

**A Randomized, Controlled Trial of High Dose vs. Standard Dose
Vitamin D for Aromatase-Inhibitor Induced Arthralgia in Breast Cancer
Survivors**

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Protocol Chair Mothaffar Rimawi, M.D.
Baylor College of Medicine
One Baylor Plaza BCM 600
Houston, TX 77030
Phone: (713) 798-1311
Fax: (713) 798-8884
Email: rimawi@bcm.edu

IND Number: 120053
NCT Number: NCT01988090

Additional Sites

Washington University
Site PI: Foluso Ademuyiwa, MD

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1. BACKGROUND

Breast cancer is the most common malignant disease in women in the Western world. In the U.S., SEER data states that over 207,000 women are diagnosed with invasive breast cancer every year, and almost 40,000 women will die of this disease (1). Systemic treatment is the most active modality in reducing distant tumor recurrences and resulting mortality in early breast cancer. Specifically, endocrine therapy with anti-estrogen agents for hormone receptor positive breast cancer is the most efficacious of systemic therapies, with aromatase inhibitors being arguably the most active anti-estrogen therapy in early stage breast cancer (2).

1.1 Treatment of Hormone Receptor Positive Breast Cancer

Approximately 70% of newly diagnosed breast cancers are positive for hormone receptors (estrogen receptors, ER; progesterone receptors, PR). While tamoxifen was part of the standard of care for patients with hormone-responsive breast cancer, its use in the adjuvant setting has largely been replaced in postmenopausal women by the third generation aromatase inhibitors (AI's) based on studies demonstrating superior efficacy of adjuvant AI's in early breast cancer.

The third-generation AI's include non-steroidal aromatase inhibitors (NSAI's) anastrozole and letrozole, as well as the steroidal aromatase inhibitor (SAI), exemestane. These AI's suppress estrogen synthesis to nearly undetectable circulating levels by inhibiting the enzyme aromatase, thereby blocking the conversion of adrenal androgens to estrogens (3) (4). The NSAI's bind reversibly to the cytochrome P450 moiety of the aromatase enzyme, interfering with estrogen biosynthesis (5) whereas exemestane is a false substrate that binds irreversibly to the aromatase

enzyme, causing its inactivation (6).

Several large trials have shown superiority of aromatase inhibitors over tamoxifen in early stage breast cancer in terms of disease free survival and recurrence. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial randomized 6186 post menopausal women with localized breast cancer to 5 years of anastrozole or 5 years of tamoxifen adjuvant therapy. The group who received anastrozole demonstrated a significantly prolonged disease free survival, with 575 versus 651 events (HR = 0.87 , 95% CI 0.78-0.97). They also enjoyed longer time to recurrence (HR 0.79 [0.70-0.90]) and a statistically significant 42% reduction in contralateral breast cancer (7).

Similarly, the Intergroup Exemestane (IES) examined 4742 post-menopausal women receiving adjuvant tamoxifen for localized estrogen receptor positive breast cancer. After taking tamoxifen for 2-3 years, 2632 women were randomized to switch to exemestane, and 2380 women continued to receive tamoxifen. At three years after randomization, women who had been switched to exemestane had a 32% risk reduction for recurrence. They also had improved disease free survival of 91.5%, compared to 86.8% in the tamoxifen group. Distant disease was reduced by 34% and contralateral breast cancer by 56% in the exemestane group (8).

Finally, the Breast International Group (BIG) 1-98 was a randomized, phase 3 double-blind trial comparing tamoxifen monotherapy, letrozole monotherapy, and sequential treatment with both agents. Despite 39.5% of women on tamoxifen monotherapy crossing over to letrozole, the letrozole monotherapy group experienced improved disease free survival of 87.9% as compared to 84.6% in women assigned to the tamoxifen monotherapy arm (9).

1.2 Musculoskeletal Side Effects of Hormonal Therapy

Traditionally, Aromatase Inhibitor induced Arthralgia (AIA) has been somewhat difficult to both define and quantify. Though a single, commonly accepted definition of AIA is lacking, patients who experience AIA most commonly describe joint pain and stiffness, predominantly affecting the hands, wrists, shoulders, and knees. However, any joint may be affected. Median time to onset of symptoms is 1.6 months. As part of the syndrome, patients may also describe morning stiffness, myalgia, tingling, numbness, decreased grip strength, and joint swelling (10) (11). The clinical tool which is becoming the standard used in many trials (12) (13) (10) to evaluate AIA is the Health Assessment Questionnaire-II (HAQ-II). It is commonly used in rheumatology literature, and has been substantiated across many trials. This is a simple survey, which is a proven, reliable, and accurate

indicator of joint pains and consequent disabilities **(14) (15)**. Decreased grip strength has also been examined in a few small trials, and it has been found to correlate with symptoms of AIA as well as MRI changes in the joints **(16) (17) (18)**.

Across all of the aforementioned large adjuvant hormonal therapy trials, significantly more women who were taking aromatase inhibitors experienced arthralgia than those taking tamoxifen. In the ATAC trial, 35.6% of women in the anastrozole arm experienced arthralgia, compared with only 29.4% in the tamoxifen arm ($p < 0.0001$) **(7)**. The IES trial showed a statistically significant difference in the incidence of arthralgia as well. Five per cent of women in the exemestane group had arthralgia, and only 3.6% of women in the tamoxifen arm experienced this symptom ($p = 0.005$) **(8)**. The BIG 1-98 study found a 34.7% incidence of arthralgia, myalgia, or both in the women who received letrozole, as compared to 30.1% in the tamoxifen group ($p = 0.05$) **(9)**.

While it is clear that aromatase inhibitors cause more arthralgia than tamoxifen, the exact incidence of this adverse effect remains unclear, as none of the aforementioned trials were engineered to examine the incidence of AIA. Thus, the measured incidence of arthralgia while on AI therapy varies widely among the large clinical trials. One cross-sectional survey specifically assessed 200 women for AIA via questionnaire. They discovered a 47% prevalence of AI-related joint pain and 44% rate of joint stiffness **(19)**.

The significance of the arthralgia syndrome associated with AI therapy is clarified by looking at a small pilot study which prospectively evaluated 100 women on adjuvant AI therapy with serial questionnaires. At a median of six months, 13% of these women discontinued aromatase inhibitor therapy because of arthralgia **(10)**. In larger studies, overall rates of non-adherence to AI therapy for any reason are even higher. From reviewing pharmacy records of 12,000 patients, one researcher found the rate of adherence to adjuvant anastrozole therapy was only 50-68% at three years **(20)**. The joint pains, as they are one of the most common and troubling side effects of AI therapy, most likely play a significant role in patient's non-adherence to medication.

The significance of AIA, however, may extend beyond issues of quality of life and compliance. It is possible that AIA is a marker of increased biologic effect. Retrospective analysis of the ATAC trial suggests that women who develop new joint pains within three months of beginning endocrine therapy (either AI or tamoxifen) have a 40% reduction in the risk of breast cancer recurrence as compared to those women without arthralgia **(21)**, similar to the increased efficacy seen in lung cancer patients who develop a rash with erlotinib. Retrospective analyses of the TEAM

and BIG 1-98 trials have also found a correlation between the development of arthralgia on AI therapy and lower breast cancer recurrence risk, as compared to those who do not develop arthralgia (22) (23). However, it should be noted that analysis of IES did not show the same correlation (24). Clearly, more needs to be learned about the etiology and the significance of AIA. Further study of AIA could potentially lead to a better understanding of factors that predict disease recurrence.

