NCT01761877

Unique Protocol ID: 1RO1 CA1615301A1

Secondary IDs: 12-0080-04, 676847

Study Title: NSAID Effects on Clinical and Imaging Breast Biomarkers

Document Title: Study Protocol

Version: 01/27/2021

Status: In Data Analysis and Follow-Up

Current Approval End: 8/24/2022

1 TITLE: NSAID and Aromatase Inhibitor Effects on Clinical and Imaging Breast Biomarkers

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4 PROTOCOL OVERVIEW

The regular use of non-steroidal anti-inflammatory agents (NSAIDs) has been associated with a reduced risk and recurrence of breast cancers that are estrogen receptor positive (ER+) (Holmes et al. 2010; Fraser et al. 2014; Zhao et al. 2009; Takkouche et al. 2008; Bowers et al. 2014). NSAIDs have been postulated to synergize with aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMS) such as tamoxifen to inhibit ER+ tumorigenesis and progression (Subbaramaiah et al. 2012). This hypothesis is consistent with evidence that NSAIDs act in the mammary gland by inhibiting cyclooxygenase 2 production of prostaglandin E2 (PGE2), which has been shown to activate aromatase in breast tissue; a link between inflammation and ER+ disease that appears to be particularly important in overweight and obese postmenopausal women(Morris et al. 2011). An alternative explanation for an apparent benefit of NSAIDs use in women on AIs and lower risk of recurrence may be related to improved patient adherence to AIs as NSAIDs may act in reducing the pain and arthralgia associated with the long-term use of AIs. Adherence to AI therapy is an independent predictor of recurrence of breast cancer (8, 9). With reported failure to adhere to AI therapy at one year as high as 30% in some women due to AI-associated arthralgia and other AI side-effects (D. Hershman et al. 2010; D. L. Hershman et al. 2010), the regular use of NSAIDs may be beneficial simply by improving adherence.

In this protocol, we are seeking to determine if NSAIDs modulate breast tissue risk factors for breast cancer and to determine if NSAIDs are beneficial for the management of AI-associated arthralgia. This will be the first study to directly assess these issues in a clinical trial.

Two separate, but complementary, study objectives are to be pursued.

4.1 Objective 1.

To test the hypothesis that NSAIDs modulate breast cancer risk and AI-associated pain, we will conduct a 12-month open-label, single-arm phase II trial of sulindac, a non-selective NSAID, in postmenopausal women with early stage, ER+ breast cancer who are receiving aromatase inhibitor therapy (AI) (e.g., anastrozole, letrozole, exemestane, etc…). The specific aims are:

a) To assess change in breast density (a surrogate biomarker of breast cancer risk) using a novel, non-radiative, non-contrast MRI method for short-interval repeated use and

b) To assess change in AI-associated pain.

Sulindac has been selected among the NSAIDs for this study because it is a potent lipophilic NSAID with anti-tumor activity that is bioavailable in breast tissue after oral dosing (Thompson et al.) and because it is the recommended NSAID for treatment of arthralgia in older women (Anthony G. Johnson 1998). *See section 9.2 for detailed information on drug selection rationale.*

For objective 1, a total target population of 100 breast cancer patients, stable on AI therapy (minimum of 3 months) for the treatment of their breast cancer will receive sulindac 150 mg bid for 12 months. Breast imaging will be conducted at baseline 1 (after a 1-month washout for non-steroidal anti-inflammatory agents (NSAIDS), baseline 2 (after 3-month observation period, right before start of sulindac), 6 and 12 months on sulindac. A one-month washout period for NSAIDs, followed by a 3-

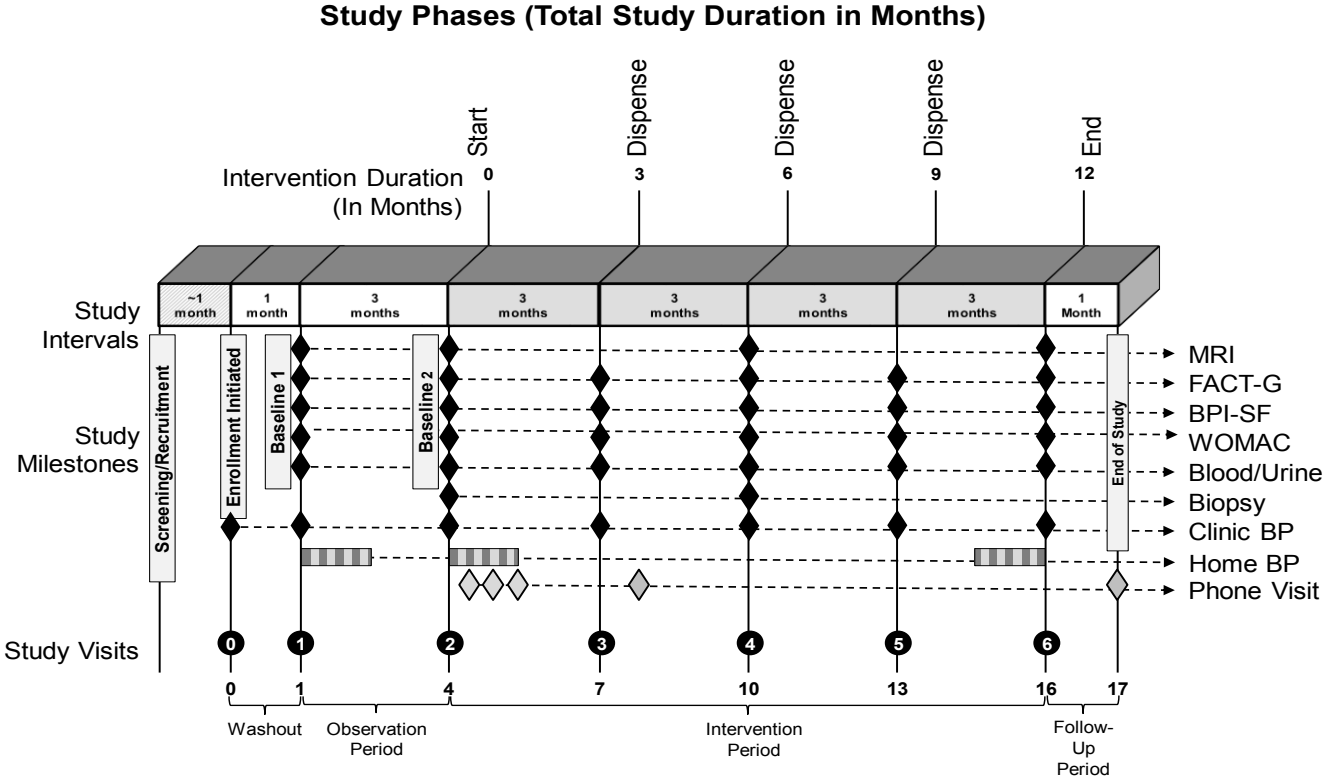

Figure 1. **Study schema and primary measurements to be conducted during the sulindac intervention study.** All participants will have an initial one-month washout period prior to a 3-month observation period during which they will discontinue NSAID use and be monitored for adherence to the trial and undergo baseline MR imaging at two time points. For the intervention period, participants will undergo MR imaging after initiating sulindac at 6 and 12 months. Participants will complete the participant reported outcome (PRO) questionnaires, return drug logs, undergo standard laboratory testing, and receive additional study drug at these visits. Blood and urine as well as clinical measures of blood pressure will be obtained at baselines, and at 3-, 6-, 9- and 12-month on sulindac to bank for analysis of metabolite levels and prostanoids. In those who consent, breast biopsies will be obtained at baseline 2 and after 6-month on sulindac for exploratory analyses of proliferation, apoptotic, cellular and whole genome expression changes in response to agent.

month observation no NSAID period, will be used to identify participant likely not to adhere to the study

regimen and to determine the extent of variability in BD over time. ***The study schema for the sulindac intervention is shown in Figure 1.***

4.2 Objective 2

In addition to the intervention arm, a total target population of 75 breast cancer patients, matched on characteristics to the sulindac intervention study, are being recruited to an observation arm (hereafter referred to as 'observation' group) for the primary purpose of determining change in BD while on AI for 12 months as determined by our novel MRI-based imaging approach to generate a non-radiative, non-contrast of a fat to water map of the breast using FWMRI.

In healthy postmenopausal women, the mean age-related change in BD by mammography at 2-yrs has been reported from randomized trials to be -1.3% (± 2.9%). Studies of women on AIs have shown that AI use for 12 months does not *significantly* decrease BD beyond that of the age-related change in the contralateral breast of breast cancer patients when compared to a placebo control (see Table 1).

Table 1. Effect of Aromatase Inhibitors on Breast Density in Randomized Studies

Study	Agent	Mean change in BD	P value	Summary
Vachon et al. 2007 (Vachon et al. 2007)	Letrozole Placebo	−2.7% −3.0%	p=0.96	No statistically significant therapy-by-subgroup interactions (for BMI and age at entry)
Cigler et al. 2010 (Cigler et al. 2010)	Letrozole Placebo	−0.01% (95% CI −3.89, 3.87) −1.32% (95% CI −8.86, 6.22)	p=0.69	No statistically significant therapy-by-subgroup interactions (for BMI and age at entry)
Cigler et al. 2011 (Cigler et al. 2011)	Exemestane	−0.17 (95% CI −4.34 , 4.00)	P=0.37	No statistically significant therapy-by-subgroup interactions (for BMI and age at entry)

Placebo	−2.93 (95% CI 2.85)		−8.70,

These data support our intent to assess change in BD with sulindac intervention using each woman as her own control taking into consideration a 3% decrease due simply to age (see Study Design Sulindac Intervention Study). To insure that this is indeed the case when using the FWMRI methodology, an observation group, matched on characteristics to women in the sulindac intervention group, has been added to specifically measure 12 months change in BD by FWMRI. Findings from the observation group will be considered in the interpretation of findings from the sulindac intervention arm *but the observation arm is not serving as a control for the sulindac intervention.* The expectation is that we will observe on average a 2-3% average decrease in BD by FWMRI at 12 months in the observation group.

After initiating the sulindac intervention under the assumption of no more than a 3% annual decrease in BD, we were approached by the NCI to conduct a separate study in a population similar to that of the sulindac group to specifically determine the magnitude of change in BD by FWMRI in women on AIs at 6 and 12 months considering time on AI. This is both to provide an estimate for interpreting our intervention study using the new methodology and to provide information on AI effect on BD at 6 months using a more sensitive method of measurement.

Thus, the observation-only arm is being recruited to determine the effects of AI alone as well as time on AIs on: 1) BD as measured by fat/water (FW) and diffusion-weighted (DW) magnetic resonance imaging (MRI) as a secondary, exploratory analysis. DWMRI is obtained at the same time as the FWMRI and does not add additional participant burden. The schema for the observation study is shown in Figure 2.

In addition to the primary objective, we will assess the association between AI use and patient reported outcomes of pain in the observation group to provide additional information on the use of NSAIDs in patients on AIs generally. Participants in the observation group will be matched on duration of AI use and age (+/- 5 years) with a minimum of 12 months of projected AI therapy to the participants in the sulindac intervention arm. The target population for the Stony Brook site will be 30 women over a period of 24 months.

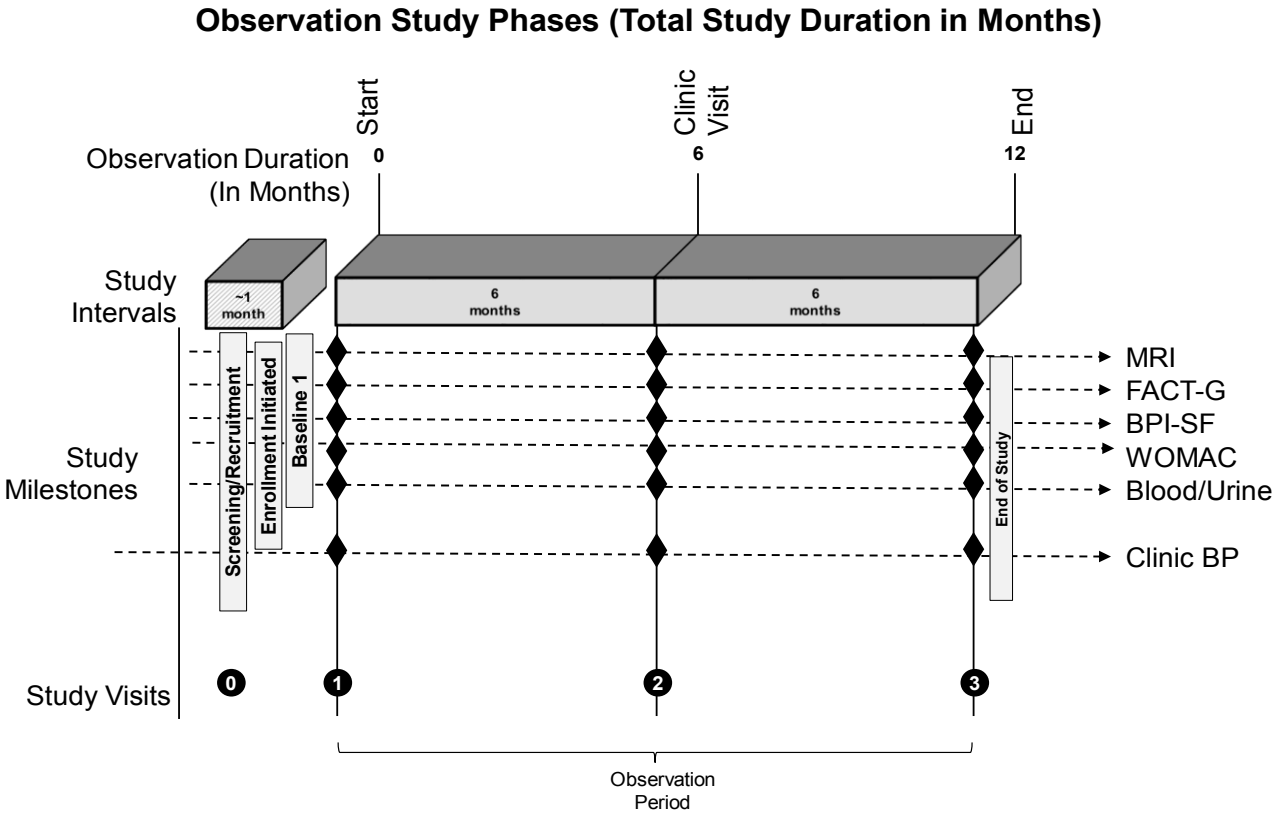

Figure 2. Study schema and primary measurements to be conducted during the observation study. All participants will have an initial baseline MR imaging and again at 6 and 12 months. Participants will complete the participant reported outcome (PRO) questionnaires. Blood and urine as well as clinical measures of blood pressure will be obtained at baselines and at, 6-, and 12-month clinic visits to bank for analysis of metabolite levels and prostanoids.

