ID: UMCC 2020.041	Cannabidiol (CBD) for Treatment of Aromatase Inhibitor-Associated Arthralgias	NCT04754399

ROGEL CANCER CENTER
MICHIGAN MEDICINE

Phase 2 Trial of Cannabidiol (CBD) for Treatment of Aromatase Inhibitor-Associated Arthralgias

Protocol Number: UMCC 2020.041

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ABBREVIATIONS

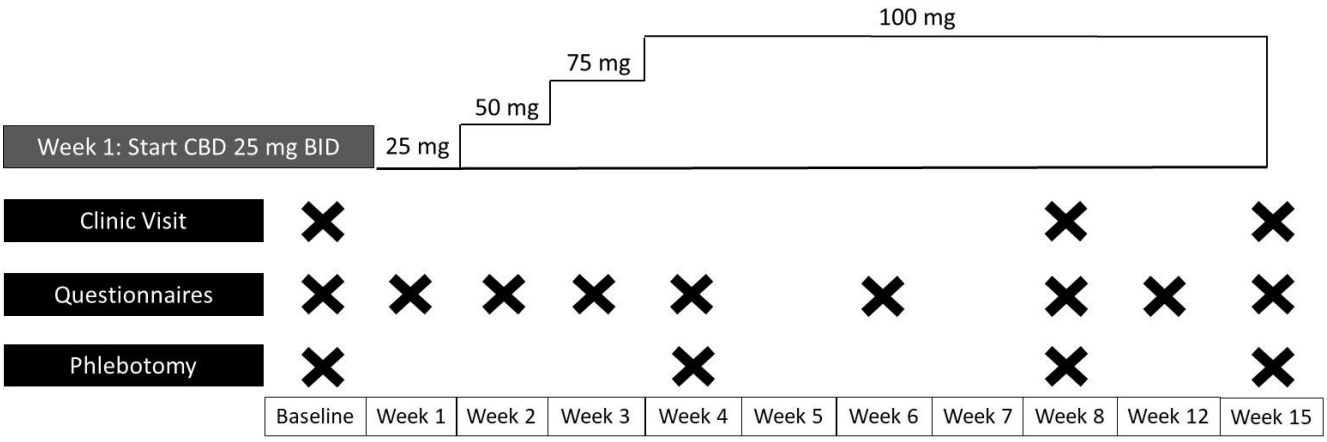
AI	Aromatase inhibitor
AIMSS	Aromatase inhibitor-associated musculoskeletal symptoms
BPI	Brief Pain Inventory
CBD	Cannabidiol
CNS	Central nervous system
DSMC	Data and Safety Monitoring Committee
ER	Estrogen receptor
GRC	Global Ratings of Change
HR	Hormone receptor
IRB	Institutional Review Board
LHRH	Luteinizing Hormone Receptor Hormone
METE	Mao Expectation of Treatment Efficacy
NSAID	Non-steroidal anti-inflammatory drugs
O-CTSU	Oncology Clinical Trial Support Unit
PANAS	Positive and Negative Affect Scale
PARP	Poly adenosine diphosphate-ribose polymerase
PR	Progesterone receptor
SAE	Serious adverse event
THC	Δ^9-tetrahydrocannabinol

STUDY SUMMARY

Title	Phase 2 Trial of Cannabidiol (CBD) for Treatment of Aromatase Inhibitor-Associated Arthralgias
Short Title	CBD for AIMSS (CBD-AIM)
Protocol Identifiers (IRB – internal)	HUM00182109
IND number	TBD
Phase	Phase 2
Design	Single arm phase II interventional trial
Study Duration	2.5 years
Study Center(s)	Single-center
Objectives	*Primary Objective:* To determine the effect of 15 weeks of CBD on AI-associated worst joint pain, as assessed with the Brief Pain Inventory (BPI) *Secondary Objectives:* To determine the effect of 15 weeks of CBD on other AI-associated pain symptoms, including average pain and pain interference, as assessed with the BPI To determine the effect of 15 weeks of CBD on other AI-associated symptoms, including anxiety, depression, insomnia, and cognitive function, as assessed with the PROMIS-29+2 Profile To examine the safety and tolerability of 15 weeks of CBD in patients with breast cancer taking aromatase inhibitor therapy To examine the effect of 15 weeks of CBD on circulating estradiol concentrations *Exploratory objectives:* To examine the impact of 15 weeks of CBD therapy on inflammatory biomarkers in patients with breast cancer taking aromatase inhibitor therapy

	To examine demographic, clinical, psychosocial, and inflammatory predictors of response to CBD therapy
Number of Subjects	44 (goal 40 evaluable patients)
Study drug	Cannabidiol 25 mg – 100 mg BID orally
Duration of administration	15 weeks
Reference therapy	N/A
Statistical Methodology	The primary endpoint of this study is the absolute difference in worst pain from baseline to 15 weeks with CBD. Differences from baseline at each time point for all patient reported outcomes (worst and average pain severity, pain interference, sleep disturbance, fatigue, physical function, anxiety, depression, and cognitive function over time) will be summarized via mean, standard deviation, and the change in the pattern over time will be explored with linear mixed models including a subject-specific random effect to account for the natural heterogeneity across patients. Normalizing transformations will be used if necessary to ensure accurate model fit. Secondarily, the proportion of patients who have at least a 2-point reduction in worst and average pain from baseline to 15 weeks will be reported with the corresponding exact binomial confidence intervals.

SCHEMA


100 mg
75 mg
50 mg
Week 1: Start CBD 25 mg BID
25 mg
Clinic Visit
Questionnaires
Phlebotomy
Baseline
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 12
Week 15

1 OBJECTIVES

1.1 Primary Objective

To determine the effect of 15 weeks of CBD on AI-associated worst joint pain, as assessed with the Brief Pain Inventory (BPI)

1.2 Secondary Objectives

1. To determine the effect of 15 weeks of CBD on other AI-associated pain symptoms, including average pain and pain interference, as assessed with the BPI

2. To determine the effect of 15 weeks of CBD on other AI-associated symptoms, including anxiety, depression, insomnia, and cognitive function, as assessed with the PROMIS-29+2 Profile

3. To examine the safety and tolerability of 15 weeks of CBD in patients with breast cancer taking aromatase inhibitor therapy

4. To examine the effect of 15 weeks of CBD on circulating estrogen concentrations

1.3 Exploratory Objectives

1. To examine the impact of 15 weeks of CBD therapy on inflammatory biomarkers in patients with breast cancer taking aromatase inhibitor therapy

