tylenol (acetaminophen)	☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Ibuprofen (e.g. Motrin®)	☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Other NSAID, specify:_____	☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Gabapentin	☐☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Pregabalin (Lyrica®)	☐☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Narcotics (specify in comments)	☐☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Other, specify: _____	☐☐☐☐ mg	☐☐	☐ Per day or ☐ Per week

Other Medications

Please list any of the following other medications taken during the reporting period.

	Dosage per pill	Number of pills	
☐ Statins (e.g., Lipitor)	☐☐☐☐ mg	☐☐	☐ Per day or ☐ Per week
☐ Aspirin	☐☐☐☐ mg	☐	☐ Per day or ☐ Per week
☐ Bisphosphonates, specify:_____	☐☐☐☐ mg	☐☐	☐ Per day or ☐ Per week

Continued on next page

Revision Date: 02/04/2016

Supplemental Agents Reporting Form (Continued)

SUPPLEMENTAL AGENTS REPORTING FORM

Patient ID _____ Patient Initials (L, F, M) _____

Today's Date: _____ Day _____ Week _____ of Study

Steroids:

Please list all steroids taken during the reporting period.

	Dosage per	Number	
☐ Steroid pills Type: _____	☐☐☐☐ mg	☐☐ pills	☐ Per day or ☐ Per week
☐ Steroid injection Type: _____	☐☐☐☐ mg	☐☐ injections	☐ Per day or ☐ Per week
☐ Steroid cream Type: _____	☐.☐☐ %	☐☐ applications	☐ Per day or ☐ Per week

Has the patient used physical therapy for joint symptoms since the last assessment? ☐ Yes ☐ No

Has the patient used acupuncture for joint symptoms since the last assessment? ☐ Yes ☐ No

Comments:

Page 2 of 2

Revision Date: 02/04/2016

VII. Vitamin B12 Intake Calendar

Intake Calendar – Vitamin B12

Patient ID_____ Patient Initials (L, F, M) _____

Texas Tech University Health Sciences Center El Paso

Instructions for the patient:

This is a monthly calendar on which you are to record when you take your Vitamin B12 tablet. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the Vitamin B12, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: _____

Revision Date: 01/05/2016

VIII. Aromatase Inhibitor - Intake Calendar

Intake Calendar – Aromatase Inhibitor _____

Patient ID_____ Patient Initials (L, F, M) _____

Texas Tech University Health Sciences Center El Paso

Instructions for the patient:

This is a monthly calendar on which you are to record when you take your AI tablet. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the AI tablet, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: _____

Revision Date: 01/05/2016

IX. Investigational Agent Accountability Record

Investigational Agent Accountability Record	Page Number:
Texas Tech University Health Sciences Center El Paso	Protocol: Vitamin B12 Study
Agent Name: Vitamin B12	Dose Form and Strength: Sublingual Vitamin B12 - 2500 mcg
Protocol Title: "A Single Arm Phase II Study of Oral Vitamin B12 for the Treatment of Aromatase Inhibitors (AI)-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer"	Dispensing Area:
Investigator Name: Zeina Nahleh, M.D.	Study Coordinator:
Patient Initials:	Patient ID:

Line No.	Date	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials	Quantity Returned	Recorder's Initials
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
15.								
16.								
17.								
18.								
19.								
20.								
21.								
22.								
23.								
24.								

X. Coversheet for Patient-Completed Questionnaires

COVER SHEET FOR PATIENT-COMPLETED QUESTIONNAIRES

Patient ID _____ Patient Initials (L, F, M) _____

Today's Date: _____ Day _____ Week _____ of Study

Instructions: Please complete form for the initial visit and for follow-up visits. **Note: The pre-registration Brief Pain Inventory Short Form is an eligibility requirement and must be completed within 7 days prior to registration.** All dates are **MONTH, DAY, YEAR.** Place an X in appropriate boxes.