4.3 Study Sites

The study will be conducted at two study sites and the data will be pooled for final analyses. The two study sites are the University of Arizona Cancer Center (UACC) in Tucson Arizona and Stony Brook Cancer Center (SBCC) in Stony Brook New York. This study is currently open and enrolling at both institutions. The general data and safety monitoring of all participants on study will be ensured by the respective sites, while an *ad hoc* data safety monitoring committee with specific competences on cardiovascular safety will be assembled at the Arizona site to review both sites' participants. The local site at SBCC is responsible for oversight of all local aspects of the study implementation as described in detail below as well as for conducting local review of data and safety for the Stony Brook participants. All data will be shared between the two study sites and biospecimens will be banked locally and distributed for biomarker analyses. Whole blood, plasma, serum and breast biopsy samples will be analyzed in the laboratory of Patricia Thompson, while urine samples will be analyzed in the laboratories of the UACC. After January 2021 and relocation of the Thompson laboratory to Cedars

Sinai Medical Center Los Angeles, the evaluation of change in gene expression related to apoptotic, proliferation, and alternative biomarkers will be conducted in the laboratory Thompson laboratory at Cedars Sinai Hospital, Los Angeles CA. A Material Transfer Agreement will be in place, covering shipping and receiving of study samples. The three sites (Stony Brook University, UACC, and Cedars Sinai) will therefore exchange coded (de-identified) samples. Lab personnel and researchers will not have access to the sample identifiers at any time and will therefore not be able to match the samples with the individual participants.

4.4 Data and sample sharing.

All data will be pooled from the two study sites for the primary endpoint analysis with each site considered a covariate in the final model as a potential confounding factor. All consent documents indicate that study data and information collected as part of participation in the study will be shared between the two study sites with mechanisms in place to protect the privacy of information of the individual participants as described in sections 27.4 and 27.5. Additionally, as part of respective subawards, urine samples will be analyzed at the UACC, while other samples (blood and breast tissue) will be analyzed in the laboratory of Dr. Patricia Thompson at Cedars Sinai Medical Center. When convenient, both sites will gather and ship the samples accordingly. A Material Transfer Agreement will be in place, covering shipping and receiving of study samples. The original consent forms specify that the study is conducted at two sites (SB and UACC) and that coded data and samples will be exchanged between the sites only for the purpose of this study. All accrual and subject participation are concluded, and the study is in long term follow up. Subjects will not be reconsented for the purposes of completing the biomarker studies that now includes the Thompson laboratory at Cedars Sinai Medical Center. The consent form also specifies banking of sample for use in future studies.

5 STUDY RATIONALE AND BACKGROUND

5.1 Women still die from ER$^+$ breast cancers.

Each year, more than 192,000 incident and 40,000 breast cancer deaths are recorded among women in the U.S. (Jemal et al. 2010). ER+, or luminal type, tumors comprise the majority of breast cancers and account for the majority of breast cancer-related morbidity and death. After an initial period of early metastasis (often within the first 2 years after diagnosis), ER+ patients carry continued risk for late disease relapse that persists years after diagnosis (Wapnir et al. 2006). Among studies with long-term follow-up, there is clear evidence that deaths from ER+ cancers continue to surpass rates in the less common but more aggressive ER- tumors.(Čufer 2007). AIs and selective ER modulators (i.e., tamoxifen) are effective in delaying or possibly preventing the progression of ER+ disease in 50-70%

of women diagnosed with ER+ tumors(Howell 2008). AIs demonstrate modest, but consistently superior, efficacy for reducing risk of breast cancer events in postmenopausal women and are now the primary modality for adjuvant hormonal therapy in these patients (Burstein et al. 2010). In spite of significant success with hormone-targeted therapies and improvements in selective use of chemotherapy, ER+ disease remains the major contributor to breast cancer deaths. Recent increased attention to ER- tumors has somewhat undermined further progress for the management of ER+ cancers.

5.2 Mammographic BD as an intermediate risk biomarker.

According to a recent review (Sedor et al. 1984), imaging biomarkers, such as mammographic density, offer potentially noninvasive, novel approaches to assess drug effects on breast parenchyma, but they require additional investigation to establish reliable, automated, and quantitative measurement techniques. Mammographic density as visualized on radiographic images is one of the strongest predictors of individual breast cancer risk (A. G. Johnson 1998). While we do not yet understand the histological or biological determinants of BD, it is clear that image features of the breast are informative on risk and may be useful as indicators of drug effects on the breast.

Considerable knowledge gaps remain with respect to imaging-based BD biomarkers and use as measures in assessing the cancer-risk lowering properties of promising prevention agents. The most important of these gaps is a lack of information on what it means, with respect to cancer outcomes, if a drug does or does not mediate a change on parenchymal features of the breast as captured by imaging techniques. This is further complicated by differential responsiveness of density to different hormone modulating drugs. Hormone deprivation with natural menopause is associated with a decrease in mammographic density (Dihlmann et al. 2001), whereas use of postmenopausal HT is associated with maintenance of and possible increases in BD, which is most strongly attributed to formulations containing progesterone (Williams et al. 2001; Arun and Goss 2004). TAM is associated with a marked reduction in BD within the first 18 months of use (Herendeen and Lindley 2003) with the recent published findings from the IBIS-I trial (Jack Cuzick et al.) providing the first evidence showing that change in BD is a strong predictive biomarker of TAM benefit for lowering risk of cancer. In contrast, use of AIs, which directly target estrogen synthesis and show improved overall efficacy for breast cancer relapse risk reduction, has not been associated with reduction in BD by mammography measures at 6, 12, or 24 months of use (Muir and Logan 1999). Part of the discrepancy between these different hormonal exposures is likely explained by complex effects of multiple factors on tissue determinants of BD and differences in hormonal manipulation on these factors. In addition, differences

in use patterns between groups also challenge comparability of findings between studies. For example, TAM has been used in both pre- and postmenopausal women whereas AIs are exclusively used in postmenopausal women. Younger women have higher starting BD than postmenopausal women; therefore, change is more dramatic and easier to capture using the relatively insensitive application of mammographic measurements. Poor sensitivity and low reproducibility of mammography-derived density measures limit use and interpretation of findings in the postmenopausal setting, when decrease is likely to be more modest and more difficult to measure.

5.3 NSAIDs and prevention of breast cancer recurrence.

Observational studies of NSAID use and risk of breast cancer, including results from the prospective Women's Health Initiative Observational Study(Harris et al. 2003), provide fairly consistently support for a 10-20% lower risk of breast cancer among regular NSAID users (Zhao et al. 2009) with stronger protective effects for ER positive than ER negative disease(Terry et al. 2004). Less well studied are the effects of NSAID use on breast cancer recurrence and whether or not NSAIDs may act synergistically with current adjuvant therapies to further reduce risk of breast cancer related death. Kwan *et al*., reported a significant reduction in breast cancer recurrences among patients who reported use of ibuprofen at least 3 days per week (RR, 0.56; 95% CI, 0.32–0.98), with combination of ibuprofen and other non-aspirin NSAIDs, including sulindac, showing similar reductions in risk of disease recurrence (RR, 0.56; 95% CI, 0.33–0.95). No reduction in risk was observed with aspirin use in this study. More recently, Holmes *et al*., reported a significant reduction in death from breast cancer among cases in the Nurses' Health Study who reported regular aspirin use. The adjusted relative risk estimates for 1, 2-5, and 6-7 days of aspirin use per week, compared with no use, were 0.91 (95% CI, 0.62–1.33), 0.40 (95% CI, 0.24–0.65), and 0.57 (95% CI, 0.39–0.82), respectively.(Holmes et al. 2010) In both studies, the NSAID result did not differ by ER status.

5.4 Extensive data from cell culture experiments, animal model systems, and human intervention trials support the anti-tumor potential of NSAIDs (Kelloff et al. 1996).

Although the mechanisms of action remain incompletely defined, at least part of the anti-cancer activity of NSAIDs is attributed to inhibition of cyclooxygenase 2 (COX2). Preclinical studies have shown that COX2 expression is upregulated in human mammary tissues and breast tumors, and it is associated with the transition from the normal to malignant phenotype in cell culture systems (Crawford et al. 2004; Berman et al. 2005; Singh-Ranger et al. 2008). In the disease setting, COX2 overexpression has been associated with more aggressive disease and increased risk of disease progression (Boland et al. 2004). Suppression of COX2 in mammary tumor cell lines and xenograft studies has been associated

with decreased tumor growth, increased apoptosis, and decreased angiogenesis (reviewed in (Howe 2007)), with effects on a number of important tumor signaling pathways, including inactivation of the Akt signaling pathway. Barnes et al., (Barnes et al. 2007) found that COX2 inhibition with the selective COX2 inhibitor celecoxib in xenograft models of the ER positive MCF7/HER2-18 and ER negative MDAMB231 cell lines resulted in significant inhibition of cell growth, increase in apoptosis, and inhibition of angiogenesis, with activity partially mediated via Akt pathway inactivation. Importantly, tumor growth inhibition in these xenograft studies was not related to change in proliferation markers (i.e., Ki67) but induction of apoptosis. These results may partially explain the recently reported lack of effect of celecoxib on Ki67 levels in ER positive tumors in women randomized to two weeks of AI alone or AI + celecoxib prior to surgical removal of their cancers.(Martin et al. 2010)

5.5 COX2 inhibitors and locally advanced or metastatic breast cancer

COX 2 inhibitors have been investigated in combination with AIs unsuccessfully in a handful of small phase II/III trials in patients with locally advanced (L. W.-C. Chow et al. 2008) and metastatic breast cancer (Falandry et al. 2009).

Studies conducted to date have been small and powered for large main effects on tumor growth. Results from the celecoxib anti-aromatase neoadjuvant (CAAN) trial in 82 patients for locally advanced breast cancer (L. W.-C. Chow et al. 2008) found no statistically significant differences in tumor response to AI as exemestane with or without celecoxib 400 mg twice daily for 3 months. Overall response rates were similar between the groups (~55-60%). Promising but nonsignificant trends for higher complete response rates among the celecoxib arm are noted by the study investigators, though larger numbers would be needed to assess the true clinical benefit. Extrapolation of the failure of COX2 inhibitors from studies from the advanced disease setting to the prevention of disease recurrence is challenging. Collectively, epidemiologic and preclinical cell and animal evidence along with the clinical trial data continue to favor efforts to address the action of NSAIDs in the breast (as proposed here) and ultimately, the potential efficacy in prevention of relapse. The study of NSAIDs in the setting of breast cancer prevention remains significant especially when one considers the widespread use of these agents and the general high tolerability.

5.6 AIs, Side Effects and Adherence

One of the major challenges for the management of ER^+ disease is the unacceptably high rate of early discontinuation of and non-adherence to adjuvant hormonal therapy (HT). In a recent study by Hershman et al., full adherence, defined as full duration and optimal schedule, was observed for only 49% of patients prescribed adjuvant hormonal therapy for breast cancer.(D. L. Hershman et al. 2010)

These reported discontinuation rates and the more recent findings by the same investigators (D. Hershman et al. 2010) of higher mortality rates in breast cancer cases enrolled in Kaiser Permanente of Northern California who discontinue (HR 1.26, 95% CI 1.09-1.46) or are non-adherent to their hormone therapies (1.49, 95% CI 1.23-1.81) is concerning and consistent with clinical trial evidence from the tamoxifen studies showing higher recurrence rates and worse outcomes with < 5 years or suboptimal HT use.(McCowan et al. 2008; Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. Swedish Breast Cancer Cooperative Group 1996; Yood et al. 2008) Failure to adhere with the recommended schedule is thought to principally arise as a consequence of intolerance to agent-related side. Interestingly, the designation of this phenomenon as 'non-persistence' (Burstein et al. 2010) is somewhat pejorative and suggests a failure on the patients' part to be strong enough to 'persist' in the daily use of these agents. Side effects of AIs include severe menopausal symptoms, sexual dysfunction, bone loss, and a somewhat drug unique function-limiting chronic joint stiffness and pain.(Conte and Frassoldati 2007; Din et al. 2010). The need to maximize efficacy and improve tolerance are evident and should be patient-oriented (i.e., including the use of currently approved medications tailored to the individual needs of the patient). Approaches to enhance both adherence and response rates for these agents are identified as important and under-addressed research and clinical gaps.(D. Hershman et al. 2010)

5.7 NSAIDs and management of joint stiffness and pain with AI use

Musculoskeletal complaints are among the most commonly reported and debilitating side effects of adjuvant hormonal therapy (SERMs and, particularly, AIs)(Thorne 2007). Among women with chronic arthralgia syndromes at initiation of AI therapy, half report symptom exacerbation. Joint related symptoms manifest early after initiation of AI therapy with peak incidence reported at 6 months.(Howell et al. 2005) While the exact mechanism is unclear, joint and muscle pain in women increases with age, with the maximum increase observed between 50 and 59 years old(Wolfe et al. 1995; Croft et al. 1993). This pattern is consistent with age-related declines in estrogen as a potential causal factor. The incidence of rheumatoid arthritis is also highest in the decade following menopause and has been linked to estrogen deprivation. Increased inflammation mediated by bradykinin and the pro-inflammatory prostaglandins is mechanistically linked to symptoms(Thorne 2007). Thus, NSAIDs are recommended for symptom management and commonly used among patients given access to over-the-counter formulations. This raises the important possibility that findings from observational studies suggesting lower breast cancer recurrence risk among NSAID users may arise as a consequence of improved tolerance to their hormonal therapy and better adherence instead of direct anti-tumor effects of the NSAIDs themselves. The effect of NSAID use on hormonal therapy adherence and pain scores has

not, to our knowledge, been formally investigated in a randomized study. Secondary analysis of patients in the CAAN trial, discussed above, showed that participants who completed the Functional Assessment of Cancer Therapy Core questionnaire (FACT-G) including the breast cancer subscale scores suggested that the participants randomized to exemestane plus celecoxib experienced positive changes in the FACT-B and FACT-G scores following 4-weeks of therapy(L. W. Chow et al. 2008). Improved measures of quality of life were significant in the coxib group when compared to negative changes in the exemestane only group and a third group that received letrozole only therapy. These data support the general thinking that the addition of an NSAID to AI might improve quality of life though effects on pain scores were not investigated as a possible explanation in the CAAN study.