2. To examine demographic, clinical, psychosocial, and inflammatory predictors of response to CBD therapy

2 BACKGROUND

2.1 Hypothesis

2.2 Rationale and Background:

Aromatase inhibitor (AI) therapy for breast cancer

Breast cancer is the most common cancer diagnosis among women in the United States, affecting one in eight women in her lifetime. With advancements in screening and treatment, nearly 90% of women diagnosed with breast cancer in the United States (US) survive beyond five years and comprise an estimated 25% of cancer survivors. About 80% of breast cancers diagnosed in postmenopausal women are hormone receptor

positive (HR+). For these women, daily oral adjuvant endocrine therapy for five to ten years following primary treatment (surgery, radiation, chemotherapy) is indicated.[1]

Third generation AIs are the preferred endocrine treatment for postmenopausal women with early stage HR+ breast cancer. Aromatase is the key enzyme that converts androgens to estrogens. In postmenopausal women, aromatase is only expressed in non-glandular tissues including fat, liver, brain, and breast tissues.[2] AIs prevent the biosynthesis of estrogen in these tissues, thus preventing the proliferation of HR+ breast cancer cells. Large-scale comparative effectiveness trials demonstrated the superiority of AIs over other endocrine treatment (i.e., tamoxifen), in terms of prolonged disease-free survival, rates of distant metastasis, and contralateral breast cancer, as well as a preferable toxicity profile.[3]

AI-Associated Musculoskeletal Symptoms (AIMSS)

Despite their clinical utility, AIMSS affect ~50% of the 200,000 patients who start AI therapy per year in the US.[4] Musculoskeletal symptoms, including arthralgias, myalgias, and joint stiffness, are the primary symptoms reported by AI-treated patients. These symptoms typically emerge within about 3 months of AI initiation, and peak at 6 months.[4, 5] Despite considerable research, the etiology of AIMSS remains poorly understood.[4, 6-9] Postulated mechanisms include inflammation and reductions in naturally anti-nociceptive properties of estrogen.[10, 11] While multiple randomized clinical trials of AIMSS treatments have been conducted, only a few interventions including acupuncture and duloxetine have demonstrated improvement in musculoskeletal pain and stiffness,[12, 13] and are currently unavailable to most patients due to access issues (acupuncture) and perceived stigma and toxicity (duloxetine).

AIMSS can lead to early treatment discontinuation in one-fifth of patients, which can increase risk of breast cancer recurrence by 45-50%.[4, 14-16] Despite well-established clinical benefits of long-term AI treatment, more than 20% of patients discontinue AI therapy prematurely, primarily because of toxicity of therapy. While the primary toxicity of therapy is AIMSS, AI-treated women also report bothersome vasomotor and gynecologic symptoms, as well as insomnia, fatigue, anxiety, and depression. In addition, studies have shown an increase in inflammatory markers in patients with co-existing symptoms, supporting an underlying inflammatory mechanism.[11] Discontinuation of AI therapy before the recommended 5-10 years has been shown to increase risk of cancer recurrence and mortality.[14-16] Therefore, well-tolerated and effective interventions to improve AI-associated symptoms, primarily AIMSS, are urgently needed.

Cannabinoids

Cannabinoids produce analgesia in patients with pain.[17] These compounds, such as cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC), act on cannabinoid receptors 1 and 2 (CB1 and CB2) and other receptors in the endocannabinoid system, which are involved in complex behaviors and responses such as pain, sleep, and mood.[18-20] THC's activation of CB1 receptors is primarily responsible for the psychoactive effects that characterize cannabis intoxication.[21, 22] In contrast to THC, CBD is non-intoxicating

and well tolerated in numerous medical conditions. CBD-related adverse events are minor, even in the context of long-term, high-dose paradigms.[23-28] CBD is a promiscuous compound that acts on numerous systems (e.g., the serotonergic 5HT1a receptor, transient receptor potential cation channel subfamily V member 1) and exerts anti-inflammatory and analgesic effects.[28] In a recent clinical trial among individuals with chronic pain due to knee osteoarthritis, transdermally-administered CBD significantly reduced pain and improved function.[29] Murine models of induced arthritis provide mechanistic support for this finding, as CBD slowed arthritis progression, prevented and/or reduced joint damage, and reduced spontaneous tumor necrosis factor release following lipopolysaccharide injection.[26, 27] Further, CBD administration during days 0-3 of monoiodoacetate-induced arthritis in a rat model dramatically reduced tactile allodynia and inhibited nerve demyelination, suggesting that early CBD administration could protect against nerve damage from inflammatory flares.[28]

CBD also exerts anxiolytic effects, which is of special import given that anxiety is common among individuals with breast cancer and is associated with worsened pain symptoms.[30-32] A recent clinical trial among individuals with social anxiety disorders showed that 300mg of CBD/day for 4 weeks resulted in decreased anxiety. Acute CBD administration (300-600 mg) has been shown to decrease anxiety compared to placebo during public speaking tasks.[33-36] In a retrospective chart review among 47 psychiatric outpatients, CBD (25-175 mg/day) reduced anxiety scores by 31% after 3 months.[37] Taken together, these anti-inflammatory, analgesic, and anxiolytic effects suggest that CBD may have value as an analgesic in AIMSS. Although CBD is widely used by the general public for pain, arthritis, and anxiety, clinical research on CBD is limited and no clinical trials have examined CBD alone for cancer pain. Thus, the proposed study will shed light on precisely how CBD is exerting its analgesic effects in patients with AIMSS, as well as rigorously investigate the safety profile in this condition.

Cannabidiol

Until recently, the only options for conducting clinical trials of CBD was to use over-the-counter products, which are highly variable in potency, there is poor quality control and testing for contaminants (e.g., heavy metals), and products are typically not consistent from lot to lot due to inherent variability in the hemp crop. However, a prescription version of CBD (Epidiolex) was recently FDA approved for treatment of refractory seizures in children. This formulation is ideal for testing in patients with AIMSS because it is non-intoxicating, is produced using Good Manufacturing Practices, which guarantee consistent product quality, and is not illegal under federal law.

Cannabidiol is relatively well tolerated at higher doses than planned in this trial; doses for treatment of refractory seizures are typically 5-20 mg/kg/day. Doses planned in this trial are 25 mg BID to 100 mg BID. For a 50 kg person, this is equivalent to a range of 1-4 mg/kg/day. For an 80 kg person, this is equivalent to a range of 0.625-2.5 mg/kg/day.