Many risk factors for developing arthralgia on AI's have been postulated, but the mechanism is still not understood. Both higher BMI and depressed mood have been associated with increased incidence of arthralgia while on AI's in post-menopausal women. Also, previous use of hormone replacement therapy, previous chemotherapy administration, and hormone receptor positivity have all been retrospectively associated with higher risk of developing new arthralgia while on aromatase inhibitor therapy. Interestingly, women from North America or the UK were more likely to develop AIA compared to women from the rest of the world, though it is not clear why these geographic differences exist (25).

1.3 Management of AIA

In terms of treatment, the only intervention that has been shown to reduce AI-induced arthralgia in a randomized controlled trial is acupuncture, which has shown significantly decreased subjective pain scores and pain-related interference as compared to sham acupuncture (26). Exercise and NSAIDs are commonly utilized by oncologists to treat AIA, though quality evidence is lacking to support this approach. Other treatments, such as steroids (27) and diuretics (28) have also been examined, but these studies have been plagued by small sample size, lack of reproducibility, and non-prospective design.

There also may be some utility in simply switching AI's. The French ATOLL trial found that 71.5% of women who discontinued anastrozole because of intolerable joint pains were actually able to tolerate and continue letrozole. However, it should be noted that 74% of women still reported significant arthralgia after 6 months of letrozole therapy, but it was generally felt to be more tolerable than anastrozole by the majority of women (29).

In one small, non-randomized trial of 27 patients, a short course of low dose prednisolone did show promise as a potentially effective treatment for AIA. Patients with AIA were given 5 mg of prednisolone daily for one week, and 67% of patients reported immediate relief in joint pain, with

63% still reporting improvement at 1 month (27). Retrospective data suggests that diuretics and bisphosphonates may play a role in reducing discomfort from AIA (28) (30). In a single arm trial, 29 women with AIA received duloxetine for 8 weeks, and 72% experienced at least a 30% reduction in average pain level (31). While these results are interesting, all of these trials are plagued by small sample size, and none of them have been performed in a randomized controlled setting. Thus, AIA is still very difficult for physicians to treat because there is no clearly effective management strategy.

1.4 Vitamin D and Breast Cancer

Vitamin D has recently begun to receive much attention because some data indicates that higher levels of vitamin D may correlate with lower breast cancer risk. However, the Institute of Medicine recently released a report stating that the evidence for Vitamin D and breast cancer prevention is “inconsistent and insufficient to inform nutritional requirements” at this point (32).

There is also some interesting data recently released which correlates higher baseline Vitamin D levels with decreased risk of distant recurrence in post-menopausal women, especially decreased risk of bone metastases (33).

1.5 Vitamin D Background

While the relationship of Vitamin D to breast cancer risk and recurrence clearly needs further study, Vitamin D deficiency is well known to cause a wide array of musculoskeletal issues, including diffuse skeletal pain and non-inflammatory arthritis. For example, among 1993 post-menopausal women from the Womens Health Initiative, low vitamin D levels were correlated with increased joint pain (34). Furthermore, in non-cancer patients, these symptoms have resolved and/or improved with single high dose vitamin D3 at 150,000 IU orally (35) (36) (37).

Optimal levels of Vitamin D are not completely agreed upon, as deficiency is usually defined as a serum 25-hydroxy vitamin D level <20 ng/mL, as supported by the Institute of Medicine (38). However, there is evidence to state that proximal muscle strength improves as vitamin D levels increase to >40 ng/mL (39). Vitamin D insufficiency and deficiency are quite common among post-menopausal breast cancer patients, ranging from 75-90% (33) in some reports, though vitamin D levels are known to vary based on geographic location. However, the tie between post-menopausal women on AI therapy and low vitamin D levels is logical because estrogen and vitamin D are closely linked. Estrogen increases activity of 1 alpha hydroxylase, which catalyzes conversion 25(OH)D to its active form, 1,25(OH)2D. Estrogen also increases the activation of the Vitamin D receptor.

Therefore, it is reasonable to suppose that a low estrogen state, as is seen in women on AI therapy, could potentially decrease the amount of active Vitamin D available, and studies have corroborated this. One retrospective analysis of the International Breast Cancer Intervention (IBIS-II) trial found that among 416 post-menopausal women who were at high risk of breast cancer, only 13% had adequate vitamin D levels (≥ 30 ng/mL), 41% had inadequate levels (20-30 ng/mL), and 46% were deficient or severely deficient (< 20 ng/mL) (40). Similarly, in the AZURE trial, only 10% of women had adequate Vitamin D levels of > 30 ng/mL, even when seasonal variation was properly accounted for (33). Clearly, Vitamin D deficiency is quite common among women internationally, and it merits further study.

There is some preliminary evidence to suggest that Vitamin D supplementation may prevent arthralgia while on AI's. Sixty women who were beginning adjuvant AI therapy were enrolled in a small study which supplemented women with low baseline Vitamin D levels (≤ 40 ng/mL) with increased doses of vitamin D at 50,000 IU per week for 12 weeks. They found that the supplementation was effective in raising women's Vitamin D levels, and higher Vitamin D level (25OHD > 66 ng/mL) correlated with less joint pain and disability from joint pain (12).

In contrast, another prospective study with similar design only supplemented the women with vitamin D levels of < 40 ng/mL with 16,000 IU of oral vitamin D3 every 2 weeks. Half of the women failed to achieve Vitamin D levels > 40 ng/mL at 3 months, and there was no improvement in joint pains (13). Considering the somewhat disparate results of these two trials, it is clear that more needs to be understood regarding the role of vitamin D in AIA, the optimal dosing, and goal vitamin D levels. Though there are some promising results in the literature, many more trials need to be done to further clarify the role which Vitamin D may play in Aromatase Inhibitor-Induced Arthralgia.

1.6 Study Rationale

As previously mentioned, Vitamin D deficiency is an exceedingly common, though relatively unexplored, condition among breast cancer patients. This study aims to shed more light on the role of Vitamin D in the setting of AIA, and to see whether prophylactic vitamin D supplementation may decrease the incidence of AIA and, thus, also improve patient compliance with AI therapy. Other studies have shown that Vitamin D supplementation may significantly improve AIA (12), though this is not clearly understood at this point. Estrogen increases activity of 1 alpha hydroxylase, which catalyzes conversion 25(OH)D to its active form, 1,25(OH)₂D. Estrogen also increases the activation of the Vitamin D receptor. Therefore, it is logical that a low estrogen state, as is seen in women on

AI therapy, could potentially decrease the amount of active Vitamin D available. Vitamin D is known to inhibit release of inflammatory cytokines IL-1, IL-6, and TNF alpha from macrophages. Furthermore, in the non-breast cancer population, it has been proven that high dose vitamin D significantly decreases levels of TNF- α and IL-6 (41). Inhibiting release of inflammatory cytokines, which may result from low estrogen and consequent low vitamin D levels, could potentially explain the etiology of AIA, if proven to be true.

We propose to perform a randomized clinical trial in post-menopausal women with ER+ breast cancer, who are beginning adjuvant aromatase inhibitor therapy. Half of the women will receive high dose Vitamin D (50,000 IU per week for 12 weeks, followed by 2000 IU daily for 40 additional weeks), and the other half of women will receive standard dose Vitamin D (800 IU daily for 52 weeks). The goal of this trial is to show us whether higher Vitamin D supplementation is a good preventative measure for AIA, and whether it is associated with increased AI compliance.

Hypothesis

Based on previous data from other trials mentioned above, high dose Vitamin D supplementation may decrease the incidence of AIA in the experimental arm as compared to the standard dose arm.