5.8 Overall significance of the study

Here we seek to obtain evidence from human studies for two clinically significant questions about the role of NSAIDs in women receiving AIs for their breast cancer. First, we will investigate the effect of AIs on BD, a putative biomarker for future chemoprevention studies and an NSAID on breast tissue as an indicator of drug action in the breast using novel imaging approaches discussed below. Second, we will examine pathways involved in BD and patient reported outcomes (PRO) of bone and joint pains, a frequent cause of patient non-adherence to AI therapy. Also, to ask if prescribed NSAID use at AI initiation reduces pain. Findings from this study will be used in decision making about a larger trial to test the question of whether NSAIDs increase the efficacy of AIs for reducing cancer recurrence by modulating risk features of the breast (*i.e.*, BD, ADC, proliferation and apoptosis biomarkers), by increasing adherence as a consequence of reducing joint and muscle pain, or both.

6 OBSERVATION STUDY GROUP

6.1 Rationale for Observation Arm

Previous randomized controlled studies have shown that AIs do not decrease BD after 12 months of use in the contralateral breast of breast cancer patients compared to a placebo (see Table 1 above). These studies do, however show the presence of a mean decline in BD related to age of 1-3%.

In healthy, postmenopausal women, the mean age-related change in BD by mammography at 2-yrs has been reported from randomized trials to be -1.3% (± 2.9%). These studies were conducted using computer assisted algorithms to estimate BD from mammograms. However, other studies using visual estimation of BD on mammography have reported that as high as 30% of women show greater that a 1-standard deviation in variance with repeated measurement. This high variability is attributable to the visual estimation of BD from mammogram and highlights the need to use methods with lower between-measure variances. In our own analysis of BD estimation using FWMRI, between-measure variability

is on the order of 1-2% with BD estimates highly correlated with those of CAD-derived BD estimates from mammograms (Abstract P6-01-18, Thomson, Thompson and Stopeck, SABCS Dec 2014). However, there are no studies that have utilized FWMRI to evaluate change in BD over 12 months for women on AIs. And while the expected change is likely to be comparable to that previously reported using CAD measures of mammograms (-1 to -3%), we will determine change in BD for women on AIs at 6 and 12 months by FWMRI and control for time on AI. Other variables such as starting BD, age and BMI will be considered as important covariates. The primary purpose of this study is to establish the magnitude of BD change as assessed by FWMRI and will be used in interpreting findings of the significance of any change in the sulindac intervention arm component of our study and for planning future interventions targeting BD change in patients on AIs.

6.2 Hypothesis and Specific Aims

We hypothesize that AI therapy for 12 months will not change BD on average more than 3%.

6.2.1 Primary Aim

Compare change in BD as measured by MRI-acquired fat-to-water ratio (FWR-MRI) in the contralateral, unaffected breast in women receiving AI therapy as part of their standard of care therapy.

6.2.2 Secondary Aims

a) To monitor changes in pain scores using the Brief Pain Inventory-Short form (BPI-SF) during 12 months of AI therapy.
b) To quantify changes in the apparent diffusion coefficient (ADC) of water measured by diffusion-weighted MRI (DW-MRI) over 12 months in the contralateral, unaffected breast in women receiving AI therapy as part of their standard of care therapy or prevention of breast cancer.

7 SULINDAC INTERVENTION STUDY

7.1 Rationale for Sulindac Intervention Study

Here, we propose that one approach to advance the indication of NSAID use for 2nd prevention is to combine their use in ER+ patients on AIs. This combination builds on the evidence that favors the anti-tumor action and the efficacy of NSAIDs for the management of muscle/skeletal complaints as an approach to enhance the benefit-to-risk ratio associated with chronic daily NSAID use. Here, we propose novel magnetic resonance imaging (MRI) approaches as a non-invasive and sensitive effect measure of sulindac, a potent, non-selective NSAID, on 'high-risk' breast tissue. In addition and importantly, because sulindac as a prodrug (Clinoril™), has been shown previously in 2 of 3 studies to spare renal synthesis of the vasodilatory prostaglandins in patients with normal renal function (Sedor

et al. 1984; Cibattoni et al. 1987; Roberts et al. 1985; A. G. Johnson 1998), we will conduct a comprehensive analysis of sulindac effect on mean arterial pressure in the chronic daily use setting to better inform on hypertensive risk related to daily sulindac use in women receiving AIs.

7.2 Specific Aims and Study Hypotheses for the Sulindac Intervention Arm

To assess the benefit of sulindac in ER+ patient receiving AIs, 100 breast cancer patients, stable on AI therapy for ER+ tumors will receive 12 months of AI + sulindac at 150 mg bid. Study participants will serve as their own controls. To control for the variability in the endpoints, we propose an initial NSAID washout period of 1 month followed by a 3 months' observation (no sulindac) period, at the end of which, we will measure change in BD by MRI between baseline 1 (post NSAID washout) and baseline 2 (no NSAID observation period of 3 months). The change in BD from the baseline MRI to the first follow-up MRI at 3 months on study will provide the baseline BD measurement for our subsequent BD analyses (**the primary endpoint**). All patients will then receive 12 months of 150 mg bid sulindac and measurements as described including MR imaging after 6 and 12 months on sulindac.

7.3 Primary specific aims

a. Compare change in BD as measured by MRI-acquired fat-to-water ratio (FWR-MRI) in the *contralateral, unaffected* breast *pre- and post-sulindac* (primary trial endpoint).
   Hypothesis: Women treated with AI + sulindac 150 mg bid will show a greater decrease in BD over 12 months when compared to their baseline change measurement.
b. Compare pain scores using the Brief Pain Inventory-Short form (BPI-SF) *pre and post sulindac*.
   Hypothesis: Women treated with AI + sulindac 150 mg bid will experience reduced pain scores over 12 months when compared to their baseline change measurement.
c. Compare mean arterial blood pressure within individuals.
   Hypothesis: Administration of 150 mg bid sulindac for 12 months to women on AIs will not lead to a clinically significant (Grade 2 or higher) increase in blood pressure when compared to their baseline change measurement.

7.4 Secondary Aims

a. Compare the apparent diffusion coefficient (ADC) of water measured by diffusion-weighted MRI (DW-MRI) in the *contralateral, unaffected* breast pre- and post-sulindac (primary trial endpoint).
   Hypothesis: Women treated with AI + sulindac 150 mg bid will show a significant decrease in ADC over 12 months when compared to their baseline change measurement.

7.5 Exploratory and Discovery Aims

a. Correlate baseline tissue characteristics (*e.g.,* cellularity) and tissue biomarkers (*e.g.*, Ki67) to FWR-MRI and DW-MRI to identify tissue correlates of MR image features at baseline.

b. Assess the association between 6-month FWR-MRI, DW-MRI, and pain scores with 12-month measures.

c. To correlate pain scores with metabolomic measurements to determine the optimal pathways for targeting therapy designed to improve pain outcomes.

d. Explore change in mammary gland tissue architecture, cellularity and proliferation/apoptotic index in women consenting to serial biopsy pre and post-sulindac.

e. Assess the effect of sulindac on measures of joint stiffness and pain obtained by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function, pain, and stiffness scores.

f. Collect and bank urine for biomarker studies of NSAID effect on renal prostaglandin synthesis to relate to mean arterial blood pressure.

8 PARTICIPANT POPULATION

Participants will be postmenopausal women with early stage (stage 0-III) hormone receptor positive breast cancer receiving aromatase inhibitor therapy with anastrozole as part of their standard breast cancer care. There is no clinical evidence to favor selection of a particular aromatase inhibitor (anastrozole, letrozole, or exemestane). Approximately 175 participants will be recruited (100 for AI Sulindac arm and 75 for AI observation only arm). As all participants will have been adherent to AI therapy for a minimum of 3 months, we expect for AI Sulindac arm that approximately 90% will continue past the 1-month washout and 3-month observation period to intervention phase for AI Sulindac arm. We estimate an additional 10% drop-out rate prior to study conclusion (12 months imaging and patient reported outcome endpoints) for a total of 80 (Sulindac intervention) and 60 (observation only) fully evaluable participants. We have focused on women with contralateral at risk breast tissue of a BIRADs density score at least 2 ($\geq$ 25% BD) or scattered fibroglandular densities at least heterogenous or greater (i.e. heterogenous or mostly dense) to ensure inclusion of women with a modifiable biomarker for our primary endpoint. From our preliminary data, approximately 75% of women prescribed AIs in our clinics would meet this eligibility requirement.

9 INFORMATION ON STUDY AGENT FOR SULINDAC INTERVENTION

9.1 Sulindac

The primary target of NSAID action is either one or both of two isoenzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), involved in prostaglandin synthesis(Anderson et al. 2003). The spectrum of action of each of the individual NSAIDs and the degree that the drugs differ or overlap in target tissues remains poorly defined(Dihlmann et al. 2001). Aspirin for example has been shown to modulate not only COX-1and COX-2 expression, but also modulates members of the □-catenin, EGFR and ras pathways; pathways strongly implicated in colon tumorigenesis. Similarly, COX-2 specific inhibitors show inhibitory action on the translocation of β-catenin to the nucleus (Williams et al. 2001). The demonstration that the COX-2 inhibitors, with lower gut related toxicity, show similar action in prevention models has driven the development of a number of highly promising COX-2 inhibition based cancer prevention trials (Arun and Goss 2004; Anderson et al. 2003). Though a strong rationale based on safety exists for the prioritization of these agents, a large body of evidence has now been accumulated that suggests that other, less target specific agents such as aspirin or sulindac may hold greater chemopreventive efficacy and perhaps anti-tumor activity due to a broader spectrum of action attributed to active metabolites (e.g., sulindac sulfone and sulindac sulfide)(Herendeen and Lindley 2003; Muir and Logan 1999) . Animal, cell culture and epidemiologic data support the concept that the observed preventive action of certain NSAID agents may be in part due to cyclooxygenase-independent activities and that certain NSAIDs, particularly sulindac, have higher potential efficacy than target specific agents such as the COX-2 specific inhibitors (Muir and Logan 1999; Karamouzis and Papavassiliou 2004).

Specifically, the anti-proliferative (cytostatic) and pro-apoptotic (cytotoxic) actions of sulindac sulfide have been attributed to p53-dependent and -independent induction of the cyclin-dependent kinase inhibitor p21waf1/cip1 with the potent pro-apoptotic activity induced by the sulfone metabolite via a COX2-independent induction of growth and differentiating factor 15 (GDF15); a member of the TGF-beta superfamily. Indeed, the potent chemopreventive activity of sulindac in models of colorectal carcinogenesis has been attributed to sulindacs ability to induce GDF15 (2). Of the NSAIDs as a class of drugs, sulindac is among the more potent inducers of GDF15. Other common NSAIDs with shorter half-lives and lower biodistribution to fatty tissues such as ibuprofen or naproxen do no induce GDF15. Dr. Thompson in collaboration with Dr. Stopeck previously completed a randomized, open-label phase I biomarker study of sulindac to assess the effects of sulindac and its metabolites on a stable derivative of COX2-derived prostaglandins (13, 14-dihydro-15-keto prostaglandin A2 [PGEM] and the induction of GDF-15 in nipple aspirate fluid (NAF) as a surrogate of tissue bioavailability. (1). Thirty women were randomized to sulindac 150 mg qd versus sulindac 150 mg bid for a short duration of 6 weeks. Sulindac was well-tolerated in the study. Sulindac intervention was associated, in a dose-independent manner,

with a non-statistically significant decrease in NAF PGEM (p=0.10). In this small study, GDF-15 showed was increased in NAF levels post intervention in the higher dose group of sulindac 150 mg bid (p=0.07). These data suggested that COX2 inhibition in the breast may be achieved at 150 mg sulindac qd but that a higher dose may be needed to fully realize COX-independent benefits, such as induction of anti-apoptotic factors (e.g., GDF-15). It is partly for this reason that we chose sulindac and the 150mg BID dose for our trial.

9.2 Rationale for Drug Selection

The spectrum of action of each of the individual NSAIDs and the degree that the drugs differ or overlap in target tissues remains poorly defined. Sulindac and its sulfide and sulfone metabolites have been widely investigated for their COX2 dependent and independent activity as potential anti-cancer agents for multiple malignancies. Selection of sulindac over the other NSAIDs for this and our phase Ib trial (1) was based on three sulindac-specific characteristics: the lipophilic nature of the metabolites and biodistribution to breast tissue; its potent COX2 independent anti-tumor activity (not present in other NSAIDs); and the potential for lower renal toxicity and cardiovascular toxicity associated with sulindac compared to other NSAIDs.