Assessment of AIMSS

No published scales have been established or validated to specifically measure the effects of treatments for AI-induced joint pain and stiffness. Therefore, we have chosen to use a combination of scales to assess the effect of CBD for improving tolerance of AI therapy. As has been used in multiple prior trials of treatments for AIMSS, patients will complete self-reported questionnaires including the Brief Pain Inventory-Short Form (BPI-SF)[38] to assess severity of joint pain/stiffness and the Global Ratings of Change (GRC) scale to identify overall change in pain/stiffness since starting AI therapy. To assess other symptoms related to endocrine therapy, patients will complete the PROMIS-29+2.[39] To assess expectation of benefit from CBD, patients will complete the Mao Expectation of Treatment Efficacy (METE).[40] Finally, patients will complete multiple questionnaires to further characterize pain and associated psychosocial symptoms, including the 2011 Fibromyalgia Survey to assess symptoms, the PANAS to assess affect, and a coping questionnaire to assess catastrophizing. All of these questionnaires are described in greater detail in section 10.

3 DRUG INFORMATION

3.1 Cannabidiol

3.1.1 Pharmacology

The mechanism of action of CBD for treatment of pain is not entirely clear. CBD has weak affinity for CB1 and CB2, but binds to other receptors, including serotonin 5-HT_{1A}.[41, 42] CBD is well tolerated in humans at doses up to 700 mg/day[43, 44] and is non-intoxicating.[45] In animal studies, CBD exerts anti-inflammatory and anti-nociceptive effects, and slows arthritis progression.[26-28] However, no systematic mechanistic studies of CBD have been conducted in individuals with chronic pain.

3.1.2 Physical and Chemical Properties

Cannabidiol is a cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. Cannabidiol, the active ingredient in EPIDIOLEX, is a cannabinoid that naturally occurs in the *Cannabis sativa L.* plant. Cannabidiol is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents.

3.1.3 Pharmaceutical Properties and Formulation

EPIDIOLEX (cannabidiol) oral solution is a clear, colorless to yellow liquid containing cannabidiol at a concentration of 100 mg/mL. Inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose. EPIDIOLEX contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

3.1.4. Pharmacokinetics

Cannabidiol demonstrated an increase in exposure that was less than dose-proportional over the range of 5 to 20 mg/kg/day in patients.

Absorption

Cannabidiol has a time to maximum plasma concentration (Tmax) of 2.5 to 5 hours at steady state (Css).

Effect of Food
Co-administration of EPIDIOLEX with a high-fat/high-calorie meal increased Cmax by 5-fold, AUC by 4-fold, and reduced the total variability, compared with the fasted state in healthy volunteers.

Effect on P-glycoprotein (P-gp) substrates
Coadministration of EPIDIOLEX with orally administered everolimus, a P-gp and CYP3A4 substrate, results in an approximately 2.5-fold increase in mean Cmax and AUC of everolimus *[see Clinical Pharmacology (12.3) in the drug prescribing information]*. When initiating EPIDIOLEX in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly. When initiating everolimus in patients taking a stable dosage of EPIDIOLEX, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring. Increases in exposure of other orally administered P-gp substrates (e.g., sirolimus, tacrolimus, digoxin) may be observed on coadministration with EPIDIOLEX. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with EPIDIOLEX.

Distribution

The apparent volume of distribution in healthy volunteers was 20963 L to 42849 L. Protein binding of the cannabidiol and its metabolites was >94% in vitro.

Elimination

The half-life of cannabidiol in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers. The plasma clearance of cannabidiol following a single EPIDIOLEX 1500 mg dose (1.1 times the maximum recommended daily dosage) is 1111 L/h.

Metabolism

Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms. After repeat dosing, the active metabolite of cannabidiol, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-COOH-CBD, which has an approximately 40 fold higher AUC than the parent drug. Based on preclinical models of seizure, the 7-OH-CBD metabolite is active; however, the 7-COOH-CBD metabolite is not active.

Excretion

EPIDIOLEX is excreted in feces, with minor renal clearance.

3.1.4 Clinical Safety

Cannabidiol had the following adverse reactions in clinical trials of EPIDIOLEX (%):

Adverse reaction	CBD 10 mg/kg/day	CBD 20 mg/kg/day	Placebo
Elevated transaminases	8	16	3
Decreased appetite	16	22	5
Diarrhea	9	20	9
Decreased weight	3	5	1
Gastroenteritis	0	4	1
Abdominal pain	3	3	1
Somnolence	23	25	8
Sedation	3	6	1
Lethargy	4	8	2
Fatigue	11	12	4
Insomnia	11	5	4
Irritability	9	5	2
Aggression	3	5	<1
Salivary hypersecretion	1	4	<1
Gait disturbance	3	2	<1
Infection	41	40	31
Rash	7	13	3
Hypoxia	3	3	1

Adverse reactions were similar across pediatric and adult patients.

Epidiolex can cause decreases in hemoglobin. The mean decrease in clinical trials was 0.42 g/dL, compared to a decrease of 0.03 g/dL on placebo.

Epidiolex can cause increases in serum creatinine; the mechanism is unknown. An increase of approximately 10% was observed within 2 weeks of starting Epidiolex. The increase was reversible in healthy adults.

4 STUDY DESIGN

4.1 Description

This will be a single arm phase 2 trial of CBD to examine the safety and efficacy of 15 weeks of CBD in postmenopausal women with AIMSS. In addition, change in inflammatory biomarkers with treatment will be examined to obtain preliminary information about the mechanism of action of CBD in this condition, and to identify predictors of response to therapy.

4.2 Number of Patients

A total of 44 patients will be enrolled, assuming a 10% dropout rate, for a total of 40 evaluable patients. Patients who discontinue trial participation prior to initiating CBD therapy will be replaced.

4.3 Number of Study Centers

This will be a single center trial run at the Rogel Cancer Center at the University of Michigan.

4.4 Study Duration

The study is anticipated to be open for 2.5 years.

5 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Female subject aged ≥ 18 years who is postmenopausal according to standard clinical criteria (see section 8.3) or who has been receiving concomitant LHRH agonist therapy.

5.1.2 _____ Taking the currently prescribed aromatase inhibitor therapy (anastrozole, exemestane, or letrozole) for adjuvant treatment of breast cancer or for chemoprevention for at least 3 weeks and no more than 2 years at the time of enrollment.

5.1.3 _____ Planning to take the same AI therapy for at least 15 weeks.