We hypothesize that the women in the high dose Vitamin D arm will have significantly less aromatase inhibitor-induced arthralgia, as compared to the women on the control arm. Consequently, we further hypothesize that the women who are taking high dose Vitamin D will also have a significantly higher compliance rate with AI therapy than the women on the control arm.

2. OBJECTIVES

2.1 Primary Objective

To evaluate whether women who are supplemented with high dose Vitamin D develop less Aromatase Inhibitor-Induced Arthralgia (AIA) than those women who receive standard dose Vitamin D.

2.2 Secondary Objectives

- 2.2.1 To assess whether high dose Vitamin D supplementation, as compared to standard dose, leads to improved compliance with aromatase inhibitor therapy.
- 2.2.2 To assess whether low baseline serum 25-hydroxyvitamin D levels are a risk factor for developing AIA

2.3 Exploratory Objective

- 2.3.1 To study whether grip strength may serve as an accurate and reliable objective measure to complement the subjective complaint of AIA.
- 2.3.2 To investigate whether high dose vitamin D may be associated with lower breast cancer recurrence than standard dose Vitamin D

3. STUDY DESIGN/SUMMARY

This is a randomized, multi-center, controlled, phase II study comparing high dose vitamin D vs. standard dose vitamin D for post-menopausal breast cancer patients who are beginning adjuvant aromatase inhibitor therapy. The study is intended to be conducted in up to 5 centers within the U.S.A which are routinely engaged in the administration of aromatase inhibitor therapy for the study specified population. All patients who are starting an AI in the adjuvant setting are eligible to participate in the study.

In order to preserve power and compensate for the interim futility analysis which tends to reduce power, the sample size of the study is increased from 88 per group to 93 per group, which is 186 total if considering a 5% drop out rate. A total of 186 patients at up to 5 centers will be randomized 1:1 to receive either 50,000 International Units (IU) oral vitamin D per week for 12 weeks followed by 2000 IU daily for 40 weeks, or 800 IU Vitamin D daily for 52 weeks. All women on both arms of the trial will also take calcium carbonate 600 mg daily.

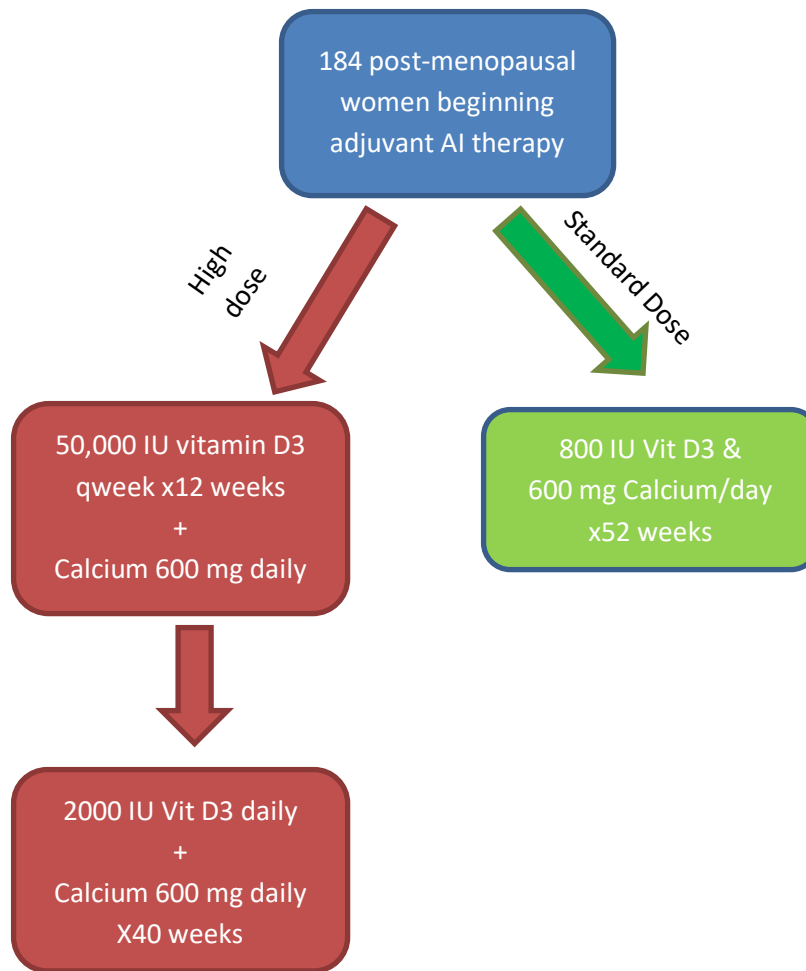
The primary endpoint for this study is development of AIA in each arm after 12 weeks of AI therapy, as determined by patient questionnaires. Secondary endpoints include compliance with AI therapy, as well as correlation of low baseline vitamin D levels with development of AIA. Grip strength is an exploratory endpoint.

Throughout the 52 week study period, participating women will complete the questionnaire and grip strength measurement a total of three times in order to assess their arthralgia while on AI therapy. Compliance with aromatase inhibitor (AI) therapy will also be assessed throughout the

study to determine if AI compliance is improved in women who are receiving Vitamin D. Additionally, women will also have periodic assessments of serum 25-hydroxyvitamin D to assess whether vitamin D levels correlate with AIA, and to ensure that calcium and 25(OH) D levels are within healthy ranges.

SCHEMA

High Dose vs. Standard Dose Vitamin D for Aromatase Inhibitor-Induced Arthralgia



4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

- 4.1.1 All participants must be female and at least 21 years of age
- 4.1.2 Signed informed consent
- 4.1.3 Patients must have had histologically confirmed stage I-III breast carcinoma that is positive for Estrogen Receptor (ER) and/or Progesterone Receptor (PR).
- 4.1.4 Post-menopausal status defined by any of the following:
 - Age >60 years
 - History of bilateral oophorectomy
 - Serum estradiol and FSH concentrations in the post-menopausal range, along with either amenorrhea for 12 months or previous hysterectomy (If patient is <60 years old, post-menopausal status must have been confirmed PRIOR to chemotherapy, if chemotherapy was given)
- 4.1.5 Beginning adjuvant aromatase inhibitor therapy, with no previous use within the last 6 weeks. Patients may take anastrozole, letrozole, or exemestane, per the discretion of the treating physician and the patient.
- 4.1.6 Bisphosphonates are allowed, at the treating investigator's discretion
- 4.1.7 Performance status (WHO/ECOG scale) 0-2.

4.2 Exclusion Criteria

- 4.2.1 History of kidney stones
- 4.2.2 Hypercalcemia at baseline, defined as any corrected calcium greater than the laboratory's normal parameters
- 4.2.3 History of either symptomatic hypercalcemia or hyperparathyroidism, at the treating investigator's discretion
- 4.2.4 Baseline 25-hydroxyvitamin D level greater than 50 ng/mL

- 4.2.5 Inability or unwillingness to comply with, or follow study procedures.
- 4.2.6 Currently taking Phenytoin or phenobarbital
- 4.2.7 Currently taking cholestyramine or orlistat
- 4.2.8 Malabsorption syndrome, such as Crohn's disease
- 4.2.9 History of chronic granulomata forming disorders, such as sarcoidosis or tuberculosis.
- 4.2.10 History of chronic fungal infection or lymphoma

4.3 Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards race in the clinical trial outlined. By the nature of the trial, the majority of women will be older because aromatase inhibitors are intended only for post-menopausal women. Due to the rate incidence of breast cancer in men and infrequent treatment with AI's in this group, this trial is open to the accrual of women only.