NSAIDs as a class of drugs are associated with elevated risk of gastrointestinal (GI) toxicity among regular users. Use of proton pump inhibitors for GI symptoms has dramatically improved the use of the more potent NSAIDs such as sulindac for patients with chronic pain associated with inflammation (Hooper et al. 2004; Brown et al. 2006). In the past decade, with the completion of the coxib trials including our own (Thompson et al., in preparation for JAMA), it is now clear that NSAIDs that specifically target the COX2 enzyme or the coxibs more than double the risk of cardiovascular disease (CVD), particularly in individuals with pre-existing risk factors (Marnett 2009). While data on CVD risk are more complete for coxibs, differential class-specific activity among the non-selective NSAIDs (Fosbøl et al. 2010) and the lack of safety data for the non-selective NSAIDs, including sulindac, prompted generalized warnings from the FDA regarding chronic NSAID use and risk of CVD. However, unlike other members of the NSAID class, sulindac is a prodrug with debated effects on intrarenal COX2 and limited data on endothelial cell effects. Findings for (Ciabattoni et al. 1984; Sedor et al. 1984; L.-O. Eriksson et al. 1990; Beermann et al. 1986; L. O. Eriksson et al. 1987) and against (Waslen et al. 1989; Roberts et al. 1985) renal sparing have been reported for sulindac at ≥ 200 mg bid in subjects with normal or mildly impaired renal function. This 'sparing' of inhibitory action on renal prostanoid synthesis has been attributed to metabolism of sulindac to the sulfone, which exhibits no COX2 activity, in the kidney. In contrast, the inability to clear sulindac sulfide in individuals with renal insufficiency makes renal status an important consideration (Berg and Talseth 1985). As such, sulindac is

considered more renal-sparing than other traditional NSAIDs (i.e., demonstrates less pressor effects) in healthy subjects and is a drug of choice in terms of benefit-to-risk for treatment (Tx) of arthralgia in older patients. (Anthony G. Johnson 1998)In light of recent findings from the coxib trials, the effect of sulindac on blood pressure and vascular contractility is inadequately studied, especially considering the potential relevance of sulindac as a potent anti-inflammatory and anti-cancer agent. Thus, given greater anti-tumor action and pro-apoptotic activity that is unique to sulindac as a drug, the strong analgesic effects, and the recommendation of sulindac in older individuals with arthralgia, we elected sulindac for our study. With this, we also included analyses of drug effects on blood pressure endpoints in women receiving AIs for their BC treatment.

The selection of sulindac for the proposed study also allow us to study the safety of sulindac in breast cancer patients on AIs who are prone to muscle and joint pain. This increases the overall significance of the study. We have excluded women at high-risk for either cardiovascular disease or gastrointestinal toxicity from participation on the sulindac arm of the study as an additional safety precaution. These women are eligible for the observation alone arm of the study. In addition, we monitor very carefully for change in blood pressure and intervene if needed for participants who experience GI symptoms by use of PPIs or with a dose reduction.

9.3 Study Dose of Sulindac

The dose of sulindac in tablet form to be studied is 150 mg twice daily or b.i.d. This is an available formulation from the pharmacy.

9.3.1 Rationale for drug and dose selection

Sulindac and its metabolites have been widely investigated as potential anti-cancer agents for multiple malignancies (J. Cuzick et al. 2009). Exposure to sulindac, particularly the primary sulfide metabolite, at doses higher (micromolar) than needed for COX2 inhibition (nanomolar) results in cell cycle arrest in the G1 phase and induction of apoptosis (Han et al. 1998). The anti-proliferative (cytostatic) and pro-apoptotic (cytotoxic) actions of sulindac sulfide have been attributed to p53-dependent and -independent induction of the cyclin-dependent kinase inhibitor p21waf1/cip1 (Yang et al. 2001). In mouse models of colorectal carcinogenesis, p21 inactivation completely eliminates the anti-polyp activity of sulindac in Apc1638 (+/-) mice (Kelloff et al. 2006), suggesting that this pathway is essential to the anti-neoplastic effect of sulindac.

Dr. Thompson in collaboration with Dr. Stopeck recently completed a randomized, open-label phase I biomarker study of sulindac to assess the effects of sulindac and its metabolites on a stable derivative of COX2-derived prostaglandins (13, 14-dihydro-15-keto prostaglandin A2 [PGEM]) and the NSAID-inducible pro-apoptotic growth differentiation factor (GDF-15) in nipple aspirate fluid (NAF) (Thompson et al.). Thirty women were randomized to sulindac 150 mg qd versus sulindac 150 mg bid for a short duration of 6 weeks. Sulindac was well tolerated in the study. Sulindac intervention was associated, in a dose-independent manner, with a non-statistically significant decrease in NAF PGEM (p=0.10). GDF-15 showed a borderline significant trend towards higher NAF levels in the sulindac 150 mg bid intervention arm (p=0.07). These data suggest that COX2 inhibition in the breast may be achieved at 150 mg sulindac qd, while a higher dose may be needed to fully realize COX-independent benefits, such as induction of anti-apoptotic factors (*e.g.*, GDF-15). Because xenograft studies suggest the mechanism of decreased tumor growth is related to pro-apoptotic effects of sulindac on established tumors, and greater pain and joint stiffness relief is achievable with higher doses, we have selected the higher 150 mg bid as the intervention dose for the proposed study. Sulindac is readily and commercially available in 150 mg and 200 mg tablets for oral administration.

10 TOXICITY FOR SULINDAC- REPORTED ADVERSE EVENTS AND POTENTIAL RISKS

10.1 Peptic ulcer and gastrointestinal bleeding

These side effects have been reported in participants receiving Sulindac. Fatalities have occurred. Risk is higher among individuals over the age of 65. GI bleeding is associated with higher morbidity and mortality in participants with impaired by other medical conditions including hemorrhagic disorders. Combined use of NSAIDs with a proton pump inhibitor (PPI) such as omeprazole at 20 to 40 mg daily is associated with a 3-4 fold reduction in incidence of NSAID-induced gastric and duodenal ulcers, erosion, bleeding and perforation in randomized clinical trials of *Helicobacter pylori* negative patients at increased risk of ulcer (60 year and/or history of ulcer)(Lanza et al. 2009). Current guidelines recommend daily use of PPIs for gastroprotection from NSAID induced peptic ulcer and bleeding in individuals at increased risk for NSAID associated adverse GI events (e.g., 65 years or older and/or history of GI ulcer or bleeding)(Lanza et al. 2009).

10.2 Serious GI toxicity

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time with or without warning symptoms in participants treated with chronic NSAID therapy. Serious GI toxicity has been observed in approximately 1% of participants treated for 3-6 months with daily NSAIDs. Although alcoholism, smoking, history of GI disease put the participant at increased risk serious GI toxicities

have occurred in individuals with no identifiable risk factors. Elderly or debilitated participants tolerate bleeding and perforation less well than other groups and are highest risk for adverse, life threatening event. High doses of NSAIDs carry a greater risk of GI toxicity than lower dose. Daily use of PPIs significantly reduces the risk of serious GI toxicity due to erosion or ulceration including perforation in patients taking NSAIDs or COX-2 inhibitors.(Lanza et al. 2009).

10.3 Hypersensitivity

Hypersensitivity is rare with fever, rash and other symptoms including abnormalities in liver function tests. Liver function tests should be administered prior to initiation of agent. If unexplained fever occurs or other evidence of hypersensitivity, drug should be discontinued.

10.4 Hepatic effects

Hepatic effects including findings consistent with cholestatic hepatitis occur rarely in participants on Sulindac. As with other NSAIDs, borderline abnormalities in liver function can occur in up to 15% of participants. Sulindac use of more than 600 mg per day has been associated with increased incidence of mild liver test abnormalities. If a participant with symptoms of liver dysfunction, agent should be discontinued and follow up tests performed.

10.5 Platelet effects

Though less active than aspirin at inhibiting platelet function, Sulindac is an inhibitor of platelet function and affects coagulation function.

10.6 Cardiovascular

Recent findings regarding selective COX-2 inhibitors have raised the possibility that non-selective NSAIDs, including sulindac, may increase cardiovascular risk, presumably to the extent that they inhibit COX-2. While not completely elucidated, the predominant theory regarding the increased cardiovascular events associated with NSAID use is thought to be secondary to the reduction in biosynthesis of PGI_2 and PGE_2 in the kidney and vessel wall. PGI_2 is a potent vasodilator that also reduces platelet aggregation in response to agonists. Thus, the preferential effects of COX2 inhibition in decreasing PGI_2 does not offset the lesser effects of COX1 inhibition on thromboxane (TxA_2) synthesis resulting in net vasoconstriction and increased platelet reactivity. Patients with pre-existing vascular disease and poor vasodilatory responses, i.e. decreased vascular nitric oxide biosynthesis in diabetes and active smokers, would be predisposed to cardiovascular events (Marnett 2009). Patients with risk factors including advanced age, smoking, diabetes, hypertension, hyperlipidemia, and prior

history of cardiovascular disease were at markedly higher risk of cardiovascular events in clinical trials of coxibs suggesting the risk/benefit ratio could be markedly improved by selecting low risk patients as we have done for our proposed trial (Solomon et al. 2008). There are only scant data regarding the association of sulindac, in particular, with risk of cardiovascular endpoints: in one large study there was no association between use of the drug and myocardial infarction. Because of their effects on renal prostaglandins, most NSAIDs have the potential to increase blood pressure and interfere with blood pressure control in hypertensive participants. Sulindac sulfite, the active metabolite of sulindac, is tightly protein-bound and so not filtered by the kidneys, and therefore apparently has less effect on blood pressure control than other NSAIDs (Spence 2007, 1986; Abate et al. 1990; Beermann et al. 1986; Koopmans et al. 1984; Koopmans et al. 1986; Lauven et al. 1990; Wong et al. 1986). We have now added a fourth aim to study the effects of sulindac on blood pressure as a plausible inexpensive and readily available biomarker of NSAID risk. Patients will be given a validated, semiautomatic electronic home blood pressure monitoring device to serially measure their blood pressure in triplicate each morning and evening for 3 days every 2 weeks for the first 6 weeks on agent and in last month of therapy. Patients with two or more BP readings above 140/90 will be seen by the research nurse and evaluated for antihypertensive therapy. Patients who develop grade 2 hypertension as determined by CTCAE version 4.0 will be monitored more closely and offered dietary and/pharmacologic intervention. Patients who develop grade 3 or higher hypertension will be removed from study intervention treated as medically indicated to control their blood pressure, and continue being followed to the end of the study as described in this protocol if participant agrees.

10.7 Pancreatitis

Pancreatitis has been reported in participants using Sulindac. If pancreatitis develops, Sulindac should be discontinued in these individuals.

10.8 Other

There have been reports of acute interstitial nephritis with hematuria, proteinuria and occasionally nephritic syndrome.

11 INFORMATION ON BREAST IMAGING PROCEDURES AND RISKS

All participants will undergo breast imaging by non-contrast MRI to obtain three-dimensional (3D) FWR and ADC mapping. Participants on the observational AI alone are will receive an MRI at baseline, 6 and 12 months. The participants on the sulindac arm will receive an MRI at baseline 1 and 2, and 6 months, and 12 months. All imaging procedures will adhere to FDA and OSHA guidelines. Images will

be acquired using an 8-channel phased array, dual breast coil on a Siemens 3.0 T MRI 16-Channel AI Breast Coil scanner on site at Arizona's University Medical Center and Stony Brook Hospital. The MRI facility is shared by the hospital and research investigators with dedicated time to research and support staff for research studies.

11.1 FWR-MRI methods

Fat-water imaging will be performed using the radial Gradient-Echo and Spin-Echo (GRASE) technique developed by co-investigator Altbach (Li et al. 2009). This method provides a robust lipid/water separation, which includes correction for field inhomogeneity and T2 decay. Radial scanning provides robustness to motion. Data are acquired with various phase shifts between the fat and water signals. The separation of fat and water is then performed using an iterative algorithm (Reeder et al. 2004). The specific sequence parameters to be used are the following: TR=6000 ms, ETL=8, matrix size=256x256, number of averages=1, slice thickness=7 mm, and FOV=34x34 cm2. Axial slices will be prescribed such that both breasts are imaged completely. For fat-water separation, four gradient echoes per spin echo period will be collected with phase shifts: (-5π/6,-π/6,π/2,7π/6) and receiver bandwidth of ±125 kHz, yielding ~18-19 slices in ~3 min.

11.2 Diffusion-weighted MRI

As a secondary objective, we are exploring the potential of diffusion weighted MRI (DW-MRI) of the breast as a quantitative and qualitative imaging approach to obtain information that reflects differences at a cellular level by providing unique insights about tissue cellularity and the integrity of cellular membranes ('functional imaging). DW-MRI has been actively pursued by our group and others for the early assessment of tumor response to treatment (Pereira et al. 2009; Theilmann et al. 2004; Woodhams et al. 2005; Abdel Razek et al. 2010; Peters et al. 2010). In the proposed study, DW-MRI will be performed to determine the ADC of water in the parenchymal/stromal tissue of the normal breast. This is a highly novel application of this technology. To minimize the effects of participant motion, a single shot echo planar imaging (SSEPI) imaging sequence will be employed. Images will be obtained at the same axial locations and FOV as in the FWR-MRI, with a TR = 6000 ms, TE=75 ms and matrix size = 128x128. ADC maps will be calculated from the exponential decay of signal between two SSEPI images, with and without diffusion weighting (b=0 and 400 s/mm2).

11.3 Risk associated with Breast MRI

The Magnetic Resonance Imaging protocols utilized in this study use standard magnetic fields and do not involve contrast reagents. Thus there are no known risks to the participants from the imaging protocols. However, patients with claustrophobia or electrically, magnetically, or mechanically activated implants (pacemakers, cochlear implants, etc.) are ineligible secondary to the increased risks from imaging inherent with their participation.

12 Information on Breast Biopsy Procedures and Risks.

During the study, participants on sulindac will be asked to provide a breast biopsy (optional) at baseline 2 and at 6 months on sulindac and all participants will undergo non-contrast, magnetic resonance imaging of the breast at various time points. These procedures and their risks are described below.