5.1.4 _____ New or worsening joint pain and/or myalgias since starting the AI therapy, with *worst* pain score of at least 4 out of 10 on the BPI over the 7 days prior to enrollment.

5.1.5 _____ Completion of surgery (mastectomy or lumpectomy/partial mastectomy) for treatment of breast cancer at least 3 months prior to enrollment. Completion of axillary surgery as indicated (not required).

5.1.6 _____ Completion of chemotherapy, if given. Concurrent use of LHRHa therapy, anti-HER2 therapy, bisphosphonate therapy, PARP inhibitor therapy, and CDK4/6 inhibitor therapy is permitted.

5.1.7 _____ Patients receiving treatment with NSAIDs, acetaminophen, opioids, duloxetine, gabapentin, and/or pregabalin must have been taking a stable dose for at least 30 days prior to enrollment if they plan to continue the drug during study participation. If they do not plan to take the medication during study participation, they should stop the medication at least 7 days before initiation of study treatment.

5.1.8 _____ ECOG Performance Status 0-2.

5.1.9 _____ Able to self-complete questionnaires in English.

5.1.10 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Metastatic breast cancer.

5.2.2 _____ Planned surgery during the 15-week study period.

5.2.3 _____ ALT/AST > 3x ULN or bilirubin > 1.5x ULN. If known Gilbert's syndrome, bilirubin may not be > 2x ULN (obtained ≤28 days of registration).

5.2.4 _____ Clinically significant laboratory abnormalities, including: Creatinine >1.5 x ULN or Hemoglobin <9 g/dL (obtained ≤28 days of registration).

5.2.5 _____ History of or currently has suicidal ideation or attempted suicide

5.2.6 _____ History of seizure other than febrile seizures in childhood.

5.2.7 _____ Current use of valproate or clobazam. If patient takes valproate or clobazam, should discontinue 7 days prior to enrollment.

5.2.8 _____ Use of cannabidiol, THC, or marijuana (oral, inhaled, or topical) within the 6 weeks prior to enrollment.

5.2.9 _____ Known allergy or hypersensitivity to CBD or any of the excipients in the medication, including sesame.

5.2.10 _____ Unable to take oral medications.

5.2.11 _____ Pregnant or breast feeding.

5.2.12 _____ Any medical condition that would interfere with the absorption of study medication. Prior gastric bypass is permitted.

5.2.13 _____ Concurrent medical or arthritis disease such as active rheumatoid arthritis or inflammatory arthritis that could confound or interfere with evaluation of pain or efficacy. Patients with osteoarthritis are eligible.

5.2.14 _____ Patients with a prior or concurrent malignancy whose natural history or treatment, in the opinion of the treating investigator, has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

6 STRATIFICATION FACTORS

N/A

7 TREATMENT PLAN

7.1 Cannabidiol

7.1.1 How Supplied, Stored, Packaged and Labeled

Cannabidiol (EPIDIOLEX, Greenwich Biosciences) will be purchased from commercial supply and stored in the University of Michigan Research Pharmacy. The Research Pharmacy will dispense one bottle per patient at the baseline study visit; if the patient is unable to come to clinic for the baseline visit then the medication will be mailed to the patient and the study medication log will be mailed or emailed to the patient. A second bottle

will be provided at the week 8 study visit; if the patient is unable to come to clinic for the 8 week visit then the medication will be mailed to the patient and the study medication log will be mailed or emailed to the patient.

EPIDIOLEX is a strawberry flavored clear, colorless to yellow solution supplied in a 105 mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution (NDC 70127-100-01). Each mL contains 100 mg of cannabidiol. EPIDIOLEX is packaged in a carton with two 5 mL calibrated oral dosing syringes and a bottle adapter (NDC 70127-100-10). The pharmacy will provide 1 mL calibrated oral dosing syringes when doses less than 1mL are required.

Store EPIDIOLEX in its original bottle in an upright position at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F). Do not refrigerate or freeze. Keep the cap tightly closed. The bottle with any unused drug will be returned to the study coordinator/Research Pharmacy at the completion of the trial.

7.1.2 Preparation and Administration

Patients should be instructed to take 25 mg (0.25 ml) twice a day approximately 12 hours apart for the first week, with food. Each week the patient should increase the dose by 25 mg twice a day until she reaches a maximum of 100 mg (1 ml) twice a day, unless she has difficulty tolerating the medication. If a dose is missed the patient should take it as soon as she remembers, although if it has been more than 8 hours she should not double up on dosing. If a dose is vomited it should not be made up.

The drug should be drawn up into a dry syringe. If the syringe is wet, it can make the drug appear cloudy; this does not affect its safety or efficacy.

Patients will be advised not to drive or operate machinery until they have gained sufficient experience on the study drug to gauge whether it adversely affects their ability to drive or operate machinery. Participants will be advised that concomitant use of alcohol or other CNS depressants may increase sedation and somnolence.

7.1.3 Accountability and Compliance

Study drug compliance during any period will be monitored by having the patient complete an IRBMED approved study drug diary.

7.2 Concomitant Medications and Therapies

7.2.1 Allowed Therapy

Patients are permitted to take concomitant aromatase inhibitor therapy, LHRH agonist therapy, anti-HER2 directed therapy, CDK4/6 inhibitor therapy, and/or anti-osteoclast therapy. Patients are permitted to use vaginal estrogen preparations.

Because of the potential for drug-drug interactions, consider a reduction in dosage of sensitive CYP1A2, CYP2B6, CYP2C8, CPY2C9, CYP2C19, and P-gp substrates, as clinically appropriate (see https://drug-interactions.medicine.iu.edu/MainTable.aspx and the drug prescribing information).

Patients who are taking opioids, NSAIDs, acetaminophen, duloxetine, gabapentin, and/or pregabalin at the time of study drug initiation should continue to take the same dose of medication for the 15 week study duration.

7.2.2 Prohibited Therapy

Patients with a history of hormone receptor positive breast cancer should avoid taking systemic or transdermal estrogen products (vaginal estrogen preparations are permitted).

Patients should not take valproate or clobazam while participating on this clinical trial.

7.3 Duration of Therapy

Patients will be treated with the study drug for 15 weeks (+/- 7 days).