Was the Brief Pain Inventory Short Form (BPI-SF) completed? ☐ No ☐ Yes

Was the Demographics Questionnaire completed? ☐ No ☐ Yes

Was the FACT-ES Trial Outcome Index completed? ☐ No ☐ Yes

If the patient marked anything other than 'Not at all' for item #9 about thoughts of suicide, who was notified and when? _____

Was the Aramotase Inhibitor Adherence Questionnaire completed? ☐ No ☐ Yes

Was the Supplemental Agents Reporting Form completed? ☐ No ☐ Yes

Was the Investigational Agent Accountability Record completed? ☐ No ☐ Yes

If any of the questionnaires were completed:

Did the patient require any assistance in completing the questionnaire(s)? ☐ No ☐ Yes

If Yes, Describe: _____

Language questionnaire(s) completed in: ☐ English ☐ Spanish

Method of completing questionnaire(s):

☐ In the clinic

☐ By telephone

☐ Other (Please specify): _____

If not completed, please give reason (select one):

☐ Illness/deteriorating health

☐ Not illness related (e.g., unable to contact, patient refusal, patient failure to return questionnaire)

☐ Institution error (e.g., forgot to administer, did not continue schedule when patient went off treatment)

☐ Death

☐ Other

I have reviewed the Cover Sheet and Questionnaire(s). All forms are complete or an explanation is given for any missing data.

Person completing form, last name: _____

Person completing form, phone: ( ) _____ - _____

Revision Date: 02/04/2016

XI. Adverse Event Summary Form

ADVERSE EVENT SUMMARY FORM

Patient ID _____ Patient Initials (L,F,M)_____

Today's Date: _____ Day _____ Week _____ of Study

Instructions: Please submit this form at 45 days (+/- 10 days) and 90 days (+/- 10 days) post-registration. Document adverse events that occur within the time period marked above. Only document adverse events related to Vitamin B12 and joint pain/stiffness due to aromatase inhibitor treatment. Do not document other toxicities related to the aromatase inhibitor treatment. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to enrollment into the study as an adverse event unless it worsens. Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. Record any observed adverse events not listed on the blank lines at the end. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the Comments section. Place an X in appropriate boxes.

ADVERSE EVENTS

Reporting period start date: ☐☐ / ☐☐ / ☐☐☐☐ (Day 1 of this Cycle)

Reporting period end date: ☐☐ / ☐☐ / ☐☐☐☐ (Day one of next cycle. If final cycle, date of first visit or contact after resolution of acute adverse events.)

Were adverse events assessed during most recent period? ☐ No ☐ Yes

Did the patient experience any reportable adverse events during this reporting period? ☐ No ☐ Yes (report below)

Date of most recent adverse event assessment: ☐☐ / ☐☐ / ☐☐☐☐

CTC Adverse Event Term	CTCAE (4.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	Hospitalization (at least 24 hours)	CTC Adverse Event Term	CTCAE (4.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	Hospitalization (at least 24 hours)
Abdominal pain	☐	☐	☐	Dyspepsia	☐	☐	☐
Agitation	☐	☐	☐	Fatigue	☐	☐	☐
Alanine aminotransferase increased	☐	☐	☐	Flatulence	☐	☐	☐
Anorexia	☐	☐	☐	Flu like symptoms	☐	☐	☐
Anorgasmia	☐	☐	☐	Headache Hot	☐	☐	☐
Blurred vision	☐	☐	☐	flashes	☐	☐	☐
Chills	☐	☐	☐	Hyperhidrosis	☐	☐	☐
Constipation	☐	☐	☐	Joint range of motion decreased	☐	☐	☐
Cough	☐	☐	☐	Lethargy	☐	☐	☐
Delayed orgasm	☐	☐	☐	Libido decreased	☐	☐	☐
Diarrhea	☐	☐	☐	Myalgia	☐	☐	☐
Dry mouth	☐	☐	☐	Nasal congestion	☐	☐	☐

* Attribution codes: 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Continued on next page

Revision Date: 02/04/2016

Patient ID _____ Patient Initials (L,F,M)_____
Today's Date: _____ Day _____ Week _____ of Study

ADVERSE EVENTS, continued

CTC Adverse Event Term	CTCAE (4.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	Hospitalization (at least 24 hours)	CTC Adverse Event Term	CTCAE (4.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	Hospitalization (at least 24 hours)
Nausea	☐	☐	☐	Vomiting	☐	☐	☐
Pain	☐	☐	☐	Weight gain	☐	☐	☐
Paresthesia	☐	☐	☐	Weight loss	☐	☐	☐
Somnolence	☐	☐	☐				
Suicidal ideation	☐	☐	☐	CTC Adverse Event Term, Other (specify using CTCAE 4.0 terminology)			
Suicide attempt	☐	☐	☐	_____	☐	☐	☐
Tremor	☐	☐	☐	_____	☐	☐	☐
Vertigo	☐	☐	☐	_____	☐	☐	☐

* Attribution codes: 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments:

Page 2 of 2

Revision Date: 02/04/2016

XII. Eligibility Criteria Checklist

Institution: Texas Tech University Health Sciences Center El Paso

Principal Investigator: Zeina Nahleh, M.D.