12.1 Breast Biopsy Procedure (sulindac intervention study only)

All participants **receiving sulindac** will be asked to provide an optional core needle biopsy at baseline and 6 months from the contralateral, unaffected breast; we estimate that ~75% will agree to the first and 60% to the second request, yielding approximately 40 participants with both baseline and 6-month biopsies. For participants who consent to breast biopsy at baseline, the breast specialist (radiologist or surgeon), as a fee for service, will use mammography images to identify two areas of increased radiographic density, located at least 2 cm apart, in the upper, outer quadrant of the contralateral (uninvolved) breast. Mammographically dense areas will be co-localized with ultrasound guidance, with their relative positions recorded by clock-face and linear distance away from the nipple. Under ultrasound guidance, an 14-gauge needle will be used to obtain 8 tissue cores from one of the two identified high-density areas. Since 5-10 cores are typically obtained during clinically indicated biopsy procedures, our tissue sampling protocol should not impose undue participant burden or risk. Representative FFPE specimens will be reviewed separately by Arizona's University Medical Center pathology department (required) for UACC site and Stony Brook University pathology department for SBCC site.

12.2 Methods for tissue biomarkers.

We estimated that 25% of subjects (n = 40) will consent to serial core biopsy procedures of the contralateral, unaffected breast at baseline and 6 months, allowing us to explore the effect of AI and AI+sulindac on molecular markers in normal tissue. To date, the response rate is 90% for initial biopsy and 75% for second biopsy.

12.2.1 Histological characterization of tissue from core biopsy

The baseline and 6 months' breast biopsy specimen obtained will be microscopically examined. The proportion of the specimen occupied by fat, epithelium, and collagen will be estimated. The presence or absence of major and medium-sized ducts will be noted; if present, the ducts will be classified as normal, distended with secretion, or showing periductal fibrosis. Lobules will be classified as well developed, sclerotic, or atrophic.

12.2.2 Laboratory assays

All breast tissue markers will be analyzed at AZCC (Thompson lab). Uncontrolled proliferation and decreased apoptosis are among the hallmark features of cancers. As an exploratory aim, we propose to evaluate the effect of 6-month exposure to AI+sulindac on proliferation (cyclin B1 and Ki67), apoptosis (cleaved caspase 3), and pro-apoptotic/anti-growth markers (i.e., GDF15 and p21) in the subjects that agree to core biopsy. These data will also be available to conduct cross-sectional analyses relating their levels to MRI-derived features of the breast to gain insight on the relationship between breast density and/or diffusion and proliferation/apoptosis indices.

12.2.3 Immunohistochemistry (IHC) for measures of proliferation and apoptosis

For direct quantitative tissue measures of proliferation and apoptosis, we will measure Ki67 expression for proliferation by IHC and cleaved caspase 3 as an indicator of apoptotic activity in normal breast tissue from high-risk women. For Ki67, we use the DAKO MIB1 antibody diluted 1:100 under diagnostically validated conditions using the Discovery XT Automated IHC system (Ventana Medical Systems) and analysis with the Aperio ScanScope™ system. The Aperio system includes a suite of automated Ki67-specific image analysis algorithms that have been FDA-cleared for in vitro diagnostic purposes. For each FFPE stained section, the Ki67 analysis algorithm tool provides measures for % positive nuclei and intensity score. To illustrate performance of the scoring algorithm and to show the range of Ki67 expression, we analyzed 10 random fields for each of 12 core biopsy from the unaffected breast of 12 patients in an unrelated study. Only ductal epithelial cells were selected for each random field. Scans are repeated 3 times, each time reselecting a random set of 10 fields. The mean number of total nuclei counted per scan was 3900. The between-scan variation (sum across 10 random regions) or inter-scan coefficient of variation (CV) was 3.52%, demonstrating a highly reproducible estimate of Ki67 expression.

Unlike proliferation, the study of apoptosis in normal, but high-risk, breast tissue and induction by pharmacologics is limited. The few studies that measured DNA fragmentation by the TUNEL assay have reported on apoptotic response to drug in tumor, not normal tissue. Because the TUNEL assay

conducted on FFPE is prone to high CVs, we have elected to measure cleaved caspase 3 since caspase induction has been reported to be induced by sulindac(90). Caspase 3 has been applied in the study of normal (not tumor) breast tissue response to long-term HT in cynomolgus monkeys wherein the untreated control group showed a mean 10.7% basal staining and similar, though slightly higher, Ki67 values (8.4%) to normal human breast (Conner et al. 2005). We will score caspase 3 in a manner analogous to Ki67 described above.

12.2.4 Alternative measure of tissue response to sulindac

Sulindac exhibits both COX-dependent and -independent actions with activity reported for a number of targets that include evidence for inhibition of cyclic-GMP phosphodiesterase resulting in increases in protein kinase G and subsequent induction of caspase (Haanen 2001). In addition, a number of studies find evidence for effects on GDF15, p21, cyclin D1, β-catenin, PPARγ, MMP-1, PI3KR1, uPA and a number of other molecules (Kim et al. 2005; Greenspan et al. 2010). Thus, because of the broad spectrum effects, we propose to conduct exploratory analyses comparing change in gene expression patterns at the tissue level, pre- and post-drug, using the Illumina DASL platform for high-density expression profiling. The DASL requires as little as 200 ng input RNA and performs in formalin fixed paraffin embedded tissue derived RNA. Expression profiling will be performed under contract as fee-for-service at Illumina (San Diego, CA). Given the small sample size, we will explore gene expression changes by assignment to placebo or sulindac and confirm positive findings with Q-RTPCR and interpret with caution. The work will be conducted in collaboration with the Informatics/Bioinformatics Shared Services of the AZCC Core Grant led by Drs. Pandi and Mount who are experts in the field of gene expression profiling (http://www.azcc.arizona.edu/research/shared-services/biss) and who have previously published with PI Thompson (Egan et al. 2010; Flowers et al. 2010), including results from a study showing mammary tumor changes in gene expression following exposure to conjugated linoleic acid (Flowers et al. 2010).

12.3 Risk associated with Breast Biopsy

A breast biopsy procedure will be offered to all participants as an optional procedure. Potential risks associated with biopsy include: bleeding/bruising/hematoma formation at the biopsy site, pain at the site, rare instances of infection, and a small scar at the site. The risk of significant bleeding complications requiring surgery or hospitalization is nil. However, there is a 30% risk of hematoma or bruising after breast biopsy that spontaneously resolves.

13 MEASURES OF PAIN IN CLINICAL TRIALS

Results from a recent study of 1147 cancer patients from the Eastern Cooperative Oncology Group suggest that measurement of past-week worst pain with the BPI-SF had the strongest relationship with pain interference scores, supporting its use as a primary endpoint measure for clinical trials in patients with persistent pain (Shi et al. 2009). Thus, to assess the severity of pain and to measure change in pain with treatment, participants in this study will be administered the BPI-SF at baselines and 3, 6, 9, and 12 months (baseline, 6 and 12 months for AI only arm) to rate their pain at its worst, least, and average during the past 24 hours using the BPI-SF developed for clinical trials by Dr. Charles S. Cleeland (Mendoza et al. 2006; Keller et al. 2004; Dworkin et al. 2010; Cleeland and Ryan 1994). The BPI-SF is a one-page form that provides patients with simple language with which to communicate about their pain using a simple numeric rating system. The BPI-SF asks patients to rate their pain at its worst, least, and average during the past 24 hours with each item rated on a 0-10 scale, with 0 indicating 'no pain' and 10 indicating 'pain as bad as you can imagine' (copy of instrument is provided in Appendix 1). The BPI-SF also rates, for exploratory analyses, how much the pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a scale of 0 to 10, with 0 indicating 'does not interfere' and 10 indicting 'completely interferes'. The primary pain-related endpoint for our study will be 12-month change in the past 24 hours' worst pain score. Past 24 hours' average and past 24 hours' least pain scores will be included as secondary pain-related study endpoints.

In addition, we will administer the WOMAC, a 24-item instrument developed to assess pain, stiffness, and physical function in participants with hip and/or knee osteoarthritis (Wolfe and Kong 1999). This instrument is well validated (Wolfe and Kong 1999) and has been modified from its original form and used extensively to examine specific joint pain changes following treatment, including drug-based interventions for back pain, rheumatoid arthritis, and fibromyalgia (Rothenfluh et al. 2008). For our study, we will use the 5-point Likert-type format.

14 INFORMATION ON PLASMA AND URINARY BIOMARKER PROCEDURES AND RISKS

14.1 Urine Sample Collection, Processing and Analyses

For the sulindac treated group, urine will be collected at both Baseline visits and at 3, 6, 9, 12 month visits. For the observational group, urine will be collected at baseline and at 6 and 12 month visits. All urine samples will be aliquoted in clinic the same day as collection and transported to the Cancer Prevention & Control (CPC) laboratory at the University of Arizona Cancer Center or to the Thompson Laboratory in the Department of Pathology within 2 hours for storage at -80^{o}C for future analyses. All urine specimens are labeled and tracked with a unique sample ID. The CPC research lab and the Thompson laboratory have Standard Operating Procedures in place established by Dr. Thompson in

both sites and follow all regulations pertaining to lab safety, sample processing, specimen classification and repository management.

14.2 Blood Sample Collection, Processing and Analyses.

14.2.1 Clinical Blood Chemistry Monitoring

Blood will be collected when enrollment is initiated following consent, at baseline visits (post-washout and post-observation) and at 6, and 12 month on sulindac visits for sulindac treated group only. CBC with differential and platelet count, chemistry panel (biochemical profile) will be performed for the active arm (sulindac) only. The chemistry panel and CBC with differential are performed by a fee for service laboratory (Sonora Quest Laboratories in Arizona and Stony Brook Laboratories in Stony Brook New York). These service laboratories hold current accreditation issued by the College of American Pathologists' Laboratory Accreditation Program. Hard copies of the laboratory results are sent directly to the clinic on a routine basis. The study nurse will be responsible for noting any values for tests used in eligibility that are outside normal ranges and alerting the participant of these values.

14.2.2 Blood Banking

For the sulindac treated group, blood will be collected at Baseline visits (post-washout and post-observation) and at 3, 6, 9, 12 month visits. For the observational group, blood will be collected at Baseline visit and at 6 and 12 month visits. Whole blood will be collected only once during the study at the first Baseline visit. Serum for banking will be collected in a Red top Vacutainer. Plasma for banking will be collected in a Lavender top EDTA Vacutainer. Whole blood will be collected from the same Lavender top EDTA Vacutainer as serum. Vacutainer tubes are centrifuged in the clinic the same day as collection. All blood specimens are labeled and tracked with a unique sample ID. Blood samples will be processed to serum and plasma and transported to the CPC (AZ) or Thompson laboratory (Stony Brook NY) within 2 hours for storage in aliquots at -80^{o}C for future analysis. At this time (January 2021), all blood samples have been collected, processed and stored as specified in the protocol. These samples will be relocated from the Thompson laboratory to the Cancer Center Tissue Biobank until approved for sharing with the Thompson laboratory at Cedars Sinai Medical Center under a Material Transfer Agreement. Only sample needed to complete agreed biomarker studies will be shared and all residual material returned to long term storage at either UACC or Stony Brook University.

14.2.3 Measurement on prostaglandin E2 and arachidonic acid pathway related metabolites associated with sulindac activity

The NSAIDs are highly efficacious for the management of musculoskeletal pain associated with prostaglandin (PG)-mediated inflammation. NSAIDs act by blocking cyclooxygenase (COX)-1 and -2

enzymes metabolism of arachidonic acid (AA) to the PGs. In addition to the well-known COX-mediated metabolism, AA and other unsaturated fatty acids (Ω-6 and Ω-3) are also metabolized by two other enzyme families: the lipoxygenases (LOX) and members of the cytochrome P450 (CYP450) enzyme family. Collectively, these Ω-6 and Ω-3 can be metabolized to over 100 metabolites known as 'oxylipins' (see Figure 3). Oxylipins exhibit a wide spectrum of biological activity including pro- and anti-inflammatory effects as well as anti-tumor activity and acting as inducers and inhibitors of pain depending on the enzymes activated and availability of substrate.

14.2.3.1 Reverse phase chromatography with UPLC-MS for oxylipin profiling

Metabolite profiling will be performed using a QToF mass spectrometer to give highly accurate (<5 ppm), reproducible mass measurements. We will also collect MS^E data at both low (5V) and high (50V) collision energies in order to obtain fragmentation data simultaneously (Plumb et al. 2006). Samples will be analyzed in positive and negative electrospray modes. Leucine enkephalin will be infused into the instrument to provide a lock mass, and the system will be calibrated using HCOONa. Data will be collected in centroid mode with a scan range of 50–1000 m/z, with lockmass scans averaged over 3 scans to perform mass correction.

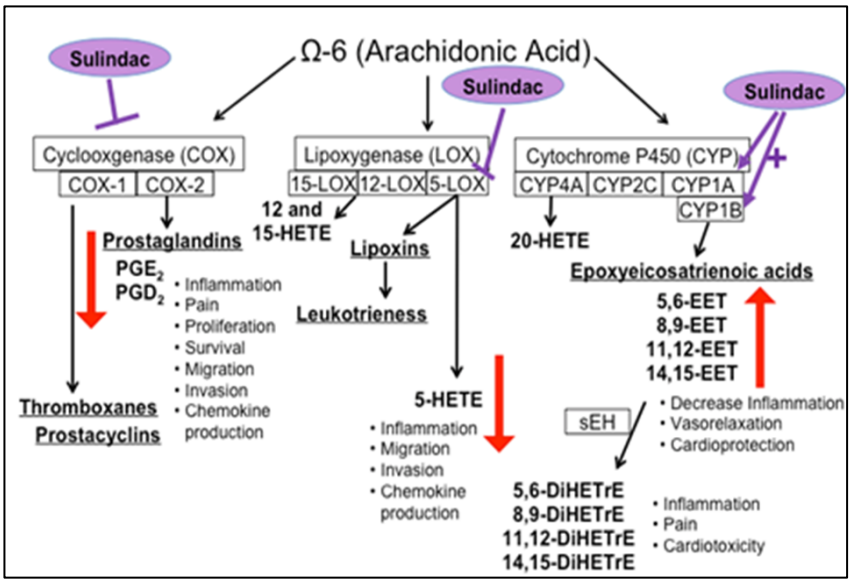

Figure 3: Oxylipin metabolites of the Ω-6 fatty acid, arachidonic acid (AA). Sulindac targets cyclooxygenase (COX) pathways and reduce production of inflammatory prostaglandins (PGs; down red arrow). Off-target effects include inhibition of 5-Lipoxygenase (LOX), resulting in reduced 5-hydroxyeicosatetraenoic acid (HETE), and upregulation of cytochrome P450 enzymes, CYP1A and 1B (resulting in increased Epoxyeicosatrienoic acids; EETs). The hypothesis is that inhibition of one enzyme should result in compensatory up-regulation of alternate pathways in order to metabolize AA, resulting in an increase in analgesic EETs; up red arrow. Biological functions are noted below those oxylipins that are the focus of the specific aims. sEH: soluble epoxide hydrolase; LT: leukotriene; HETE: hydroxyeicosatetraenoic acid; Lx: lipoxin; DiHETrE: dihydroxyeicosatrienoic acid.