5. REGISTRATION PROCEDURES

5.1 Guidelines

Patients should be registered in the electronic database as soon as the patient has signed the informed consent. Following registration, the patient's enrollment status in the electronic database will be listed as pending. Prior to enrollment in the electronic database, the eligibility worksheet must be reviewed and signed by the study coordinator and a Breast Center physician investigator, in accordance with Lester & Sue Smith Breast Center clinical research standard operating procedures. Eligibility data will then be entered in the electronic database and the subject will be randomized.

Study treatment may begin only after eligibility has been confirmed by both a study coordinator and a Breast Center physician. Once eligibility has been reviewed, it is recommended that treatment begin within a timely manner. Although there is no protocol-required timeframe, every effort will be made to ensure that study treatment begins within 7-14 days of subject enrollment.

5.2 Eligibility exceptions

Any requests for protocol exceptions must be approved in writing by the protocol chair, Dr. Mothaffar Rimawi or his designee at the Lester & Sue Smith Breast Center. Request for protocol exceptions must be made via email or fax to the lead study coordinator. Protocol chair or her designee should be copied on all requests and associated correspondence. Exceptions will be granted in very limited circumstances if the protocol chair or her designee determine that it is in the best interest of the patient to participate and that the goals of the study will not be affected. Once a determination has been made, the requesting physician will be notified in writing. In the event that an eligibility exception is granted, the requesting physician must submit the exception to the Baylor College of Medicine IRB in accordance with institutional standard operating procedures.

Although every effort should be made to comply with study calendar and procedures will be made, on occasion, the protocol chair or her designee may allow patients to go the study on whose baseline studies fall slightly outside the specified windows. This will not constitute a protocol exception and need not be reported to the IRB.

6. STUDY PROCEDURES

Patients enrolled on study will have the following study assessments and procedures performed as described. For a summary of required assessments, please refer to the study calendar in Appendix B.

6.1 Screening and Baseline assessments

A signed, written informed consent must be obtained before any study-specific assessments are initiated. Results from assessments performed prior to written consent as part of a patient's routine diagnostic workup may be used for screening purposes. The following assessments will be obtained at screening, within 28 days prior to beginning study medication:

- Subject demographic information, to include age, ethnicity, and race
- Medical history, including past and current conditions, and past surgical history
- Whether patient has used Hormone Replacement Therapy (HRT), for how many years, and how long ago she stopped.
- Use of chemotherapy, including taxanes or not including taxanes
- Measurement of body weight, height, and Body Mass Index
- Completion of Health Assessment Questionnaire (HAQ-II)

- Grip strength measurement
- Laboratory assessments to include:
 - Calcium level
 - Albumin level
 - Vitamin D level -- serum 25(OH)D
 - FSH, LH, and estradiol levels must be obtained if required as detailed above in 4.1.4 to determine menopausal status. Menopausal status should be interpreted by the treating physician and approved by study chair based on the cutoff values provided by the reporting laboratory.
- Review of all medications taken within 28 days of planned treatment start date
- Study coordinator will educate the patient about the importance of compliance with Aromatase Inhibitor therapy.
- If a Bone Mineral density test has not been completed within 3 months of starting AI therapy, a Bone Mineral Density test must be ordered as a screening assessment, and the test must be completed within 28 days of starting Aromatase Inhibitor therapy

If the above studies are within acceptable parameters as defined by the eligibility criteria, the patient will be randomized to begin either high dose Vitamin D or standard dose Vitamin D, as described in [Section 7](#).

6.2 Follow-up at Week 4

The following assessments should be performed at 4 weeks (28 days) from the start of study medication. To allow for weekends, holidays, etc., study procedures may be completed within a window of +/- 5 business days.

- Laboratory assessments to include a calcium level, 25-hydroxyvitamin D level, and albumin.

6.3 Follow-up at Week 12

- Measurement of body weight and BMI
- Laboratory assessments to include a calcium level, 25-hydroxyvitamin D level, and albumin.
- Patient is to complete the Health Assessment Questionnaire (HAQ-II)
- Study coordinator will perform grip strength measurement, using the Smedley dynamometer, as described in Section 6.8.2 [Grip Strength Measurement](#).
- Record all concomitant medications added and/or changed.
- Assess compliance to aromatase inhibitor therapy, as outlined in Section 6.8.3

- Assess compliance to vitamin D treatment, as outlined in Section 6.10
- Non-serious and serious adverse events should be recorded and graded appropriately as discussed in section 9.6.
- Administration of study medications will continue as described in Section 6.9.

6.4 Follow up at Weeks 24 and 36

- Laboratory assessments to include a calcium level, 25-hydroxyvitamin D level, and albumin.
- Record all concomitant medications added and/or changed.
- Assess compliance to aromatase inhibitor therapy by counting remaining pills in bottle, as per Section 6.8.3
- Assess compliance to vitamin D treatment, as outlined in section 6.10
- Non-serious and serious adverse events should be recorded and graded appropriately as discussed in Section [9.6](#).
- Administration of study medications will continue as described in Section 6.9.

6.5 Follow up at week 52, and End of Treatment Visit

The following assessments should be performed within five to ten business days of the completion of study therapy. End of treatment is defined as Week 52. These assessments should also be performed for patients who discontinue treatment prematurely (unless otherwise noted below).

- Measurement of body weight and BMI
- Laboratory assessments to include calcium level, 25-hydroxyvitamin D, and albumin.
- Patient is to complete the Health Assessment Questionnaire (HAQ-II)
- Grip strength measurement
- Record all concomitant medications added and/or changed.
- Assess compliance to aromatase inhibitor therapy
- Access compliance to vitamin D and calcium treatment

Non-serious and serious adverse events should be recorded and graded appropriately as discussed in section 9.6.

At this point, patients will have completed study treatment and should proceed with the completion of their adjuvant therapy, as determined by the treating physician. Patients may take Vitamin D at any dosage they wish, at the discretion of the patient and the treating physician.

6.6 Safety Follow-up

6.7 Upon completion of the therapeutic regimen, subjects will be followed for adverse events for a period of 30 days after the last dose of Vitamin D on study. Patients with abnormal laboratory or clinical findings that are believed to be treatment related will be followed until the condition resolves, stabilizes, or until the laboratory values are no longer considered clinically significant. New adverse events that occur during the 30 day follow-up period will only be recorded if the investigator believes there is a reasonable possibility that the adverse event is drug-related. The safety follow-up may be conducted by a phone visit or a clinic visit; if clinically indicated, a clinic visit should be performed along with relevant lab work. Per standard of care and NCCN guidelines, bone density scan will be repeated, at the treating physician's discretion, every 1-2 years while the patient is on AI therapy. Per NNCN guidelines, patient will have DEXA scan every 2 years while on AI therapy, or every year if accelerated bone loss is suspected, or therapeutic intervention applied. Duration of Follow-up

All subjects will be followed for breast cancer recurrence at approximately 6-month intervals from the completion of the study period (52 weeks) to the completion of the five years of adjuvant therapy. Follow-ups may be conducted by phone, email, or clinic visit, and will be discontinued in the event of subject death, recurrence, loss to follow up after at least 3 documented attempts to contact her, or withdrawal of consent.

6.8 On Study Assessments and Procedures

6.8.1 Health Assessment Questionnaire

Each subject will be asked to complete the Health Assessment Questionnaire (HAQ-II) at baseline, 12 weeks, and 52 weeks. The questionnaire will be completed in the office, during the clinic visit, and it will be administered by the study coordinator. Generally, the questionnaire can be completed in less than 5 minutes by most patients. The questionnaire will be available in English, Spanish, and Vietnamese.

