A Randomized, Double-blind, Placebo-controlled Study of 4-hydroxytamoxifen Topical Gel in Women with Mammographically Dense Breast

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Abstract

Background: Tamoxifen uptake for risk reduction has remained low due to concerns about toxicity despite the efficacy and effectiveness data available. Studies of tamoxifen in the adjuvant and preventive setting have demonstrated that a decline in mammographic density (MD) of approximately 10% is consistently associated with better outcomes. Additionally, MD is one of the strongest independent predictors of breast cancer risk, apart from older age and *BRCA1/2* mutation, among women. 4-hydroxytamoxifen topical gel (4-OHT) is a transdermal agent, shown in preliminary studies to be well-tolerated with similar decreases in Ki-67 to oral tamoxifen in presurgical DCIS studies and significant drug concentration in breast parenchyma but very low levels in the systemic circulation. This study examines changes in MD, a potential surrogate biomarker of prevention activity, as the primary endpoint for this one-year early-phase prevention trial using 4-OHT gel in high-risk women.
Trial design: Multicenter, randomized, placebo-controlled study of 4-OHT gel (2mg per breast) versus placebo in 158 women with heterogeneously or extremely dense breast tissue for 12 months using standard of care imaging, stratified by enrollment site and baseline breast density category.
The primary objective of this study is to evaluate the change in percent MD (using Cumulus software) from baseline to the week 52 in women applying 4 mg (2mg per breast) 4-OHT gel versus placebo. The secondary objectives are to compare the Cumulus vs Volpara breast density measurement methods; evaluate the percentage of women with lowering of BIRADS density; estimate percentage of women with ≥ 10% absolute decrease in quantitative MD percentage; explore patient reported experience assessed by BESS questionnaire; laboratory toxicity assessment (F VIII, vWB factor, SHBG, lipid profile); compare the 2D vs. 3D breast density measurement methods to estimate percent change in mammographic breast density; evaluate serum measurements of parent drug and related metabolite levels and factors related to 4-OHT exposures, such as IGF pathway members, CRP, estradiol, and 4-OHT; collect tissue for biomarkers (among women undergoing optional pre- and post-treatment biopsies); examine the persistence in change of mammographic density one year after 4-OHT vs. placebo gel application has stopped.
Eligibility criteria: Inclusion: Women age 40-69 years, or less than 40 years if 5-year breast cancer Gail risk is greater than/equal to 1.66%; heterogeneously or extremely dense breast tissue based on mammography. Exclusion: abnormal uterine bleeding, or prior diagnosis of endometrial hyperplasia, endometrial polyps, or endometrial cancer; prior use of SERMS and AIs, except for a maximum of 3 months and at least 12 months prior.
Statistical methods: Considering an attrition rate of 19%, 128 evaluable women are expected to have both baseline and 52-week measurements of percent MD. With 64 women in each group, there is 80% power to detect a decrease of 6% in the 4-OHT group versus 2% in the placebo group with a common standard deviation of 8% using a two-sided t-test with a significance level of 0.05.
Study accrual: Activated January 2018. Reached full accrual of 158 participants on 10/27/2020.

Trial Schema

Women age 40-69 years, or less than 40 years if Gail risk is greater than 1.66% with mammographically dense breast (hetereogenously dense or extremely dense based on ACR BIRADS 4th or 5th edition classification)

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Baseline measures: Mammographic density, liver function tests, Tamoxifen exposure/toxicity: BESS questionnaire, Tamoxifen metabolites, estradiol, SHBG, IGF related markers, CRP, vWB Factor, F VIII, lipid profile
Optional breast biopsy: Tissue biomarkers: TDLU involution. Collagen structural changes, estrogen related transcription (SET index), Ki-67, COX-2, p16, CD68

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Randomization 1:1 stratified by study site and baseline breast density (heterogenously (C) or extremely (D) dense)

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Intervention: 2mg per breast 4-OHT gel versus placebo gel applied to both breast per day for 12 months

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Clinic visit at 6 months (can be a telephone visit if affected by COVID-19), phone calls at 1, 3 and 9 months

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Final clinic visit at 12 months (repeat baseline measures and optional breast biopsy; can be a telephone visit if affected by COVID-19)

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Post- Intervention follow-up at 24 months (up to 32 months for participants affected by COVID-19). Standard of care bilateral mammogram

Primary Endpoints

- To estimate and compare the percent change in mammographic breast density (using Cumulus software) from baseline to Month 12 in women applying 2mg 4-OHT gel per breast versus placebo.