14.2.3.2 Mass spectrometry (MS) data preprocessing

MS profiles will be pre-processed using Waters' TransOmics software, which has been developed specifically for Waters instrumentation and metabolomics studies. TransOmics algorithms are set to use only "well behaved" peak groups for alignment of datasets and then fill missing peaks using baseline raw data, allowing for subsequent data analysis.

14.2.3.3 Lipidomics approach and metabolite identification

Metabolite identification of 108 oxylipins relies heavily on the use of standards. However, a major goal of the training for this work is to expand the methodology to captures numerous metabolites. Therefore, where the structural identity (i.e. common name) of metabolites associated with pain and/or sulindac intervention is unknown, they will be identified using TransOmics, The Human Metabolome Database (hmdb), METLIN (*metlin.scripps.edu*), Platform for RIKEN Metabolomics, Chemspider, Lipidmap, Lipidbank, National Institute of Standards and Technology (NIST) chemical web book, and in-house databases.(Wishart et al. 2009; Cui et al. 2008; Smith et al. 2005; Kopka et al. 2005; Akiyama et al. 2008) Where necessary, specimens will be pooled and reconstituted at higher concentrations to enable

effective structure elucidation. Tandem mass spectrometry (MS/MS) and MS^E using UPLC-QToF-MS can generate detailed fragmentation patterns for unknown metabolites. The high mass accuracy (<2 ppm) facilitates generation of empirical formulae (parents and fragments), aiding structural characterization. Pure standards of identified metabolites not already contained in the internal standard mix will be purchased and spiked into samples to confirm identification.

14.2.3.4 Pathway integration

Relevance of identified metabolites to BC and pain-related pathways will be determined using literature review and pathway integration databases [e.g. ConsensusPathDB (cpdb.molgen.mpg.de/), Kryto Encyclopedia of Genes and Genomes (KEGG; www.genome.jp/kegg/kegg3a.html), MetaCyc,(Caspi et al. 2012) and LIPID MAPS. This work is a particular area under rapid applications expansion for which onsite training and workshop activities will be of high value, allowing me to analyze my own data and become expert in the field.

14.3 Risk associated with Blood and Urine Sample Collection

There is minimal to no risk associated with urine collection to the participants with minor risk of bruising or soreness at the site of blood draw.

15 PARTICIPANT ELIGIBILITY

15.1 Eligibility criteria:

a. Postmenopausal women with of first incidence of early stage (stages 0 – III) hormone receptor positive breast cancer stabilized on aromatase inhibitor (AI) therapy for at least 3 months
b. Patients must have started on AI at least three months before consenting with plans to continue on AI therapy for a minimum of 16 months (12 months for AI only arm) or until the end of the study intervention.
c. Patients must have an unaffected, non-irradiated contralateral breast with a baseline BD score of ≥ 25% as measured by standard digital mammography (BIRADs score ≥ 2 or scattered fibroglandular densities at least heterogenous or greater) performed within 12 months of consent to the study
d. A willingness to follow the study protocol, as indicated by provision of informed consent to participate
e. A willingness to avoid taking NSAIDs outside of the trial (rare NSAID use for musculoskeletal symptoms accepted, and/or daily use of aspirin < 81 mg is allowed for the duration of the study) [apply only to AI Sulindac arm]

f. Normal renal function as determined by a serum creatinine ≤ upper limit of normal (ULN= 1.5mg/dl) or a creatinine clearance above 60 ml/min [apply only to AI Sulindac arm]
g. No known contraindication to NSAID use [apply only to AI Sulindac arm]
h. Normotensive or controlled blood pressure (< 140/90) on no more than two anti-hypertensive medications [apply only to AI Sulindac arm]

15.2 Exclusionary criteria:

a. Current or anticipated need for daily aspirin or NSAID. Daily use of no more than 81 mg of aspirin for cardiovascular protection is permitted.
b. Known intolerance to NSAIDs [applies only to AI + Sulindac arm]
c. Age ≥ 75 years
d. History of cardiovascular disease including prior myocardial infarction, angina, stroke, or transient ischemic attack (TIA) [applies only to AI + Sulindac arm]
e. Diabetes requiring drug therapy [applies only to AI + Sulindac arm]
f. Current smoker [applies only to AI + Sulindac arm]
g. Current uncontrolled hypertension [applies only to AI + Sulindac arm]
h. Blood pressure > 140/90 at baseline by home monitoring [applies only to AI + Sulindac arm]
i. History of GI bleeding in the past 5 years. [applies only to AI + Sulindac arm]
j. Patients with active GI symptoms including burning pain in the middle of the stomach between meals or at night, stomach bloating, heartburn, nausea or vomiting despite PPI therapy. [applies only to AI + Sulindac arm]
k. History of a bleeding diathesis or current anticoagulant therapy [applies only to AI + Sulindac arm]
l. History of claustrophobia
m. Have electrically, magnetically, or mechanically activated implants including cardiac pacemaker, cochlear implants, magnetic surgical clips or prostheses.
n. Current use of any corticosteroids or immune suppressive therapies [applies only to AI + Sulindac arm]

16 STUDY PARTICIPANT IDENTIFICATION

Participants who have been consented will be identified on study-related documentation and forms with a unique 7 alphanumeric study identifier. These numbers will be issued to participants sequentially

and no participant identification numbers will be re-assigned in the event that the participant is withdrawn from the study.

17 ASSIGNMENT TO STUDY GROUPS

The study will be a non-randomized trial with participants explicitly consented to either AI Sulindac arm or AI only arm. All the consented participants in AI Sulindac arm will be given the study intervention.

18 STUDY PLAN AND SCHEDULE OF EVENTS

The proposed study will be a non-randomized trial of postmenopausal women currently receiving aromatase inhibitor therapy for early stage hormone receptor positive breast cancer as part of their standard of care. Women will receive sulindac 150mg po BID. An additional observation group of approximately 75 women will NOT receive sulindac. We will attempt to recruit all eligible patients from the breast cancer clinics of the University of Arizona Cancer Center and Stony Brook Cancer Center.

For the observational group, approximately 75 participants will be enrolled with 60 expected to complete all measures. As all participants will have been adherent to AI therapy for a minimum of 3 months, we expect that no less than 80% will complete the study requirements, for a total of 60 fully evaluable participants.

For the sulindac treated group, approximately 100 participants will be recruited. As all participants will have been adherent to AI therapy for a minimum of 3 months, we expect that approximately 90% will continue past the observation phase to intervention phase. We estimate an additional 10% drop-out rate prior to study conclusion (12 months imaging and patient reported outcome endpoints) for a total of 80 fully evaluable participants. We have focused on women with contralateral at risk breast tissue of a BIRADs density score at least 2 ($\geq$ 25% BD) or scattered fibroglandular densities at least heterogenous or greater (i.e. heterogenous or mostly dense) to ensure inclusion of women with a modifiable biomarker for our primary endpoint. From our preliminary data, approximately 75% of women prescribed aromatase inhibitors in our clinics would meet this eligibility requirement.

19 PARTICIPANT RECRUITMENT AND INFORMED CONSENT

Investigators and staff at the University of Arizona Cancer Center and at the Stony Brook Cancer Center will be SEPARATELY responsible for identifying and recruiting candidate participants, evaluating their

suitability for participation in the study, following participants during the treatment phase of the trial, monitoring participants for possible toxicity, and continuing to follow participants for subsequent toxicity during the post-treatment follow-up period.

Recruitment will proceed under the auspices of each center's individual Clinical Trials Office. Working in accordance with HIPAA regulations, study coordinators or treating medical staff will identify potential participants and they will be screened for eligibility by the research nurse assigned to the study. Recruitment will occur in the breast cancer and high risk clinics of the University of Arizona Cancer Center and Stony Brook Cancer Center. Currently, approximately 500 new patients with breast cancer are treated in the breast clinics of the University of Arizona Cancer Center and 400 in the Stony Brook Cancer Center annually. Thus, it can be anticipated that at least 50 patients per year would qualify for the study to meet accrual goals.

A preliminary determination of eligibility will be made through review of medical records and contact with the participating physicians.

The investigator and/or research nurse will explain all aspects of the study in lay language to the potential eligible participants, answer all questions regarding the study, and confirm eligibility. If the participant decides to participate in the study, she will be asked to review, sign and date the Informed Consent Form (ICF). The ICF has to be completed prior to initiating any study related procedures. The study agent will not be released to a participant who has not signed the ICF. Participants may terminate or withdraw from the study at any time and for any reason, including development of an AE or SAE, noncompliance, medical contraindication, or desire without prejudice.

20 SCREENING AND BASELINE VISIT PROCEDURES

Only participants in the sulindac treated group will be asked to provide an optional core biopsy sample at their baseline visit; we estimate that ~75% will agree to the first. For participants who consent to breast biopsy at baseline, the breast specialist (radiologist or surgeon), as a fee for service, will use mammography images to identify two areas of increased radiographic density, located at least 2 cm apart, in the upper, outer quadrant of the contralateral (uninvolved) breast. Mammographically dense areas will be co-localized with ultrasound guidance, with their relative positions recorded by clock-face and linear distance away from the nipple. Under ultrasound guidance, a 14-gauge cutting needle will be used to obtain up to 8 tissue cores from one of the two identified high-density areas. Since 5-10 tissue cores are typically obtained during clinically indicated biopsy procedures, our tissue sampling

protocol should not impose undue participant burden or risk. Representative FFPE (formalin fixed and paraffin embedded) specimens will be reviewed at each of the two study sites separately. At Stony Brook, tissue histology will be reviewed by pathology under the direction of Dr. Ken Shroyer, a board-certified anatomical pathologist who specializes in breast pathology. Additional cores will be coded for processing by Dr. Thompson's laboratory (relocated to Cedars Sinai Medical Center January 2021) for evaluation of apoptotic, proliferation, and alternative biomarkers. At this time (January 2021), all tissues samples have been collected, processed and stored as specified in the protocol. These samples will be relocated to the Cancer Center Tissue Biobank until approved for sharing with the Thompson laboratory at Cedars Sinai Medical Center under a Material Transfer Agreement. Only sample needed to complete agreed biomarker studies will be shared and all residual material returned to long term storage at either UACC or Stony Brook University. All biomarker studies after January 2021 will be conducted according to a Material Transfer Agreement between Stony Brook University and Cedars Sinai Medical Center. All pathology reviewed materials will be stored as digitized images using the Aperio Instrumentation for cross-site pathology review at Stony Brook University.

All screening and pre-washout evaluations will be completed within 21 days of initiating the study Week 1 Day 1 of the study schedule. As the target population will be postmenopausal, no serum pregnancy test will be performed.

The following events will occur at screening/baseline visits for participants in the sulindac treated group.

a. Medical history including demographics (race, ethnicity, age, and etc.);
b. Review medication use within the past 30 days;
c. Review concomitant medication and supplement use;
d. Vital signs (Blood pressure, pulse);
e. Height and weight;
f. Hematology (CBC/differential and platelet count);
g. Chemistry panel (to include Urea Nitrogen, Creatinine, ALT, AST)
h. Urinalysis
i. Fecal occult blood test
j. Participants will undergo a 30 day NSAID washout period.
k. Participant may be reevaluated for study participation after the washout period.
l. Screening/baseline lab work will be collected after the washout period.
m. FWR-MRI and DW-MRI of contralateral, unaffected breast, qualify of life questionnaire (FACT-G) and pain measurements using BPI-SF and WOMAC instruments. Participant will be given a

validated, semiautomatic electronic home blood pressure monitoring device to measure their blood pressure in each morning and evening for 3 days every 2 weeks for the first 6 weeks right after the washout period.

The following events will occur at screening/baseline visits for participants in the control arm.

a. Medical history including demographics (race, ethnicity, age, and etc.);
b. Review medication use within the past 30 days;
c. Review concomitant medication and supplement use;
d. Vital signs (blood pressure, pulse);
e. Height and weight;
f. Blood and urine samples obtained for research biomarkers.
g. FWR-MRI and DW-MRI of contralateral, unaffected breast, quality of life questionnaire (FACT-G) and pain measurements using BPI-SF and WOMAC instruments

21 TREATMENT PLAN AND EVENTS

21.1 Sulindac treated group

Clinic visits will be scheduled at 3-month intervals (±28 days), during which a focused physical exam, FACT-G, pain measurements (BPI-SF and WOMAC), and indicated laboratory tests (CBC, chemistry panel) will be performed. At each visit, unused study agents will be collected, counted, and returned for appropriate disposal.

The following on study events will occur.

a. Participants will receive and complete study log (calendar)
b. Participants will be given a validated, semiautomatic electronic home blood pressure monitoring device to measure their blood pressure in each morning and evening for 3 days every 2 weeks for the first 6 weeks on agent and in last 6 weeks of therapy.
c. Sulindac 150mg b.i.d. will be self-administered, by mouth, daily for a total of 12 months
d. A chemistry panel (to include Urea Nitrogen, Creatinine, ALT, and AST) and hematology (CBC/differential and platelet count) will be performed at the post-washout, post-observation, 6 months and 12 months on sulindac visits.
e. Blood for serum sulindac and metabolites levels will be obtained at baseline (both post-washout and post-observation visits) and at months 3, 6, 9 and 12 on sulindac.
f. Blood pressure will be measured in the clinic at all clinic visits.
g. Blood pressure will be monitored at home.

h. The FACT-G, BPI-SF and WOMAC instruments will be administered at 3, 6, 9 and 12 months' clinic visit.
i. A breast core biopsy at baseline 2 and 6 months on sulindac for planned biomarker studies and storage for future studies.
j. Non Contrast breast MRI will be obtained at baseline, post observation and months 6 and 12 on sulindac.
k. Unused tablets and/or empty sulindac will be returned at study visits for pill count.
l. A urine sample for research biomarker studies will be obtained at baseline (post-washout and post-obseravtion visits) and at 3, 6, 9, and 12 months on sulindac.
m. A +/- 28 days window will be allowed for specimen collection and all procedures.