6.8.2 Grip Strength Measurement

At baseline, and 12 weeks, and 52 weeks, the study coordinator will measure the patients' grip strength using the Smedley Dynamometer. The study coordinator will be trained on using the dynamometer. They will be instructed to take 3 consecutive grip strength measurements on each hand, and they will use and record the highest result for each hand.

6.8.3 Compliance with AI therapy

Compliance with aromatase inhibitor therapy will be evaluated by a physical pill count at the scheduled clinic visits on Weeks 12, 24, 36, and 52. Subjects will be instructed to bring their used bottles of aromatase inhibitor to each return visit, along with any unused tablets. Study staff will count the number of remaining tablets at each visit to assess compliance. In the event that the subject forgets to bring their used study meds to their clinic visit, compliance will be assessed by direct questioning of the subject. In this case, subjects should be counseled to bring their used drug bottles to their next scheduled clinic appointment so that compliance may be confirmed by pill count. Subjects should be instructed to report any missed doses of aromatase inhibitor to the study coordinator.

Compliance with the aromatase inhibitor will be calculated by the ratio of number of pills actually taken to the number of pills that should have been taken. Compliance will be defined as a ratio ≥ 0.80 . Study staff should ensure subject understanding of dosing instructions for subjects whose compliance is less than 100%. In addition, the importance of compliance with anticancer therapy should be reinforced. In the case of non-compliance, the study coordinator will ascertain, from the patient, the main reason for the non-compliance, and this will be recorded as study data.

Subjects who miss doses as a result of physician-prescribed drug holidays will not be considered non-compliant. Calculation of the compliance ratio should thus be adjusted such that the "number of pills that should have been taken" reflects the drug holiday.

6.9 Agent Administration

6.9.1 Vitamin D3, 5000 IU

One half of the patients will be randomized to receive Vitamin D3 at a dose of 50,000 IU weekly for 12 weeks, followed by 2000 IU of vitamin D3 daily for 40 additional weeks. Patients will receive high dose vitamin D through the study, via 5000 IU capsules, which are available over the counter. They

will receive this study medication after all screening assessments have been completed, and eligibility has been confirmed by the study coordinator.

Patients should be carefully instructed by study personnel on how to take Vitamin D3. Patients will be instructed to take Vitamin D, 50,000 IU (10 capsules) PO on a weekly basis, on the same day each week, and at approximately the same time each dose. Vitamin D should be taken shortly after a meal. Patients may take concomitant medications along with their Vitamin D dose, provided that the medications do not interact with vitamin D absorption (e.g.cholestyramine, orlistat, phenytoin, or phenobarbital). Vitamin D3 at 50,000 IU per week will be provided for the patient by the study. This cost has been accounted for in the budget.

6.9.2 Vitamin D3, 2000 IU

After completing 12 weeks of high dose vitamin D, the patients randomized to this arm will then complete 40 additional weeks of 2000 IU daily. The pills are available in 2000 IU strength, and the patients will take 1 pill daily, with food. Again, study personnel will instruct patients on how to take vitamin D, with the same instructions and precautions provided above, in [Section 6.9.1](#).

Vitamin D3 at this dosage is available over the counter at any retail pharmacy. Patients will be provided with Schiff Vitamin D3 2000 IU Dietary Supplements, which are available at 200 pills for \$14.00. The study will cover this cost, and the research coordinator will dispense the medication at clinic visits as necessary.

6.9.3 Caltrate-D

The patients who are randomized to the standard dose Vitamin D arm will take 1 Caltrate-D pill daily. Each pill contains 600 mg of Calcium and 800 IU of Vitamin D3. Patients will be instructed to take one pill daily, with food. Again, the medicine will be provided to them by the study, at no cost to the patient. Study personnel will instruct patients on how to take vitamin D, with the same instructions and precautions provided above, in [Section 6.9.1](#).

6.9.4 Calcium, 600 mg

Patients on the high dose Vitamin D arm will be asked to take over-the-counter Calcium supplement, as is recommended as standard of care. This will not be supplied by the study, but patients will be instructed to take NatureMade Calcium 600 mg dietary supplement tablets – 1 tablet daily.

6.10 Compliance

Compliance with Vitamin D supplementation in both arms will be assessed via the research coordinator counting remaining pills in the bottle at specified visits when compliance is assessed. (Compliance with AI therapy and with vitamin D supplementation will be assessed at all the same visits). Compliance will be defined as having taken $\geq 80\%$ of expected doses of Vitamin D.

6.11 Prohibited Therapies

Patients may not take additional Calcium and Vitamin D aside from the study medications. Patients who are on cholestyramine or orlistat will not be allowed on the trial. Also, patients who are taking phenytoin or phenobarbital are not allowed on the trial either because of interaction between Vitamin D and anti-epileptic medications.

6.12 Discontinuation of Treatment

In the event that study treatment is discontinued prematurely, subjects should undergo the study procedures as described in Section 6.5. NOTE: Subjects who discontinue study therapy will still be included in the overall evaluation of response (intent-to-treat analysis), regardless of the reason for therapy discontinuation. Study treatment may be discontinued for any of the following reasons.

- Breast cancer recurrence or new breast cancer
- Failure of the subject to attend the majority of scheduled visits. The protocol chair or her designee will determine when non-compliance with clinic visits should lead to removal from study.
- Lost to follow-up
- Withdrawal of consent.
- Unacceptable major toxicity, as determined by the treating investigator.
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment.
- At subject's own request. Note: The reason for discontinuation from the study must be documented.

- Study is closed for any reason (e.g. new information shows that the patient's welfare would be at risk if she continued study treatment).
- General or specific changes in the participant's condition which render the participant unacceptable for further treatment in the opinion of the treating investigator physician.
- 25-hydroxyvitamin D level exceeds 120 ng/mL at any point during the study
- 25-hydroxyvitamin D level is persistently >70 ng/mL, as outlined in [Section 8.1](#).
- Corrected calcium level >11.0 mg/dL on any measurement during the study, or corrected calcium level >10.5 mg/dL on three consecutive measures, as outlined in [Section 8.1](#).
- Symptomatic hypercalcemia which warrants discontinuation, at the discretion of the treating investigator physician, with symptoms including but not limited to confusion, lethargy, constipation, nausea/vomiting, abdominal pain, or muscle weakness.
- Development of symptomatic calcium-based renal stones

6.13 Withdrawal from Study

Subjects may be withdrawn from follow-up for the following reasons:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up (after at least three documented attempts to contact her).
- Study is terminated for any reason.
- Subject death

6.14 Criteria for Removal from the Study

Participants will be removed from study when any of the criteria listed in Section 6.12 applies. All patients who are randomized in the study will be included in the overall evaluation of response (intent-to-treat analysis). All reasons for discontinuation of therapy should be documented clearly in the medical record.

6.15 Subject compensation

Participation in this trial is entirely voluntary. No cash compensation shall be provided for participants. However, subjects may be given parking vouchers for study-specific visits, in accordance with Lester & Sue Smith Breast Center clinical research standard operating procedures.

7. DRUG FORMULATION/STORAGE/SUPPLY

7.1 Vitamin D3, 5000 IU

Vitamin D3 at 5,000 IU strength is available over the counter at most retail pharmacies, and it will be supplied to patients through the study. They will be instructed to take 10 capsules one day each week, as described above in section 6.9.1, so that total dose is 50,000 IU weekly. The pills will be stored at controlled room temperature 15° to 30° C (59° to 86° F), in an appropriately labeled bin which is housed in a locked closet within the locked pharmacy.