7.3.1 Criteria for discontinuation of treatment ("off study")

The following will result in study treatment discontinuation:

- Discontinuation of AI therapy, defined as:
    - Discontinuation of the currently prescribed AI therapy for more than 7 days
- Evidence of new cancer or cancer recurrence
- Unacceptable toxicity (see section 8.1)
- Delay of 14 consecutive days of study treatment (CBD) due to any reason
- The participant may discontinue study treatment (CBD) at any time for any reason including participant request to be withdrawn from study
- Death

8 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) for adverse event and serious adverse event reporting.

8.1 Dose Modifications and Guidelines for Adverse Event Management

8.1.1 Dose Modifications

Dose levels:

Dose level 1	25 mg BID
Dose level 2	50 mg BID
Dose level 3	75 mg BID
Dose level 4	100 mg BID

If the dose is reduced because of toxicity, that dose should be maintained for the remainder of the trial and not re-escalated.

Toxicity Grade	What to do
Grade 1 – possibly, probably, or definitely related to study drug	For ALT/AST > 3x ULN, discontinue study medication. For all other grade 1 toxicities, monitor as needed until the problem has resolved (i.e., grade 0), stabilized (i.e., remains as grade 1), or is otherwise explained. If Grade 1 symptoms persist, the PI or Co-I will assess whether the dose should be reduced by 1 dose level or, if the patient is receiving dose level 1, whether the patient should discontinue study medication.
Grade 2 – possibly, probably, or definitely related to study drug	For total bilirubin > 2x ULN, discontinue study medication. For all other grade 2 toxicities, monitor as needed until the problem has resolved (i.e., grade 0), stabilized (i.e., remains as grade 1 or grade 2), or is otherwise explained. If Grade 2 symptoms persist, the PI or Co-I will assess whether the dose should be reduced by 1 dose level or, if the patient is receiving dose level 1, whether the patient should discontinue study medication.
Grade 3 – possibly, probably, or definitely related to study drug	If the patient was receiving dose level 1 at the time of toxicity development, the patient should discontinue study drug. For patients receiving dose level 2 or higher, if the symptoms resolve or improve to grade 1 or 2 within 7 days, the dose should be reduced by 1 dose level and the drug restarted at the time of symptom improvement. This dose is to be maintained if no further Grade 3 toxicity is noted. If the symptoms do not resolve or improve to grade 1 or 2 within 7 days, the patient can continue to hold study drug for another 7 days. If the symptoms resolve or improve to grade 1 or 2, the dose should be reduced by 1 dose level and the drug restarted at the time of symptom improvement. This dose is to be maintained if no further Grade 3 toxicity is noted. If

	the symptoms remain Grade 3 possibly, probably, or definitely related to the study drug, the patient should be permanently removed from protocol treatment. If upon restarting the medication at the lower dose the patient again experiences Grade 3 toxicity, the patient can again be given a 7-day drug holiday. Subsequently the patient may be rechallenged one dose level lower. If symptoms do not recur (i.e., if symptoms resolve to grade 0), the dose should be maintained. Alternatively, if Grade 1 or Grade 2 symptoms occur, the PI or Co-I will assess whether the patient should be removed from protocol treatment.
Grade 4 – possibly, probably, or definitely related to study drug	Study drug should be permanently discontinued.

Patients who experience hypersensitivity reactions to the study medication should discontinue the study medication.

8.2 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study.

8.3 Contraception

Only post-menopausal women (including those rendered postmenopausal with LHRH agonist therapy) are eligible for enrollment on this clinical trial. Postmenopausal is defined as one or more of the following:

- Absence of menses for at least 12 months
- Concurrent use of LHRH agonist therapy
- Prior bilateral salpingo-oophorectomy
- Serum or plasma concentrations of estradiol within postmenopausal range according to local lab values

9 STUDY CALENDAR

Required Studies	Screening [a]	Baseline [b]	Weeks 1, 2, 3 (+/- 2 days) [c]	Weeks 4, 6 (+/- 2 days) [c]	Week 8 (-2, +7 days) [c]	Week 12 (+/- 2 days) [c]	Week 15 (-2, +7 days) [c, j]	Off Study (if prior to week 15) [d]
Informed consent	X							
Medical History	X							
Performance status[m]	X							
Study visits[i]	X[q]	X			X		X	X
Study coordinator phone calls[k, n]			X	X	X	X	X[l]	X[l]
Vital signs [e]	X							
Concomitant medications	X	X						
Adverse event assessment			X		X		X	X
Patient reported questionnaires [f]								
- **BPI**	X	X	X	X	X	X	X	X
- **PROMIS**		X		X (wk 4 only)	X		X	X
- **GRC**			X[o]	X (wk 4 only)	X	X	X	X
- **METE**		X						
- **FM Survey**		X					X	X
- **CSQ**		X					X	X
- **PANAS**		X					X	X
- **PHQ9 [p]**	X	X						
Phlebotomy [g]								
- **Research**	X[r]				X		X	X
- **Clinical labs (aspartate aminotransferase, alanine aminotransferase, total bilirubin, serum creatinine, complete blood count)**	X			X (wk 4 only)	X		X	X
AI therapy (standard of care)		→	→	→	→	→	→	
Dispense study medicine		X			X			
CBD treatment [h]		→	→	→	→	→	→	
Medication log		X			X		X[i]	X[i]

a. Screening and baseline visits can take place on the same day. The informed consent can be completed either in person or remotely using SignNow. The BPI and PHQ9 will be completed after signing the ICF and can be completed by phone or electronically. Screening clinical lab studies must be completed within 28 days of registration; if they have already been completed for another reason (other than participating in this clinical trial) they do not need to be repeated.
b. Baseline visit can take place up to 4 weeks after the screening visit. Patient does not need to be seen by physician or advanced practice provider.
c. Timed based on initiation of CBD therapy.
d. This is the visit conducted at the time of AI discontinuation and/or study drug discontinuation as per section 7.3.1. These questionnaires should be completed within 3 business days of medication discontinuation. Patients will return remaining study drug and medication log at that study visit or at their next routine clinic