21.2 Observation group

Clinic visits will be scheduled at 6-month intervals (±28 days), during which FACT-G, pain measurements (BPI-SF and WOMAC), and correlative blood and urine samples will be collected.
The following on study events will occur.

a. The FACT-G, BPI-SF and WOMAC instruments will be administered.
b. Non Contrast breast MRI will be obtained.
c. A urine and blood samples collected for research biomarkers.

22 DEFINITIONS

22.1 Follow-up

All participants in the sulindac treated group will have a follow-up visit or telephone contact scheduled one month after the last dose of study medication/end-of-treatment to follow-up for AEs and SAEs that may have occurred during or after discontinuation from the study. AEs and SAEs that are still ongoing at the time of discontinuation will continue to be followed weekly until resolution or stabilization of condition. Abnormal laboratory values will be followed every 14 days until resolution or one month post last dose of study drug(s) whichever occurs first.

22.2 End of Treatment

Study drug discontinuation is the time when study agent(s) administration is permanently discontinued for any reason.

22.3 Withdrawal of Participant from Study

Participants will be withdrawn from the study under the following circumstances:

a. Study closure,
b. Unacceptable adverse event(s), as judged by the study physician,
c. Participant decision to withdraw from the study or, in the judgment of the investigator, further participation would not be in the best interest of the participant,
d. The participant is noncompliant with study procedures

22.4 Post-Intervention Evaluation and off-study monitoring

A Post-Intervention office visit will be scheduled at the end of 12 months on sulindac (±28days) or at early termination, if applicable, during which a focused physical exam and indicated laboratory testing (CBC, chemistry panel) will be performed. Unused study agents will be collected, counted, and returned for appropriate disposal. After completing the Post-Intervention Evaluation, study personnel will place a telephone call one month after end of the treatment to record any previously unrecorded AEs and/or review unresolved AEs. Participants will be followed until all AEs are resolved.

23 AGENT ADMINISTRATION

23.1 Sulindac

Study agent (sulindac tablets, 150 mg active) will be self-administered according to investigators' instructions, including taking the tablets with a meal and not within one hour of reclining or sleeping. The usual adult dose is 150 or 200 mg bid taken with meals, and the maximum daily dose is 400 mg. Toxicities associated with sulindac are those consistent with other NSAIDs. The most common side effects are gastrointestinal and include, but are not limited to, abdominal pain, cramping, nausea, gastritis, and even serious gastrointestinal bleeding and liver toxicity.

24 TOXICITY MONITORING AND RESPONSE PLAN

Note: Risk for toxicity with sulindac increases with longer use (≥6 months) and higher doses. Dose reductions of 50% to 150 mg qd will be allowed, and 2 drug holidays totaling no more than 4 weeks will be permitted. Participants will be advised not to use over-the-counter NSAIDs without first consulting study staff.

a. Participants will receive a study log on which to record time of sulindac doses. Participants will be instructed to use the study log daily to record concomitant medication use and adverse events. Participants will be instructed to return the log at their 3 month visits for adverse event review and concomitant medication review by nurse coordinator.

b. During the initial 6 weeks of heaviest in-home blood pressure monitoring, site study personnel will place telephone calls every two weeks (±3 days) to document these data reducing to monthly after the first 6 weeks on agent.
c. Participants will be educated to contact us at any time during the study to report any adverse event that fails to resolve in 3 days or results in a visit to the doctor or hospital.
d. Participants with two or more BP readings above 140/90 will be seen by the research nurse and evaluated for antihypertensive therapy.
e. Participants who develop grade 2 hypertension as determined by CTCAE version 4.0 will be monitored more closely and offered dietary and/pharmacologic intervention. Participants who develop grade 3 or higher hypertension will be removed from study, and treated as medically indicated to control their blood pressure.
f. Participants experiencing a ≥ Grade 2 toxicity (NCI, CTCAE version 4), regarded as possible, probable or definitely related to study agent during the study agent administration period will suspend the study agent(s) for a maximum of 2 consecutive days per event.
g. With any NSAID trial, GI upset requiring dose reductions or the temporary need to take an NSAID may arise. Dose reductions of 50% to 150 mg qd will be allowed until symptoms resolve or indefinitely, and 2 drug holidays totaling no more than 4 weeks will be permitted during the study period.
h. If the event remains unresolved at lower dosing, the participant will discontinue study agent and end of treatment procedures will be performed.
i. If the event resolves, the participant will resume the original study schedule.
j. Study agent will be discontinued if the same event which caused suspension of the study agent occurs more than twice during the study.
k. Participants that miss >28 days of study agent during the study agent administration period, regardless of cause, will discontinue study agent and proceed with end of treatment procedures.
l. Participants experiencing a ≥ grade 2 toxicity possibly, probably, or definitely related to study agent will reduce dose by 50% if symptoms resolve within 7 days. If the symptoms recur on lower dose, the subject will be withdrawn from study and proceed with end of treatment procedures.
m. Only one dose modification will occur in this study.

For the observational group, there is no toxicity or risk associated with this study. Thus participants will not be followed past conclusion of the study. No toxicity data will be collected and no adverse events are to be expected.

25 END OF TREATMENT PROCEDURES

a. Vital signs (Blood pressure, pulse);
b. Hematology (CBC/differential and platelet count);
c. Chemistry panel (to include Urea Nitrogen, Creatinine, ALT, AST)
d. Urinalysis
e. Review concomitant medications;
f. Review adverse events [apply only to AI Sulindac arm];
g. Return unused tablets/empty sulindac bottle [apply only to AI Sulindac arm];

End of Treatment procedures will be performed within 28 days of the study agent(s) administration period. For participants who are withdrawn from the study during off study agent(s) period, end of treatment procedures will be performed within 7 days of the date of withdrawal.

Following discontinuation of study agent participants experiencing adverse events will be contacted weekly by telephone or clinic visit until resolution or stabilization of condition. Abnormal laboratory values will be followed every 14 days until resolution or one month post last dose of study agent(s) whichever occurs first.

26 DRUG FORMULATION AND PROCUREMENT

26.1 Sulindac

26.1.1 Physical and Chemical Characteristics

Sulindac is a non-steroid, anti-inflammatory indene derivative designated chemically as (Z)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl] methylene]-1H-indene-3-acetic acid. It is not a salicylate, pyrazolone or propionic acid derivative (Figure 4). It has a molecular weight of 356.42 and is a yellow crystalline compound which is a weak organic acid practically insoluble in water below pH 4.5 but very soluble as the sodium salt or in buffers of pH 6 or higher. Sulindac is available in 150 mg and 200 mg tablets for oral administration.

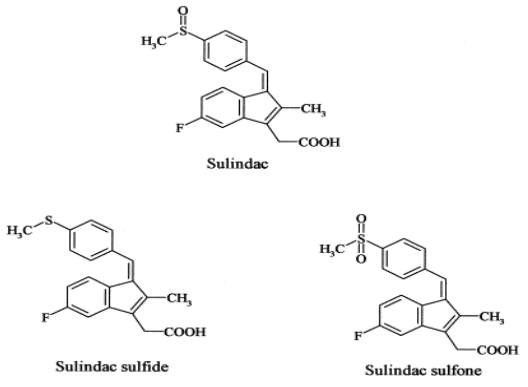

Figure 4. Structural Formulas for sulindac and its metabolites in man

26.1.2 Inactive ingredients

Cellulose, magnesium stearate, starch.

26.1.3 Availability

Sulindac is readily and commercially available in 150 mg and 200 mg tablets for oral administration. Generic sulindac will be obtained from the Arizona Cancer Center UMC North Outpatient Pharmacy and Stony Brook Hospital Investigational Pharmacy from the pharmaceutical supplier of their choice. Study agent will be stored in the Arizona Cancer Center UMC North Outpatient Pharmacy and Stony Brook Hospital Investigational Pharmacy.

26.1.4 Agent Distribution

Sulindac distributions to the study coordinator for study participants will follow receipt of a prescription signed by a study physician.

26.1.5 Agent Accountability

Arizona Cancer Center UMC North Outpatient Pharmacy and Stony Brook Hospital Investigational Pharmacy must maintain a careful record of the inventory and disposition of all agents received using the NCI Drug Accountability Record Form (DARF) or similar record. Duties include maintaining adequate records of receipt, dispensing and final disposition of study agent(s). This responsibility has been delegated to Kelly Myrdal, Pharm. D., and designated UACC and SBCC pharmacy staff. Include on receipt record from whom and to whom study drug was shipped, date, quantity and batch or lot number. The study coordinator will maintain source document, and note quantity and date study agent are dispensed to and returned by each participant.

26.1.6 Packaging and Labels

Sulindac will be purchased in bulk as 150 mg tablets and packaged into individual bottles containing 180 tablets each or as requested by the study nurse. Bottles will be labeled with participant name and address, study and drug identifying information, dosing instructions, pharmacy information along with pharmacist identifier, a contact phone number, and the participant number will be added to the label prior to distribution to the participant.

26.1.7 Storage

Study medication will be stored at room temperature (59° to 86° F), protected from environmental extremes and in a locked cabinet or room prior to being issued to participants. Participants will be instructed to store the study agent under similar conditions and out of reach of minor children.

27 STATISTICAL CONSIDERATIONS

27.1 Observation Group

We will enroll 75 women with the expectation that 60 will complete the entire observation period of 12 months with all MRI measures for the purposes of providing a comparison (non-placebo) for our open-

label, single arm study of sulindac in breast cancer patients receiving aromatase inhibitors in the adjuvant setting for the prevention of breast cancer recurrence. The observational arm will control for the unknown effects of AI as well as time on BD as measured by fat/water and diffusion-weighted magnetic resonance imaging (MRI), patient reported outcomes, effects of sulindac on AI adherence and provide additional information on use of NSAIDs in patients on AIs generally. This request is being made as a consequence of having to redesign our trial from randomized to non-randomized, open label when the study section recommended, and NCI accepted, a cut to the 5th year of funding. This significantly impacted the available funds to cover costs of acquiring the placebo and required a reduction in sample size to complete accrual to the study. The slope between 0 and 12 months that includes measures at 0, 6 and 12 months will be estimated using linear regression analysis (to allow for the possibility of slight variability in the timing of the measurements).

Statistical analysis for the imaging primary endpoints will initially estimate the slope between 0 and 3 months (no study drug) and the slope across 3, 9 and 15 months (sulindac treatment) separately for each woman. The slope between 0 and 3 months is the difference between the two measurements (divided by the time interval), while the slope while on sulindac will be estimated using linear regression analysis (to allow for the possibility of slight variability in the timing of the measurements). Preliminary analysis will assess whether the pattern of change with sulindac treatment is linear. Mean slopes and 95% confidence intervals will be estimated for the baseline (no study drug) and sulindac treatment periods. Comparisons of the mean slope with and without sulindac will be performed using a paired t test since the imaging endpoints as Fra50 from FWR-MRI (Aim 1 and primary trial endpoint) and ADC from DW-MRI (Aim 2) will be restricted to images from the unaffected, contralateral breast. The BPI-SF measure of past-week worst pain is a discrete, ordinal value. Statistical analysis will proceed using a proportional odds model with a robust variance estimate to account for potential correlation among measures in the same woman. The independent variable will be time; differences in the values observed during the baseline and sulindac treatment periods will be estimated using a linear contrast of the estimated coefficients. Adjustment for the inflated alpha level due to the use of three primary study endpoints (FWR-MRI, DW-MRI, and BPI-SF) will be performed using the Bonferroni correction. The incidence of any ≥ grade 2 hypertensive adverse events will be compared during the baseline and sulindac treatment periods using McNemar's test. Since this is a safety endpoint, no multiple comparisons adjustment of the alpha level will be performed.

27.2 Sample size justification for primary aims and trial endpoint

Our TOTAL sample size ensures adequate power to test all *three* primary aims. For the observational group, a sample size of 60 with complete follow-up matches our intervention arm and ensures an

adequate comparison group size to test unknown effects of AIs on BD as measured by fat/water-MRI as well as to assess the two additional endpoints of pain and hypertension.

To justify the sample size for the sulindac intervention, we considered the primary trial endpoint, which is to compare the difference in the slope of the FWR-MRI-derived log (Fra50) between the baseline and sulindac treatment periods. Based on previous findings using mammographic density measures in randomized trials of AI (see Table 1), we assume there will be no more than a 5% change during the 12 month on intervention study and only a 1-2 % difference between the two baseline periods (observational period in the intervention arm of 3 months) due to between measurement variability. For the sulindac treated group, we assume an initial sample size of 100 women and allow the possibility of up to 20% dropout for the end of intervention follow-up measurement. This results in at least 80 evaluable women.

With 80 women we will be able to detect a decrease of 0.368 standard deviation (SD) units in the slope while on sulindac treatment versus the baseline slope with 80% statistical power, assuming a two-sided α of 0.017 (*adjusted for multiple comparisons*). To estimate what this change would be in relation to BD, we used the relationship between BD and log(Fra50) from our previous study. Based on an analysis of our cross-sectional data, the estimated SD of log(Fra50) is 2.40. Thus, a decrease of 0.368 SD units corresponds to a change of -0.883 (-0.368*1.40). Based on the regression line, this is equivalent to a 4% average decrease in BD as determined by CAD assisted BD by mammography. Note, that while this is the effect size that we are able to detect, enthusiasm for the potential to move sulindac forward for an efficacy trial would be much greater with average decreases of more than double that of projected age related change. Thus, the study is well powered to detect even small differences. However, effect sizes < 8% average decrease in Fra50 will not be considered highly impactful in interpreting the results from a clinical perspective given the average age-related decline in BD is 1-3%.