7.2 Vitamin D3, 2000 IU

Vitamin D3 at 2000 IU strength is available over the counter at most retail pharmacies. The patients on the high dose arm will be provided with this medication for weeks 13-52 of the study. The pills will be stored at controlled room temperature 15° to 30° C (59° to 86° F), in an appropriately labeled bin which is housed in a locked closet within the locked pharmacy.

7.3 Caltrate-D, Calcium 600 mg & Vitamin D3 800 IU

The patients on the standard dose arm will be provided with this medication throughout the study. The pills will be stored at controlled room temperature 15° to 30° C (59° to 86° F), in an appropriately labeled bin which is housed in a locked closet within the locked pharmacy.

7.4 Drug Accountability

The investigator is responsible for accountability, reconciliation, and record maintenance of the study drugs (all doses of Vitamin D mentioned in sections 7.1-7.3). In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of study drug supplied to and returned by patients.

8. DOSING DELAYS/DOSE MODIFICATIONS

8.1 Dose Modifications/Delays

For any patient in the study, if 25-hydroxyvitamin D level exceeds 120 ng/mL at any point, the patient will be taken off the study medication. If the 25 (OH)D level is >90 ng/mL, we will hold the vitamin D supplementation for 4 weeks, and then recheck vitamin D level. If it is <70 ng/mL after 4 weeks, the patient may resume vitamin D at 50,000 IU every other week if the patient was on the lead-in phase of the high dose arm. If the patient was on the continuation phase of the high dose arm, she would instead take 1000 IU/day. If the patient was on the standard dose arm, she would take Caltrate-D once every other day. If the 25-hydroxyvitamin D level did not fall to <70 ng/mL after 4 weeks of a drug holiday, then the vitamin D will be held for an additional 4 weeks. At the end of this 8 week period, patients will resume reduced vitamin D dosing as described above if the level has fallen to <70 ng/mL. However, if the level is still ≥ 70 ng/mL, then the patient will be taken off the study medication.

Similarly, if the calcium level is >11.0 mg/dL at any time during the study, the patient will be taken off the study. If the calcium level is between 10.5 and 11.0 mg/dL, the patient may follow the same vitamin D reduction schedule outlined above in which the vitamin D supplementation is held for 4 weeks, and may only be resumed at half dose if the calcium level is within normal limits, according to reference lab values. If the calcium level has not normalized after 8 weeks of drug holiday, then the patient will be taken off the study medication.

8.2 Special Considerations

The 25-hydroxyvitamin D levels which are checked in the study are not revealed to the patient and doctor unless they specifically request that information, or if any of the calcium or Vitamin D levels exceed the pre-specified thresholds laid out in [Section 8.1](#). However, if the physician or patient wishes to know her vitamin D level, they may obtain this information from the study coordinator. For those who are on the standard dose vitamin D arm and have vitamin D <20 ng/mL, the physician may choose to replace vitamin D levels with 4000 IU of vitamin D3 daily, beginning at any point *after* 12 weeks of study enrollment. Vitamin D level will be checked every 4 weeks until it is ≥ 30 mg/mL. At that point, the patient will resume Caltrate-D once daily for the remainder of the study period.

9. ADVERSE EVENTS & SAFETY MONITORING

9.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at <http://ctep.cancer.gov/reporting/ctc.html>.

Information on certain adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

9.2 Definitions

9.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

9.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;

- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.
- Any other event, which, in the opinion of the investigator, could be considered serious.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

9.2.3 Expectedness

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

9.2.4 Attribution

The investigator will determine the relationship of each adverse event, if any, to investigational treatment or study procedure. Causality should be assessed using the following categories: Unrelated, Unlikely, Possible, Probable, or Definite.

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The event having often been reported in literature for similar drugs as drug related (e.g. skin rashes, blood dyscrasia)
- The event being related by time to drug administration terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

The investigator may change his/her assessment of causality in light of follow-up information. All adverse events will be recorded, regardless of whether the event is thought to be related to investigational treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

9.3 Anticipated Toxicities

If Vitamin D levels are allowed to become too high, hypercalcemia is the most common side effect. Symptoms may include anorexia, nausea, vomiting, abdominal pain, confusion, lethargy, constipation, muscle weakness, weight loss, polyuria, kidney stones, and heart arrhythmias.

9.4 Toxicity Management

Calcium and 25-hydroxyvitamin D levels will be followed closely while the patients are on study to avoid hypervitaminosis D. Levels of 25-hydroxyvitamin D and calcium will be monitored and managed as outlined in [Section 8.1](#). For corrected calcium level greater than 11 g/dL, management will be according to standard of care and the judgment of the treating physician. It is recommended that the patient be hydrated with one liter of IV normal saline, and given one dose of pamidronate at 90 mg IV, if renal function is within normal limits. The use of calcitonin will be at the treating

physician's discretion. The patient will be followed closely and treated until the calcium level normalizes. The patient will not be re-challenged with the study medication in this case.

If the patient develops calcium kidney stones, she will also be taken off the study. She will be referred to her primary care physician and/or urology for further management of the kidney stones.

9.5 Adverse event follow-up

Investigators should follow-up subjects with adverse events until the event has subsided (disappeared) or until the condition has stabilized. Subjects will be followed for adverse events and serious adverse events for 30-days from the last dose of study drug.

During the 30-day follow-up period, new onset, non-serious adverse events should only be recorded if, in the opinion of the investigator, there is a reasonable possibility the event is attributable to the investigational product. All serious adverse events occurring within the 30-day follow-up period must be reported, regardless of suspected causality.

9.6 Reporting Procedures

9.6.1 General

Adverse events will be captured in both the source documents and on the appropriate study-specific case report forms (CRFs). Given that each of the medications being utilized in this trial has a well-established safety profile, this protocol will utilize targeted AE reporting for all non-serious adverse events, as described below.

9.6.2 AE reporting requirements

- AE of any grade that requires a modification to treatment (e.g. dose modification, dose delay, or drug discontinuation)
- All grade 3 and 4 AEs, regardless of causality
- Any clinically significant laboratory abnormality, as defined in section 8.1
- All serious adverse events (SAEs), as defined in section 8.1

9.6.3 Serious Adverse Events

Any serious adverse events that occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the

investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events must be reported to the PI within 1 business day of becoming aware of the event. The protocol chair will then report SAEs to the Baylor College of Medicine IRB, in accordance with standard operating procedures. Events should be reported using a MedWatch form (FDA Form 3500), which is available for download on the FDA website.

The SAE report should comprise a full, written summary detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information and follow-up reports should be forwarded to all appropriate entities within 24 hours.

Instances of death, if brought to the attention of the investigator AT ANY TIME after cessation of study medication, and linked by the investigator to a previous clinical trial, should be reported to the FDA.

The PI will disseminate information regarding serious adverse events to the participating investigators within 5 days of review of the information by the Protocol Chair (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study medication.

9.6.4 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as possible.

9.6.5 Food and Drug Administration (FDA)

In this trial, unexpected adverse events believed to be definitely, probably, or possibly related to the medications will be reported to the Food and Drug Administration via MedWatch (using the online

form available at <https://www.accessdata.fda.gov/scripts/medwatch/>; by telephone 1-800-FDA-1088; or by fax 1-800-FDA-0178. FDA Form 3500A — Mandatory Reporting, available at: <http://www.fda.gov/medwatch/report/hcp.htm>).