visit. Also if a patient discontinues study drug early, she should continue to complete questionnaires according to the study calendar through the 15 week timepoint.
e. Height and weight at screening visit. If these values have been documented in the medical record within 90 days they do not need to be repeated.
f. Questionnaires will be completed electronically within 2 days before the scheduled visit, at the time of the visit, or within 2 days after the visit. It is preferable to have patients complete the questionnaires before or at each visit. Emailed reminders will be sent to patients from REDCap, and telephone reminders may also be used. If a scheduled visit is rescheduled after the questionnaires have been completed by the patient, they will not be considered out of window. If a patient declines to complete questionnaires electronically they may be completed on paper (baseline and week 8 and 15) or by phone (all timepoints).
g. It is preferred, but not required, that subjects fast for at least 8 hours prior to all blood collections (except for week 4). Time of blood draw and fasting status should be recorded. Details about research labs are in section 15.2.1.
h. Study medication should begin the first Wednesday morning after the baseline visit whenever possible. If the baseline visit is on a Wednesday, the participant can start the study medication the evening of the baseline visit. The medication should be taken with food twice a day approximately 12 hours apart.
i. At weeks 8 and 15 or off study, patient will meet with research study coordinator or otherwise return the medication log and/or remaining medication to the study team, depending on the timepoint. Patient does not need to be seen by physician or advanced practice provider. Patients will return medication log #1 at the 8 week study visit and return all remaining study drug and medication log #2 at the 15 week study visit, or at the off study visit if it occurs at a different time. If they forget to bring the medication and log to the visit, they should return the items at their next routine clinic visit.
j. For patients who wish to continue on therapy beyond the 15 week study visit, clinicians can provide a written prescription for off-label Epidiolex and/or provide recommendations for patients to go to local cannabis dispensaries in Michigan (since recreational cannabis is legal in this state), but drug will not be provided by the clinical trial following the week 15 study visit.
k. Study coordinator calls are to assess adverse events including suicidality and (if applicable) determine if there is a reason that the patient should not increase the dose by one dose level (as per section 8.1.1). If there is a question about whether the patient should or should not increase the dose, the study coordinator will contact the PI or Co-I. Also if patients have not completed questionnaires or if they decline to complete questionnaires electronically, the study coordinator should ask the questions by phone.
l. The study coordinator should follow-up with the patient by phone 30 days following the off-study visit to assess resolution of any AEs as per section 16.5.
m. Performance status assessment at screening will be performed by a licensed physician (or physician's assistant or nurse practitioner) or registered nurse. Can have been performed up to 28 days before the screening visit, and can be performed during a virtual visit.
n. The study coordinator will ask about suicidal ideation on the phone calls using question 9 from the PHQ9: "How often have you been bothered by the following in the past week: Thoughts that you would be better off dead, or thoughts of hurting yourself in some way? Not at all, several days, more than half the days, nearly every day". If a patient reports anything other than "Not at all" to the question, the patient's oncology treatment team will be notified and the patient will be managed according to usual clinical protocols. If the treatment team is not available, the PI or another of the co-Is will be notified.
o. GRC should be completed at week 2.
p. The study coordinator should review the response to PHQ9 question 9 prior to dispensing the study medication to the patient. If the answer to the question is anything other than "Not at all", the study medication should not be dispensed and the patient's clinical team or covering provider should be notified immediately.
q. The screening study visit can be conducted virtually if the necessary patient information (other than lab results) can be found in the medical chart. Patient will need to undergo phlebotomy prior to enrollment in the study if screening lab studies have not otherwise been performed within the past 28 days.
r. If clinical lab studies do not need to be performed at screening because they have been performed within the 28 day window, the research blood specimens at screening can instead be collected at baseline.

10 STUDY PROCEDURES

10.1 Screening Evaluations

A review of inclusion/exclusion criteria will be conducted to determine the patient's eligibility for enrollment. Study procedures will be reviewed with the patient, and documentation of informed consent will be obtained. After signing the informed consent form (ICF) either in person or electronically using SignNow or other process approved by the UM IRBMED, patients will be assigned a unique study ID number in sequential order. Patients will complete the BPI and PHQ9 questionnaires after signing the ICF in order to confirm eligibility. Those who are found to be ineligible will be replaced.

The following medical history elements will be abstracted from the medical record: date of breast cancer diagnosis, tumor information (e.g., tumor histology, receptor status), treatment information (e.g., surgery type and dates, chemotherapy doses and dates, radiation therapy doses and dates), information about other relevant medical co-morbidities and concomitant medications (as outlined on the case report form). The patient's email address and phone number will also be recorded.

10.2 Patient-Reported Outcomes

The validated instruments used in this study are as follows:

Brief Pain Inventory (BPI): The BPI is a 17-item patient self-rating scale that assesses sensory and reactive components of pain.[38] For sensory components, it addresses severity, location, chronicity, and degree of relief due to therapy. For reactive components, it assesses depression, suffering, and perceived availability of relief. Reliability has been demonstrated over short intervals using test retest item correlation; worst pain, r=0.93, usual pain, r=0.78, pain now r=0.59. It has been validated in patients with both cancer and non-cancer pain.[46, 47] Ratings of pain interference with various activities increased as ratings of pain severity were higher. The proportion of patients receiving opioid analgesics also increased with increased severity rating.

The BPI uses 0 to 10 numeric rating scales for item rating because of its simplicity and lack of ambiguity. Since pain can be variable over a day, the BPI asks patients to rate their pain at the time of completing the questionnaire, and also at its worst, least, and average over the previous 7 days. The primary endpoint for this clinical trial will be based on the 7-day worst joint pain and/or myalgias as reported on the BPI. The ratings can be combined to give a composite index of pain severity. Also, using numeric 0 to 10 scales, with 0 being "no interference" and 10 being "interferes completely", the BPI asks for ratings of the degree to which pain interferes with mood, walking and other physical activity, works, social activity, relations with others, and sleep. The mean of these scores can be used as a pain interference score. This will be completed at each timepoint.

PROMIS-29+2 Profile v2.1: A validated questionnaire that assesses patient-reported symptoms over the past 7 days in 9 PROMIS domains (fatigue, sleep disturbance, physical functioning, depression, anxiety, ability to participate in social roles and activities, cognitive function-abilities, and pain intensity and interference). Raw scores for each domain are calculated and then converted to a T-score, with a mean of 50 and a standard deviation of 10. Higher T scores represent more of the concept being measured.[39] Pain severity and interference will be excluded since overlaps with BPI. This 26-item questionnaire will be completed at baseline, 4, 8, and 15 weeks (and off study if patient discontinues before week 15).

Global Ratings of Change (GRC) Scale: This is a single-item measure to assess the overall change in pain and stiffness since stopping AI therapy. It is a 7-point Likert scale from -3 to +3. This will be completed at 2, 4 8, 12, and 15 weeks (and off study if patient discontinues before week 15).