To insure that the use of the new methodology of FWMRI yields a similar change in BD over 12 months and that we interpret change in the sulindac intervention in a more informed manner, a cohort of women similar to those in the sulindac intervention will be followed for BD using FWMRI at 0, 6 and 12 months. Assuming an 80% complete rate, we will have 60 women for complete analysis. To detect a decrease of 0.368 standard deviation (SD) units in the slope while on observation, assuming a two-sided α of 0.05 (single test), we will have >80% to detect a 3% average decrease in BD at 12 months similar to that determined by standard mammography and CAD. This value will be considered when 'interpreting' the impact of any effect size observed in the sulindac arm. This will not however be used in a statistical analysis as a comparison group.

Justification of the sample size for the additional primary specific aims for the intervention with sulindac. For the BPI-SF past-week worst-pain score (Aim 2), we hypothesize that sulindac treatment will lead to a decrease in pain scores compared with baseline. The standardized decrease of 0.368 SD units corresponds to a 0.8-unit decrease, based on the SD of 2.25 observed at baseline in a recent study of acupuncture for AI-associated joint symptoms as referenced in the original grant submission. For Aim 3, we hypothesize no additional grade 2 or higher hypertensive adverse events in women taking sulindac compared to the same women during baseline. The power for McNemar's test depends heavily on the number of discordant pairs (i.e., those women who have grade 2 or higher hypertensive adverse events on either sulindac or baseline, but not both or either). We hypothesize that only 10% of the women will be discordant, since we expect almost 90% will not have grade 2 or higher hypertension during either period. The sample size of 75 women will allow us to detect an increase to 9% of women with grade 2 or higher hypertension when taking sulindac but not during the baseline period, versus 1% of women during the baseline period but not while taking sulindac, with 77% statistical power (assuming a one-sided test at α = 0.05).

27.3 Conduct of and Justification for Planned Futility Analysis

As discussed in the funded grant submission, we would like to limit women's exposure to agents that are unlikely to effect change in the breast in a clinically meaningful way. Therefore, we will include a futility analysis for the primary trial endpoint of FWR log(Fra50) after 40 women have reached the 15-month endpoint. This analysis is for futility only, so it will not affect the overall α level. Briefly, the observed results from these women will be used to compute the difference between the slope during sulindac treatment versus the baseline period. Predicted results for future participants will be generated from a log-normal distribution with the observed mean and SD. One thousand bootstrap samples with a sample size of 80 women will be generated to estimate conditional power. The study will continue if conditional power ≥80% is met. If we fail to pass futility, we plan to **stop accrual to the study and suspend study agent for women who are active.** We plan to follow all women who initiated trial agent to their next imaging endpoint (9 or 15 months, whichever comes first). Considering a dropout rate of 10% by 9 months and 20% by 15 months, and a planned accrual rate of 5 participants/month starting in month 6 of funding, we expect to have 40 evaluable participants followed to 15 months by approximately 3 years; by then, ~90 participants will have completed 9-month measures, and ~100 will have initiated the trial.

27.4 Statistical analysis for secondary aims

We will use linear regression modeling, with transformation as needed to reduce skewness in the observed distributions, **to correlate** baseline breast tissue characteristics and other biomarkers with FWR-MRI. Linear regression will also be used to test the association between the 9- and 15-months primary outcome measures. The dependent variable will be the end of intervention measure (12 months on sulindac), with the 6-month on intervention measure and the post NSAID washout baseline included as explanatory variables. Interactions between the 6 month on intervention and baseline values will also be tested to determine if the association changes based on these characteristics. Comparison of changes in the breast tissue or breast tissue markers of women consenting to serial biopsy will also be assessed using linear regression, with the baseline value included as explanatory variables. Additionally, the demographic characteristics of women who agree to biopsy versus those who refuse will be statistically compared to assess the possibility of selection bias.

Analysis of the secondary measures of specific joint stiffness and pain using the WOMAC scale will be analyzed by comparing the slope of the values during the sulindac treatment period versus baseline as outlined above. The longitudinal 'in-home' arterial pressure measurements will also be analyzed by comparing slopes during treatment versus baseline. If the difference in slopes is not significant, we also will assess whether there is a difference in the intercepts during the two periods (to determine whether a shift in values occurred). Since these are secondary exploratory analyses and hypothesis generating, we will not adjust for multiple comparisons.

All the secondary aims are exploratory in nature. For biomarker related aims, the minimum sample size is expected to be 40 to compare changes in the breast tissue in women consenting to serial biopsy. Forty women will allow us to detect a standardized difference of 0.45 SD units with 80% power (assuming a two-sided α of 0.05). Justification of the sample size is similar to that for the primary endpoints outlined above. To determine the detectable increase in MAP, we assume a simplified design in which the difference between the average value during sulindac treatment and baseline will be compared. We will have 80% statistical power to detect a 4 mm Hg increase in MAP in women while on sulindac versus baseline (one-sided test). This estimate is based on the SD of 13 mm Hg observed in a recent study of middle-aged women referenced in the funded grant submission, which demonstrated an adjusted hazard ratio of 1.43 for incidence of CVD death for a 1-SD increase in MAP.

28 ADMINISTRATIVE CONSIDERATIONS

28.1 Regulatory Board Review

The study protocol at Stony Brook will be activated after review and approval by the Stony Brook Cancer Center Protocol Review Committee and by Stony Brook University Human Subjects Protection

Program. Approval of this protocol by the Stony Brook University Human Subjects Protection Program will also include approval of the protocol consenting document, or Informed Consent Form (ICF) and the accompanying HIPAA consenting instrument specific to Stony Brook participants in the study.

28.2 Compliance with Protocol and Protocol Revisions

Study PI and Co-PI will conduct the study as described in this protocol. Any protocol revisions made in amendments to the protocol by the Principal Investigator will be approved by the Stony Brook University Human Subjects Protection Program prior to implementation, except where necessary to avoid imminent hazard to a study participant. If an amendment alters the study design or increases the potential risk to the participant, the ICF will be revised and submitted for approval to the Stony Brook University Human Subjects Protection Program. The revised ICF will be used to obtain consent from participants currently enrolled in the study or after withdrawal from the study if they are affected by the Amendment.

28.3 Participant Informed Consent

All study participants will sign the most current ICF that has been approved by the Stony Brook University Human Protection Program prior to enrollment on the study. Investigators will have ensured that participants are clearly and fully informed about the purpose, potential risks and any other critical issues regarding this clinical trial.

28.4 Data Management and Safety Monitoring

ALL participant safety and data integrity will be monitored by the UACC Data and Safety Monitoring Board in conjunction with the Quality Assurance/Quality Control Program (QA/QC) at UACC and SBCC. Prior to study registration, a review of the potential participant's eligibility will include a confirmation of the inclusion/exclusion criteria and proper execution of informed consent. All participants registered to this study will be entered into the University of Arizona Cancer Center database for accrual and treatment status tracking and for SBCC participants, a password protected study site database will track accrual and treatment status. The data access is site specific, password-protected and role-based. All participant study files will be stored in a secure area limited to authorized staff at UACC and SBCC respectively. Summary data will be shared for the ad hoc data safety board in Arizona that will review all serious adverse events as well as those specific to Sulindac including hypertension related or any cardiovascular events.

The Principal Investigator will ensure the accuracy, completeness and timeliness of the data reported in these forms. Source documentation supporting the Case Report Form (CRF) data should indicate the participant's participation in the trial and should document the dates and details of study procedures, adverse events, and participant status.

28.5 Data Sharing

Original Principal Investigators for this study protocol, Alison Stopeck, MD and Patricia Thompson Carino, PhD have relocated to Stony Brook University in Stony Brook, New York. At this time, the investigators at the University of Arizona Cancer Center and at Stony Brook University have entered into a data sharing agreement for analysis and participant safety purposes. Each data field in the database is classified per PHI definition and each study member is assigned to one study site or both. Access to data is controlled based on study sites and roles. Necessary approvals from each institution and all investigators will be obtained. Revised ICF's and PHI's have been submitted and approved by the University of Arizona IRB which will indicate the data sharing plan between institutions and investigators and allow subjects the option for their coded data to be included or excluded from sharing. All UACC study participants previously consented will be re-consented under the revised ICF and PHI. If a study participant does not consent to their coded data being shared for analysis purposes with the investigators at Stony Brook University, then that subject's data will ONLY be utilized at the University of Arizona Cancer Center. All prospective study participants will be consented with the revised ICF and PHI. Investigators will have ensured that participants are clearly and fully informed about the purpose, potential risks, and any other critical issues regarding the data sharing plan. No participant PHI will be shared with the Thompson laboratory following her relocation to Cedars Sinai Medical Center. Her laboratory will only receive coded tissue and blood samples for the purposes of obtaining measures of proliferation, protein expression and transcriptomics.

29 DATA AND SAFETY MONITORING PLAN

29.1 Protocol Data and Safety Monitoring Plan and Risk Level Designation

Risk Level. This trial has been designated as a medium risk study. Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are not designated as high risk per NCI and the IND is not held by the investigator. The observational group has been designated as a no risk group. There is no planned safety analysis for the observational group.

29.1.1 Identification of the DSMB obligated for oversight responsibilities

The University of Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial semi-annually. In addition, the investigators will convene a specialty data safety monitoring committee (DSMB) comprised of a cardiologist (Dr. Joe Alpert, former Chair of the Department of Medicine and Cardiologist and DSMB member of numerous phase III cardiology trials), statistician (Dr. Paul Hsu), and pharmacist to monitor accumulating toxicity data with specialty emphasis on review of cardiovascular events and blood pressure measures as the trial proceeds. The specialty DSMB will meet every 12 months to review accumulating data from the trial.

29.1.2 Identification of the entity obligated for routine monitoring duties

Routine monitoring for the SBCC site will be provided by the Quality Assurance/Quality Control (QA/QC) Program at SBCC Cancer Clinical Trial Office to ensure that the investigation is conducted according to protocol design and regulatory requirements.

29.1.3 Monitoring progress and data review process

Routine monitoring of participant data will be conducted at least every 6 months.

The first routine monitoring visit will include at a minimum:
Informed consent of cases enrolled;
Participant eligibility, up to two participants;
Data review, up to two participants.

All subsequent monitoring visits will consist of randomly selected participant cases based on current enrollment and include continuing review of previously selected cases, as applicable. A monitoring visit report and follow-up letter will be completed within two weeks of the routine monitoring visit; a copy will be maintained in the study file. A query/finding form will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in CRF. Source documentation supporting the CRF data should indicate the participant's participation in the trial and should document the dates and details of study procedures, adverse events, and participant status. Case report forms, which include the inclusion/exclusion criteria form, adverse

event forms and serious adverse event forms should be completed with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All participant forms and study files will be stored in a secure area limited to authorized staff. *Note:* Routine monitoring of regulatory documents and test article will be conducted at least annually. A process to implement study closure when significant risks or benefits are in place.

30 DESCRIPTION AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) and adverse events (AEs) will be monitored and discussed routinely using procedures described below. Cumulative SAE review is performed by the SAE Initial Trend Analysis Team monthly. This review not only identifies individual events but also identifies any patterns of adverse events in Investigator initiated trials. If there is concern for excessive risk/toxicity identified by the DSMB, the Committee may recommend suspension of accrual or study closure.

30.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the adverse events record form and reviewed by the Principal Investigator.

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4
(**http://ctep.cancer.gov/protocolDevelopment/electronicapplications/docs/ctcaev4.pdf**)

And will address:

a. Grade
b. Relationship to study drug (not related, unlikely, possible, probable, definitely)

c. Causality other than study drug (disease related, concomitant medication related, inter-current illness, other)
d. Date of onset, date of resolution
e. Frequency of event (single, intermittent, continuous)
f. Event outcome (resolved, ongoing, death)
g. Action taken (none, held, dose reduced, discontinued, medication given)

30.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

a. Results in death;
b. Is life-threatening;
c. Requires in-patient hospitalization or prolongation of an existing hospital stay;
d. Results in disability persistent or significant disability/incapacity, or:
e. Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above. Serious adverse events will be captured beginning on Day 1 when participants consent to the study and continuing one month following the last dose of study agent.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the DSMB Coordinator. All SAEs which meet the criteria for a reportable event will be reported to the University of Arizona Human Subjects Protection Program and the Stony Brook University Human Subjects Protection Program within 10 working days of the event date or receipt of notification of the event.

Reportable events must meet all three of the following criteria

a. Unanticipated or unexpected in nature, frequency or severity, AND
b. Related or possibly related to participation in the research (there is a reasonable possibility that it is related), AND
c. The event suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (not already referenced in existing study documents, such as the protocol, consent form or Investigator's Brochure).

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every six months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

30.3 Plan for assuring data accuracy and protocol compliance

Routine study activity and safety information will be reported to the DSMB every six months, or more frequently if requested. These reports will include:

a. Study activity, cumulative and for the period under review;
b. Safety (narrative description on non-serious and serious adverse events);
c. Predetermined protocol early stopping rules for efficacy/futility;
d. Monitoring and protocol compliance;
e. Comments
f. Annual reports from specialty DSMB for review of cardiovascular toxicity
g. Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.
h. Data, safety and study progress will be reported to:
    I. Human Subjects Protection Program (IRB) at least annually;
    II. Sponsor (if applicable) at least every six months.
    III. Sponsor or funding agency, as applicable: The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study.

30.4 Additional Adverse Events Reporting

All SAEs which meet the criteria for a reportable event will be reported to the University of Arizona Human Subjects Protection Program, the Stony Brook University Human Subjects Protection Program and to the FDA within 10 working days of the event date or receipt of notification of the event. The holder of the IND is responsible for reporting of all SAEs in an appropriate fashion and timeline as mandated by law.

31 PARTICIPANT PAYMENT

Participants will be reimbursed $50.00 for the time necessary to obtain MRI imaging, urine, blood, and adverse events logs at the baseline visit(s), and at 6 and 12 months on sulindac/study visits (total maximum $200 for sulindac group, $150 for observation group).

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