10. CORRELATIVE/SPECIAL STUDIES

10.1 Grip Strength

To further investigate whether grip strength may serve as a simple, objective measure of AIA, we will measure grip strength at baseline, week 12 and week 52 visits (see study Calendar in Appendix B), and see whether changes in grip strength do correlate with changes in joint pain, as represented in the HAQ score. Research coordinators will measure grip strength as outlined in [Section 6.8.2](#).

11. SPECIMEN BANKING

Any leftover study blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. All samples will be stored indefinitely in the Lester & Sue Smith Breast Center Tumor Bank, located at One Baylor Plaza, Houston TX 77030. Samples will not contain any traditional patient identifiers; however, samples will be coded such that specimens are traceable back to the patient. The link between the specimen code and the patient will be maintained in a secure area, accessible only to the Tissue Bank Coordinator. Samples will only be released for use in future studies after approval by the protocol chair and other regulatory bodies, as appropriate. The samples will not be sold to third parties.

12. MEASUREMENT OF EFFECT

The primary assessments for this study will be the average score on the Health Assessment Questionnaire (HAQ-II), as well as the score from the visual analog scale.

12.1 Definitions

- 12.1.1 Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Vitamin D.
- 12.1.2 Evaluable for response: All the patients who have been randomized will be considered evaluable for response, regardless of how much treatment they have received,

consistent with an intention to treat analysis. These patients will have their response classified according to the definitions stated below. Any patient who began the study medication, but does not complete the HAQ at 12 weeks, will be deemed to be a study failure (i.e. the development of AIA will be assumed), consistent with an intention to treat analysis.

12.2 Measurement of Aromatase Inhibitor-Induced Arthralgia

Many trials which specifically examine AIA or other joint pathologies use a widely validated clinical tool termed the Health Assessment Questionnaire (HAQ-II). It is commonly used in rheumatology literature, and has been substantiated across many trials. This is a simple survey, which is a proven, reliable, and accurate indicator of joint pains and consequent disabilities (14) (15). An abbreviated version of the HAQ-II, which takes about 5 minutes to complete, will be used in the study (see Appendix A).

This questionnaire asks 20 questions in 8 categories of functioning: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. For each question, the patient is scored on a scale of 0-3, depending on how much difficulty they have performing the task. A score of 0 correlates with no difficulty at all, and a score of 3 denotes that the patient is unable to do the task. The highest numerical score from each category is used, and the average of these 8 numbers is the composite score on the HAQ-II. Scores of 0-1 are considered to represent mild to moderate difficulty, 1-2 represents moderate to severe disability, and 2-3 represents severe to very severe disability. Average score in a population based study is 0.49, whereas patients with osteoarthritis and rheumatoid arthritis have average scores of 0.8 and 1.2, respectively. Most investigators agree that “minimal clinical important difference” is 0.2 (42). Thus, the study uses this as a cut-off point.

The visual analog scale is the other major component of the HAQ-II. In this, the patient is asked to mark, with a vertical line, where their pain lies on a horizontal line which is 15 cm long, with the far left side of the line representing no pain at all, and the far right side representing unbearable pain. To obtain the individual’s score, the distance between the far left side of the line and the patient’s mark is multiplied by 0.2. This converts the number of centimeters into the appropriate score and will yield a value from 0 to 3.

For the purposes of this study, AIA will be defined as any of the following criteria: 1) increase in HAQ-II score from baseline by 0.2 or greater; or 2) increase in visual analog pain score by 0.3 or greater. The HAQ-II questionnaire and its visual analog pain score are used in the definition of

AIA because the questionnaire has been validated through many other studies which examine joint pain, and it is very simple to do in the office in less than 5 minutes. Though grip strength will be measured at various time points throughout the study, it will only be used in the exploratory analysis to see whether it may be an appropriate measure for AIA. Grip strength measurement is a relatively easy, inexpensive, objective criteria which may help to more clearly define AIA. This data will be very useful in the future, as it may serve to support a clearer, more objective definition of AIA for use in future studies, and for use in clinical practice.

12.3 Compliance with AI therapy

Compliance with aromatase inhibitor therapy will be evaluated by a physical pill count at the scheduled clinic visits on Weeks 12, 24, 36, and 52. Subjects will be instructed to bring their used bottles of aromatase inhibitor to each return visit, along with any unused tablets. Study staff will count the number of remaining tablets at each visit to assess compliance. In the event that the subject forgets to bring their used study meds to their clinic visit, compliance will be assessed by direct questioning of the subject. In this case, subjects should be counseled to bring their used drug bottles to their next scheduled clinic appointment so that compliance may be confirmed by pill count. Subjects should be instructed to report any missed doses of aromatase inhibitor to the study coordinator.

Compliance with the aromatase inhibitor will be calculated by the ratio of number of pills actually taken to the number of pills that should have been taken. Compliance will be defined as a ratio ≥ 0.80 . Study staff should ensure subject understanding of dosing instructions for subjects whose compliance is less than 100%. In addition, the importance of compliance with anticancer therapy should be reinforced. In the case of non-compliance, the study coordinator will ascertain, from the patient, the main reason for the non-compliance, and this will be recorded as study data.

Subjects who miss doses as a result of physician-prescribed drug holidays will not be considered non-compliant. Calculation of the compliance ratio should thus be adjusted such that the “number of pills that should have been taken” reflects the drug holiday.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint will be development of aromatase inhibitor induced arthralgia. Secondary endpoints will be compliance with aromatase inhibitor therapy and baseline vitamin D level.

Exploratory endpoints will be grip strength and breast cancer recurrence. Women on the study will be randomized to receive either high dose vitamin D or standard dose vitamin D for a total of 52 weeks (see attached [Schema](#)). All women will have their arthralgia and vitamin D levels assessed periodically throughout the study.

13.2 Sample Size/Accrual Rate

The primary objective of this study is to determine if supplementation of high dose Vitamin D prevents AIA in women being treated with adjuvant aromatase inhibitors. The Health Assessment Questionnaire II (HAQ-II) will be used to assess joint pain symptoms. Previously published estimates of AIA incidence showed that 33% of women on standard dose of vitamin D, and 19% of women on a high dose of vitamin D, developed AIA (**43**). Assuming a one-sided test with $\alpha=0.10$, $\beta=0.20$, we would need 93 women in each arm to detect a different rate of AIA development using the Chi-square test. Assuming 5% dropout rate in the first 12 weeks, we will accrue 93 women to each arm, for a total of 186 women. Sample size calculations were conducted using nQuery Advisor 7.0, Statistical Solutions, USA. Given that there are over 8000 office visits each year in our Baylor Clinic and Smith Clinic, we should easily be able to recruit an average of 4-6 women/month to the study, which would allow us to complete accrual in approximately 3 years.

13.3 Guidelines for Lead Institution and Other Site Institutions

Patients should be registered in the electronic database, ONCORE as soon as the patient has signed the informed consent. Following registration, the patient's enrollment status in the electronic database will be listed as pending. Prior to randomization the eligibility criteria must be reviewed and confirmed by the site PI and the coordinating center. Eligibility data will then be entered in the electronic database and the subject will be randomized. Study treatment may begin only after eligibility has been confirmed by both a site PI and the coordinating center. Once eligibility has been reviewed, it is recommended that treatment begin within a timely manner.

13.3 Eligibility exceptions

Any requests for protocol exceptions must be approved in writing by Dr. Mothaffar Rimawi at the Lester & Sue Smith Breast Center. Request for protocol exceptions must be made via email or fax to the lead study coordinator. Both Dr. Rimawi and the local PI should be copied on all requests and associated correspondence. Once a determination has been made, the site study coordinator and local PI will be notified in writing. In the event that an eligibility exception is granted by the

coordinating center, the local site must submit the exception to their local IRB in accordance with institutional standard operating procedures.