Secondary Endpoints

- To compare the Cumulus vs. Volpara breast density measurement methods to estimate percent change in mammographic breast density from baseline to Month 12 in women applying 2mg of 4-OHT gel per breast vs. placebo.
- To compare the percentage of women who underwent a change in BIRADS density category, comparing pre-and post- treatment measurements, for recipients of active agent versus placebo.
- To estimate percentage of women with ≥ 10% absolute decrease in quantitative mammographic density percentage between baseline and 12 months, comparing treated group (2mg per breast 4-OHT gel) to placebo.
- To compare the 2D vs. 3D breast density measurement methods to estimate percent change in mammographic breast density from baseline to Month 12 in women applying 2mg of 4-OHT gel per breast vs. placebo.
- To describe symptoms assessed by BCPT Eight Symptom Scale (BESS) questionnaire and laboratory toxicity assessment (Factor VIII (F VIII), Von Willebrand (vWB) factor, Sex Hormone-Binding Globulin (SHBG), lipid profile).
- To evaluate serum measurements of 4-OHT and related metabolite levels and factors related to tamoxifen exposures, such as Insulin-like growth factor (IGF) pathway members, C-reactive protein (CRP), estradiol.
- To evaluate tissue biomarkers (among women undergoing optional pre- and post-treatment biopsies):
  Terminal duct lobular unit (TDLU) Involution
  Collagen structural changes
  $SET_{ER/PR}$ index: estrogen related transcription
  Ki-67, COX-2, p16, CD68.
- To examine whether any reductions in mammographic density seen after 1 year of 4-OHT vs. placebo gel application persist at 24 months, one year after gel application has stopped

Inclusion Criteria

- Women age 40-69 years, or less than 40 years if 5-year breast cancer Gail risk is ≥ 1.66%.
- Mammographically dense breast (heterogeneously dense (C) or extremely dense (D), based on ACR BIRADS© fifth edition classification or heterogeneously dense (3) or extremely dense (4), based on ACR BIRADS© fourth edition classification) in either breast.
- ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix A)
- Participants must have normal organ and marrow function defined as ALL of the below:
  - White Blood Cells ≥3,000/microliter
  - Platelets ≥100,000/microliter
  - Total bilirubin ≤1.5X institutional upper limit of normal (ULN)
  - AST (SGOT)/ALT (SGPT) ≤1.5X ULN
- Participant must have a gynecology examination within the last 5 years (gynecology examination is not required if participant had a hysterectomy).
- Premenopausal women using a hormonal or non-hormonal Intra-Uterine Device (IUD) birth control method will be eligible, if they have been on the same IUD for at least 3 months prior to enrollment and plan to continue using the same method throughout the study.
- Women who are using postmenopausal hormones, and are planning to continue the same regimen through the study intervention are eligible to participate.
- Willingness to avoid exposing breast skin to natural or artificial sunlight (i.e. tanning beds) for the duration of the study.
- Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to 4-OHT gel.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, thromboembolic disease, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant, unwilling to use adequate contraception during study treatment duration, had given birth, or nursed at any time during the last 12 months
- Women with a previous history of invasive breast cancer or bilateral DCIS or current untreated DCIS. Women with a history of cancer within the last 3 years, except for non-melanoma skin cancer. Women with unilateral DCIS (with or without radiation therapy) are eligible as long as they have an unaffected breast.
- Prior bilateral breast surgery (mastectomy, segmental mastectomy, or breast augmentation surgery including breast implants or breast reductions).
- Women with "mosaic mammographic screening views", i.e., whose larger breast size precludes being imaged within a single mammographic screening view.
- Women with active liver disease.
- Women with a uterus and abnormal uterine bleeding, or prior diagnosis of endometrial hyperplasia, endometrial polyps, or endometrial cancer.
- Prior use of SERMS and AIs, except for a maximum of 3 months and at least 12 months prior.
- Skin lesions on the breast that disrupt the stratum corneum (e.g., eczema, ulceration).
- Treatment with any investigational drug or investigational biologic within 30 days of initiating study treatment or during the study.