Mao Expectancy of Treatment Effect (METE): The METE is a validated 4-item self-report questionnaire rated on a scale of 1-5 (from total disagreement to total agreement), which assesses a patient's expectation that CBD will relieve her AIMSS symptoms.[40] The instrument had good internal consistency (Cronbach's α 0.95) in a prior study of acupuncture in patients with cancer.[48] Will be completed at baseline.

Fibromyalgia (FM) Survey: The FM survey is a combined measure of widespread pain (body map of painful sites) and symptom severity (e.g., fatigue, cognitive problems, headache, poor mood, scores range 0-12), as a self-reported proxy of centralized pain, assessed at baseline. This is a continuous measure with scores ranging from 0-31.[49, 50] Will be completed at baseline and week 15 (or off study if patient discontinues before week 15).

Coping Strategies Questionnaire catastrophizing scale: The CSQ catastrophizing subscale is a validated 6 item subscale that assesses pain catastrophizing, a thinking style has been associated with the progression of acute pain to chronic states, and with poorer outcomes generally.[51] Will be completed at baseline and week 15 (or off study if patient discontinues before week 15).

Positive and Negative Affect Scale (PANAS): The PANAS is a validated 20-item instrument that measures positive and negative affect.[52] It can be scored to include a metric of affect balance (e.g., greater negativity over positivity).[53-55] Will be completed at baseline and week 15 (or off study if patient discontinues before week 15).

Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 is a validated 9-item instrument to assess depression that is used in both research and clinical practice.[56] Question 9 specifically addresses suicidal ideation.

11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms and the laboratory studies (LFTs, creatinine, hemoglobin). More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

11.2 Stopping Rules

N/A

12 STATISTICAL CONSIDERATIONS

12.1 Statistical hypothesis

Use of CBD in postmenopausal women with breast cancer who are experiencing AIMSS will result in improvement in joint pain and stiffness. As a secondary hypothesis, use of CBD will result in improvement in anxiety.

12.2 Sample size determination

The primary endpoint of this study is the absolute change in worst pain from baseline to 15 weeks with CBD. Analysis will be based on intention-to-treat, and all patients who complete the 15 week assessment with BPI will be evaluable for the primary endpoint. There are no available prior data on symptom response in patients with AIMSS treated with CBD. Therefore, the statistical plan for this study was based on data from other studies of patients with AIMSS. Based on prior data from acupuncture therapy for treatment of AIMSS, we expect a baseline worst pain score of 6.5 and standard deviation of 3. Therefore, with a sample size of 40 evaluable patients, a two-sided type I error of 5%, we can detect a standardized effect size of 0.45 or a change in worst pain of 1.4 points with 80% power. Based on IMMPACT guidelines, a 2-point reduction in pain is considered to be clinically meaningful for an individual patient.[57] We power to find a slightly smaller effect size based on potentially more heterogeneity in our sample (i.e. higher variability). To account for anticipated treatment discontinuation rates of 10%, we will need an additional 4 patients (for 40 completing patients).

An increased sample size of 44 patients and a longer duration of therapy (15 weeks) were chosen to allow for precise evaluation of the efficacy of CBD and to expand our ability to perform and interpret the correlative studies. Further, the funder of this study voiced concern that a smaller sample size (of 20 patients) and a shorter treatment duration (8 weeks) were insufficient to evaluate the primary endpoints of this study.

12.3 Statistical Analyses

12.3.1 Primary endpoint

The primary endpoint is defined as the absolute change in BPI worst pain from baseline to 15 weeks. This change will be reported with the corresponding 95% confidence interval. Differences from baseline at each time point for worst pain will be summarized via mean and standard deviation. Patient reported outcomes will be analyzed using linear mixed effects models and include a subject-specific random effect to account for the natural heterogeneity across patients. Normalizing transformations will be used if necessary to ensure accurate model fit.

12.3.2 Secondary endpoints

1. The proportion of patients who have at least a 2 point reduction in *worst* pain from baseline to 15 weeks will be reported with the corresponding exact binomial confidence interval.
2. The proportion of patients who have at least a 2 point reduction in *average* pain from baseline to 15 weeks will be reported with the corresponding exact binomial confidence interval. Differences from baseline at each time point for average pain and pain interference will be summarized via mean and standard deviation. Patient reported outcomes will be analyzed using linear mixed effects models and include a subject-specific random effect to account for the natural heterogeneity across patients. Normalizing transformations will be used if necessary to ensure accurate model fit.
3. Differences from baseline at each time point for all other patient reported outcomes (sleep disturbance, fatigue, physical function, anxiety, depression, and cognitive function over time) will be summarized via mean and standard deviation. Patient reported outcomes will be analyzed using linear mixed effects models and include a subject-specific random effect to account for the natural heterogeneity across patients. Normalizing transformations will be used if necessary to ensure accurate model fit.
4. Safety will be assessed throughout the trial and adverse events will be reported using descriptive statistics and stratified by dose.
5. We will report the proportion of individuals with undetectable levels of estradiol at baseline and 15 weeks with corresponding exact binomial 95% confidence intervals. The exact levels of estradiol at baseline and 15 weeks will be summarized using descriptive statistics.

12.3.2 Exploratory endpoints

1. In this exploratory aim, all inflammatory markers and cytokine levels will be summarized using descriptive statistics at baseline and 15 weeks. The changes in inflammatory biomarkers will be assessed using one sample t-test of the difference (or sign test). Linear models will examine the association between the 8 and 15-week worst pain score (controlling for baseline worst pain score and change in pain worst

pain) and baseline and 8 and 15-week inflammatory markers and cytokines. Normalizing transformations will be used if required.[58, 59] We are limited in the number of covariates in each model based on sample size, so we will be careful of overfitting recognizing that patient and disease characteristics may be confounders in analysis. No correction for multiple comparisons will be applied based on the hypothesis generating nature of the aim.

2. In this exploratory aim, all questionnaire scores will be summarized using descriptive statistics at baseline and 15 weeks. The changes in survey responses will be assessed using one sample t-test of the difference (or sign test). We will use a linear model to examine the association between the 15-week worst pain severity (as measured by the BPI) and the baseline worst pain severity, and baseline and 15-week FM score. Similarly, separate models of the 15-week worst pain score will control for baseline worst pain severity and assess associations with baseline and 15-week PANAS scores and catastrophizing scores. We are limited in the number of covariates in each model based on sample size, so we will be careful of overfitting recognizing that patient and disease characteristics may be confounders in analysis. No correction for multiple comparisons will be applied based on the hypothesis generating nature of the aim.