Study: A Single Arm Phase II Study of Oral Vitamin B12 for the Treatment of Aromatase Inhibitors (AI)-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer
IRB Approval #E15122

Patient's Initials: _____

Patient ID: _____

Today's Date: _____ **(mm/dd/yyyy)**

Eligibility Criteria Checklist

Inclusion Criteria: Please check "**Yes**" or "**No**" for each of the following criteria. The answers for **questions 1-7 and 11-13 should be "Yes", question 10 can be blank (if applies per conditional statement) or should be yes,** and the answers to **questions 8 and 9 should be "No**". Any answers different from these indicate that the patient is ineligible for participation in this study.

		Yes	No
1.	Is the patient a woman with histologically confirmed estrogen receptor (ER) and/or progesterone receptor (PgR) positive invasive carcinoma of the breast (Stage I-III) with no evidence of metastatic disease (MO)?		
2.	Has the patient completed mastectomy or breast sparing surgery, and has she recovered from all side effects of the surgery? Has the patient recovered from all Grade 2 or higher side effects of chemotherapy and/or radiation therapy with the exception of alopecia and peripheral neuropathy? Concurrent bisphosphonate and trastuzumab therapies are allowed.		
3.	Is patient post-menopausal, as defined by at least one of the following: a. ≥ 12 months since the last menstrual period OR b. Prior bilateral oophorectomy OR c. Previous hysterectomy with one or both ovaries left in place (or previous hysterectomy in which documentation of bilateral oophorectomy is unavailable) AND (unless ≥ 50 years of age) FSH values consistent with the institutional normal values for the post-menopausal state.		
4.	Is patient currently taking one of the following aromatase inhibitor (AI) doses for at least 14 days prior to registration and does she plan to continue for at least an additional 180 days after registration? a. Anastrozole (Arimidex®) 1 mg daily OR b. Letrozole (Femara®) 2.5 mg daily OR c. Exemestane (Aromasin®) 25 mg daily		
5.	Does the patient have an aromatase inhibitor (AI) associated musculoskeletal symptoms that began or increased after starting AI therapy? New musculoskeletal pain should not be due specifically to fracture or traumatic injury.		

		Yes	No
6.	Has the patient completed the Brief Pain Inventory-Short Form (BPI- SF) within 7 days prior to enrollment? Does the patient have an "average pain" of at least 4 on the BPI-SF?		
7.	Does the patient have a Zubrod performance status of 0-2?		
8.	Does the patient have a known allergy or hypersensitivity to vitamin B12?		
9.	Does the patient have any contraindicated concurrent illnessesincluding: a. History of alcohol or other substance abuse or dependence within 365 days prior to enrollment? b. Chronic liver disease? c. End stage renal disease?		
10.	**Answer this question only if the patient is receiving treatment with narcotics, tramadol, gabapentin, and/or pregabalin.** Has the patient been taking a stable dose of any of the medications mentioned above for at least 30 days prior to registration?		
11.	Is the patient able to complete study questionnaires in English or Spanish?		
12.	Is the patient willing to submit blood samples for laboratory testing [to test for Serum Vitamin B12, C-Reactive Protein (CRP), homocysteine level, and Methyl Malonic Acid (MMA)]? Baseline samples must be obtained prior to beginning protocol treatment.		
13.	Patient or her legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.		

If subject is eligible, all inclusion are marked "yes" and all exclusion are marked "no"	Yes	No
Is this subject eligible?		

Printed name of person completing this form Date

Signature of person completing this form Date

XIII. Laboratory Results Form

Vitamin B12 Study – E15122

Institution: Texas Tech University Health Sciences Center El Paso

Principal Investigator: Zeina Nahleh, M.D.

Study: A Single Arm Phase II Study of Oral Vitamin B12 for the Treatment of Aromatase Inhibitors (AI)-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer

IRB Approval # E15122

Patient's Initials: _____

Patient ID: _____

	Week 0 (Baseline)	Week 6	Week 12
Date			
Serum Vitamin B12 (pg/mL)			
C-Reactive Protein (mg/L)			
Homocysteine Level (µmol/L)			
Methylmalonic Acid (µmol/L)			

Laboratory Results