Statistical Considerations

- A total of 158 women enrolled and randomized 1:1 into one of two groups: placebo or 4-OHT gel 2 mg per breast. Treatment will last for 52 weeks. Considering an attrition rate of 19%, we expect to have 128 evaluable women who will have both baseline and 52-week measurements of percent MD of the breast, 64 women in each group.

- With 64 women in each group, we will have an 80% power to detect a minimum decrease of percent MD of 6% in treatment group against 2% in placebo group, with a common standard deviation of 8%, using a two-sided t-test with a significance level of 0.05. The proposed difference between the active treatment and placebo groups and the standard deviation are based on conservative estimates from the published work by Cuzick et al [8]. The sample size calculation was performed using nQuery + nTerim 3.0.

- Stratification by study site and baseline breast density category (heterogeneously dense (C), extremely dense (D)) using random permutated block design with the block size of 4

Study Drug Administration

- Patients will self administer 4-OHT/placebo gel daily to both breasts
- Each 4-OHT/placebo gel canister contains~100 mL gel product (200 mg of 4-OHT in 100 mL of gel) and will be metered to dispense 2 mg of 4-OHT per pump.
- Daily dose of gel application is 4 mg (2 mg per breast).

Toxicity

Grade	Relationship	Arm 1	Arm 2	Total
3	Possible	2	1	3
3	Unlikely	1	2	3
3	Unrelated	7	6	13
	Grade 3 Totals	10	9	19
2	Definite	3	0	3
2	Possible	12	12	24
2	Probable	4	4	8
2	Unlikely	8	20	28
2	Unrelated	39	46	85
	Grade 2 Totals	66	82	148
1	Definite	4	0	4
1	Possible	51	31	82
1	Probable	7	18	25
1	Unlikely	16	34	50
1	Unrelated	60	33	93
	Grade 1 Totals	138	116	254

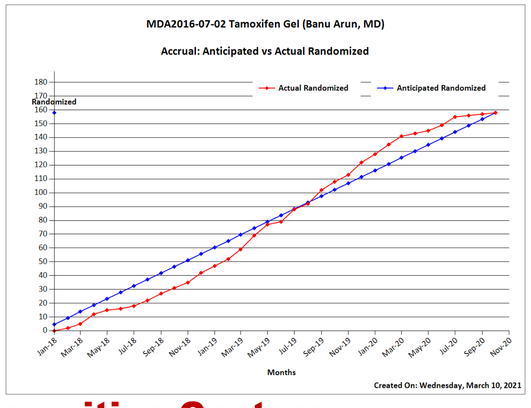
The table summarizes all adverse events (AEs) by grade, relationship, and treatment arm of all 158 patients randomized.
Patients appear in this table for each AE they experienced; a patient may have had multiple toxicities. A total of 421 AEs have been recorded, 19 Grade 3, 148 Grade 2, and 254 Grade 1.

Of all recorded AEs, the most prevalent Grade 3 toxicities included: (21.1%) Neoplasms Benign; (10.5%) Gastrointestinal Disorders; and (10.5%) Appendicitis. All other Grade 3 AEs had a prevalence < 5.6%.
Grade 3 AEs that were "Possibly" related to study agent were Cataract (1 participant), Headache (1 participant) and Elective Hysterectomy in a participant with a family history.

The most prevalent Grade 2 toxicities included: (7.4%) Hot Flashes, (5.4%) Sinusitis, and (5.4%) Upper Respiratory Infection. All other Grade 2 AEs had a prevalence < 5.0%.

Accrual

Maximum Accrual on the trial was achieved on 10/27/2020.



Recruiting Centers

UT MD Anderson Cancer Prevention Agent Development Program: Early Phase Clinical Research Consortium; Consortium PI: Powel H. Brown, MD, PhD

- UT MD Anderson Cancer Center; Lead Protocol PI: Banu Arun, MD
- Dana-Farber Cancer Institute; PI: Judy E. Garber, MD, MPH
- Moffitt Cancer Center; PI: Nagi B. Kumar, PhD, RD, FADA
- Northwestern University; PI: Seema Khan, MD
- University of Arizona; PI: Pavani Chalasani, MD, MPH
- University of Minnesota; PI: Heather C Beckwith, MD
- University of Wisconsin; PI: Lee G. Wilke, MD

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