3. We will report the proportion of individuals with undetectable levels of estrone and estrone sulfate at baseline and 15 weeks with corresponding exact binomial 95% confidence intervals. The exact levels of estrone and estrone sulfate at baseline and 15 weeks will be summarized using descriptive statistics.

13 REGISTRATION GUIDELINES

Study related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration. All eligibility will be reviewed and confirmed by PI or co-I prior to enrollment.

Patients must be registered before receiving any study treatment and must begin study treatment within 4 weeks of registration. See study calendar (section 9) for details.

14 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log.

15 SPECIAL INSTRUCTIONS

15.1 Patient-reported questionnaires

Prior to the first time the patient completes the questionnaires: Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment. They should also be told that their treating provider will not be told about symptoms that they report on the questionnaires, and they should mention them during their visit.

When patients are completing them at the time of the clinic visit, it is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Discourage family members from influencing patient responses to the questions.

The study coordinator will review the questionnaires after completion on paper to ensure that no questions were accidentally skipped or that more than one answer was provided. Whenever possible, questionnaires will be completed online, although if a patient states that she is unable or unwilling to complete the questionnaire online then a paper form will be provided.

If a patient is unwilling to complete the questionnaires at the time of the study visits (baseline, week 8, and week 15) and has not yet done so within 2 working days following the visit, the study coordinator will follow-up with the patient by phone to remind her to complete the questionnaires. The questionnaires should be completed electronically, or the study coordinator can have the patient answer the questions by phone. They should be completed within 2 days after the baseline visit and within 7 days after week 8 and 15 visits.

For the assessment times that are not linked with a study visit, patients will be sent an email link via REDCap to questionnaires 2 days before each assessment time weeks 1-6 and 12. If they have not completed the questionnaire by the scheduled assessment time (based on date of CBD initiation) they will be sent a reminder by email and/or phone. If they do not answer the questions by 2 days after the assessment they will be contacted by the study coordinator to complete them by phone.

15.2 Correlative Studies

15.2.1 Blood correlative studies

The following samples will be collected:

A. 10 cc blood will be collected for isolation of plasma at screening (or baseline as per study calendar), 8, and 15 weeks and stored in 500 ul aliquots at -80C.

B. Blood will be collected in TruCulture system 1 ml tubes containing either LPS or media at screening, 8, and 15 weeks. Within 15 minutes of the blood draw the samples should be incubated at 37C for 24-48 hours, then the supernatant will be isolated and stored in 250 ul aliquots. (instructions for blood processing: https://myriadrbm.com/products-services/truculture/truculture-video/)

Samples will be collected at the time of standard of care phlebotomy whenever possible. Patients will fast for at least 8 hours prior to phlebotomy whenever possible. The study coordinator will record time of blood draw and whether or not patient was fasting.

15.2.2 Correlative analyses

Thawed samples will be batch-analyzed for estrogens, high sensitivity C reactive protein, and a panel of pro-inflammatory (e.g., IL-6, IL-1, TNF-α, IL-17) and regulatory cytokines (e.g., IL-10) using high sensitivity tandem mass spectroscopy-based, immunoturbidimetric, and multiplex assays, respectively.[60] Stimulated cytokine and chemokine analysis will be performed using the TruCulture system.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version.

16.2 Human Subjects Protections

16.2.1 Rationale for Subject Selection

This clinical trial is open to all patients with AIMSS with minimal restrictions in order to permit inclusion of as broad a population as possible. Only patients who read English will be enrolled because not all of the patient reported questionnaires have been linguistically validated in other languages.

16.2.2 Participation of Children

Patients must be at least 18 years of age to participate.

16.3 Institutional Review

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed and approved by a properly constituted IRB. Any amendments to the protocol must be reviewed and approved by the IRB.

16.4 Data and Safety Monitoring Plan

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan.

The study team will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee (DSMC) on a quarterly basis for independent review.

16.5 ADVERSE EVENTS

16.5.1 Experimental Therapy

For the most recent safety update, please refer to the current Study Agent Prescribing Information.

16.5.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment through 30 days after the last dose of study treatment. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

16.5.3 Definitions

1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

- Symptoms of the original or targeted disease are not to be considered adverse events for this study. The following symptoms are indicative of underlying disease (breast cancer) or its treatment and will not be reported as adverse events (unless the event is considered serious):

- AI-associated arthralgias (will be collected on patient-reported questionnaires)

- Symptoms and signs due to prior treatments (chemotherapy, radiation therapy, surgery)

- Adverse events related to disease progression

- Hospitalization or treatment related to breast surgery or breast reconstruction procedures

- Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.

1. Serious Adverse Event

An adverse event is considered “serious” if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered ‘life-threatening’ if, in the view of either the investigator, its occurrence places the patient or subject at

immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

2. Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

3. Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

16.5.4 Adverse Event Characteristics

1. CTCAE Term

AE description and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site. (http://ctep.cancer.gov)

2. Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

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.

16.5.5 Serious Adverse Event Reporting Guidelines

1. The Principal Investigator must be notified within 2 business days of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment.
2. The investigator must report all events meeting the criteria and definition of a serious adverse event that are unexpected and possibly related (definite, probable or possible) to study treatment administration as per the local IRB reporting requirements.
3. All Serious Adverse Events that are unexpected and possibly related (definite, probable or possible) to study treatment administration will be reported to the IRB using the CTSU Serious Adverse Event form.

- The Clinical Trial Support Unit Staff will coordinate with the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) office for the reporting of any and all IND safety reports to the FDA as per the requirements outlined in 21 CFR 312.32. This includes reporting of all Serious Adverse Events (SAEs) that are both unexpected and related to the drug as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. If the unexpected and related SAE is

either fatal or life-threatening, then the SAE must be reported as soon as possible but in no case later than 7 calendars days after the sponsor's initial receipt of the information.
A summary of all non-expedited safety reports will be submitted in the annual report.

16.5.6 Routine Reporting

All other adverse events will be reported per current institutional guidelines.

16.5.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB according to the local IRB policies.

16.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC and IRB as applicable. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events. Since only postmenopausal women are eligible to enroll on this trial, it is unlikely that participants will become pregnant during study participation.

16.7 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

16.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the approved protocol version. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events. All deviations will be reported to the IRB per current institutional guidelines.

16.9 Food and Drug Administration (FDA)

Prior to study commencement, an Investigator Initiated New Drug (IND) application, if needed, will be submitted to the FDA for review and approval.

16.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Oncology Clinical Trials Support Unit (O-CTSU).

17 REFERENCES

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