13.4 Primary Endpoint

Descriptive and summary statistics will be computed for all demographic and clinical data in each treatment group. The HAQ-II will be used to assess joint pain symptoms; a higher score indicates more severe joint pain. Scores will be evaluated for the development of AIA between baseline and Week 12, as well as between baseline and Week 52, though development of AIA at 12 weeks will be the primary endpoint. The scores will be dichotomized as “development of AIA” (as defined above, in Section 12.2) or “no development of AIA.” Group differences in AIA rate will be assessed using the Chi-square test. Development of AIA at week 12 will be used to test the primary objective. The week 52 data will be measured and reported as well. As exploratory analyses, development of AIA will be assessed using logistic regression, adjusting for potential confounders such as age at diagnosis, race/ethnicity, BMI, receipt of chemotherapy, taxane use, and use of hormone replacement therapy. All statistical tests are one-sided with $\alpha = 0.10$ as the level of significance.

13.5 Secondary Endpoints

Compliance will be determined via counting remaining pills in patient’s bottles at weeks 12, 24, 36, and 52 weeks. Compliance rate over 52 weeks of AI therapy will be compared between the two arms using longitudinal data analysis. The association between low baseline vitamin D levels and AIA will be assessed using the multivariate logistic regression model with adjusting for treatment effect and other confounding factors.

13.6 Exploratory Endpoints

For each patient on the study, grip strength will be correlated with AIA score using logistic regression analysis and Spearman correlation at three time points throughout the study – baseline, week 12, and week 52. At five years, we will also compare breast cancer recurrence rates in each arm using Kaplan-Meier survival analysis and log-rank test.

13.7 Futility Analysis

One interim analysis will be added to the study. It is expected to take place half-way through the study after 46 patients in each of the treatment group are enrolled and evaluable for the primary endpoint. The purpose of the interim analysis is to allow the study to stop early for lack of efficacy (futility). A non-binding O’Brien-Fleming spending function is used to calculate the futility boundary. Calculations were performed using nQuery Advisor + nTerim 3.0 (Statistical Solutions, Boston, MA).

The following table summarizes the futility boundary at each analysis when 50% and 100% patients are enrolled and evaluable at the interim analysis and the final analysis. The futility boundary in the term of p-value scale at the interim analysis is calculated as $p=0.47$ (or $Z=0.076$). If the one-tailed p-value exceeds 0.47, it will be recommended that the trial stop for futility.

Looks	Information	n per group	Futility Boundary (Z value)	Futility Boundary (one-tailed p value)
1	50%	46	0.076	0.47
2	100%	93	1.28	0.05

In order to preserve power and compensate for the interim futility analysis which tends to reduce power, the sample size of the study is increased from 88 per group to 93 per group, which is 196 total if considering a 5% drop out rate.

14. DATA AND SAFETY MONITORING

14.1 Data Management and Reporting

All patients who received any amount of study drug will be included in the safety analysis. Subjects will be monitored at each clinic visit and at any contact with the subject throughout the study for the occurrence of AEs and SAEs. The investigator or site staff will inquire about the occurrence of AEs/SAEs at weeks 12, 24, 36, and 52. Adverse events will be graded according to the NCI Common Terminology Criteria v. 4.0. All relevant AE's, as described in Section 9.6, that occur during active treatment will be recorded in subject source documents and on CRFs, regardless of relationship to investigational treatment. Non-serious adverse events that occur within the 30 day follow-up period will only be recorded on the CRFs if the investigator believes there to be a possible relationship to study medication. Serious adverse events should be recorded, regardless of relationship to drug.

Safety analyses will include summaries of adverse event rates (both frequency and incidence tables), baseline laboratory parameters and changes from baseline, frequency of CTC toxicity grades for both laboratory and non-laboratory data. The investigators and others responsible for patient care at individual sites should institute any supplementary investigations of major adverse events based on their clinical judgment of the likely causative factors.

14.2 Meetings

We will utilize the Data and Safety Monitoring Plan of the Dan L. Duncan Cancer Center at Baylor College of Medicine. During the clinical trial, clinical data on all participants enrolled on the study will be reviewed in our monthly breast center Data and Safety Monitoring Meeting.

We will have the trial reviewed at our Data Review Committee which will review accruals, serious adverse events, and cumulative toxicity data. The DRC will make recommendations about safety and tolerability.

15. REGULATORY CONSIDERATIONS

15.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center. Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation. The Protocol Chair (or his designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

15.2 Informed Consent

An investigator will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study investigator and supporting agencies and/or allow these bodies, a regulatory authority, or

Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

15.3 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

16. MULTI-CENTER GUIDELINES

16.1 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below.

All data collected will be entered by the participating site into the Coordinating Center Electronic Database (eCRF), via ONCORE.

16.2 Records Retention

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. Records must be maintained for at least 5 years following

the conclusion of the study, or in accordance with institutional policy, whichever is longer. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

16.3 Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation.

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18.*Appendix A: Health Assessment Questionnaire (HAQ)*

HEALTH ASSESSMENT QUESTIONNAIRE©Stanford University School of Medicine
Division of Immunology & Rheumatology

Name _____

Date _____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK

	<u>Without ANY</u> <u>difficulty</u> ⁰	<u>With SOME</u> <u>difficulty</u> ¹	<u>With MUCH</u> <u>difficulty</u> ²	<u>UNABLE</u> <u>to do</u> ³
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ARISING				
Are you able to:				
-Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EATING				
Are you able to:				
-Cut your meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty ⁰	With SOME difficulty ¹	With MUCH difficulty ²	UNABLE to do ³
HYGIENE				
Are you able to:				
-Wash and dry your body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Take a tub bath?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Get on and off the toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Bend down to pick up clothing from the floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
GRIP				
Are you able to:				
-Open car doors?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Open jars which have been previously opened?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Turn faucets on and off?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ACTIVITIES				
Are you able to:				
-Run errands and shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Get in and out of a car?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Do chores such as vacuuming or yardwork	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

NO		SEVERE
PAIN		PAIN
0		100

APPENDIX B STUDY CALENDAR

Study Procedure	Baseline (- 28 d)	Week 4	Wk 12	W 24	W 36	W 52	EOT	Safety Follow-up ² (+/- 7 d)	Follow-up for recurrence ³ (+/- 30 d)
Informed Consent	X								
Demographics	X								
Medical history	X								
Body weight measurement	X		X	X	X	X	X		
Health Assessment Questionnaire	X		X			X	X		
Grip Strength Measurement	X		X			X	X		
Review concomitant meds	X		X	X	X	X	X		
Bone Mineral Density Test ⁴	X								
Adverse Event Assessment			X	X	X	X	X	X	
Assess compliance ¹			X	X	X	X	X		
Assess disease & vital status									X
Calcium, Albumin, and 25(OH) Vit D levels	X	X	X	X	X	X	X		

1. Compliance assessment as determined by pill count and/or pill diary.
2. A safety follow-up should be performed 30 days after the last dose of study medication, even in the event of early discontinuation. Physical exam and laboratory assessments need only be performed if clinically indicated.
3. Recurrence follow ups will be performed every 6 months for the 4 years following the completion of the 52 week study period.

Study Procedure	Baseline (- 28 d)	Week 4	Wk 12	W 24	W 36	W 52	EOT	Safety Follow-up ² (+/- 7 d)	Follow-up for recurrence ³ (+/- 30 d)
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4. The Bone Mineral Density test must be ordered as a screening assessment, and results must be available within 28 days of starting AI therapy. If not completed within 28 days, patient will be taken off trial.