

COVER PAGE

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A Phase I Dose Escalation Study of Topical Bexarotene in Women at High Risk for Breast Cancer

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SCHEMA

A Phase I Dose Escalation Study of Topical Bexarotene in Women at High Risk for Breast Cancer

Part 1: Dose Escalation Group

Screening/Baseline Clinic Visit Day -30 to 0

Women with ADH, ALH, LCIS, Breast cancer survivors (DCIS or invasive) ≥ 5 years from their diagnosis, BRCA 1/2 mutation carriers, or elevated risk for breast cancer $\geq 1.7\%$ in 5 years or lifetime risk $\geq 20\%$



Intervention (N=30) Dose Assignment by a 3+3 dose escalation with 3 dose levels (Day 0):

Bexarotene 1% gel 10mg/breast/every other day or Bexarotene 1% gel 10mg/breast/daily or Bexarotene 1% gel 20mg/breast/daily for treatment duration of 4 weeks



Start Treatment (Day 1)



Phone Call (Day 8)

Assess AEs and review Gel Diary



Study Visits (Day 15 and Day 28 (End of Study))

Assess for AEs & review gel diary. Labs to assess safety (CBC, LFTs, Lipid Profile, Thyroid Function Tests, Calcium) on Day 15 and 28 visits. Serum bexarotene collected on Day 0 and Day 28 visit. Optional breast biopsy at Day 28 visit.



Follow Up Call (30 days \pm 7 days after Day 28)

Assess for any further AE and document resolution of any acquired AE during treatment



Primary Endpoint: Safety and Toxicity

Secondary Endpoints: Serum and Tissue Bexarotene level, calcium, lipid and thyroid function biomarkers

Part 2: Dose Expansion Group

Screening/Baseline Clinic Visit Day -30 to 0

Women with ADH, ALH, LCIS, Breast cancer survivors (DCIS or invasive) that are ≥ 5 years from their diagnosis, BRCA 1/2 mutation carriers, or elevated risk for breast cancer $\geq 1.7\%$ in 5 years or lifetime risk $\geq 20\%$



Intervention (N=10) (Day 0):

Bexarotene 1% gel at maximum tolerated dose from Part A Dose Escalation Group for 4 weeks.



Start Treatment (Day 1)

Start application of bexarotene gel to one unaffected breast



Phone Call (Day 8)

Assess adverse events and review Gel Diary



Study Visits (Day 15 and Day 28 (End of Study))

Assess for AEs & review gel diary. Labs to assess safety (CBC, LFTs, Lipid Profile, Thyroid Function Tests, Calcium) on Day 15 and 28 visits. Serum bexarotene collected on Day 28 visit. Mandatory breast biopsy at Day 28 visit.



Primary Endpoint: Safety and Toxicity

Secondary Endpoints: Serum and Tissue Bexarotene level, calcium, lipid and thyroid function biomarkers



Follow Up Call (30 days \pm 7 days after Day 28)

Assess for any further AE and document resolution of any acquired AE during treatment

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1. OBJECTIVES

The overall objective is to evaluate the safety and toxicity of topical bexarotene 1% gel to the breast in healthy women at high risk for breast cancer and bexarotene concentration in the breast tissue.

1.1 Primary Objectives

A. Dose Escalation Group

We will conduct a trial to determine the recommended phase II dose of topical bexarotene 1% (w/w) gel for evaluation in healthy women. This will be determined by assessing the safety and toxicity of topical bexarotene gel application (tested at three different dose levels by dose escalation, 10 mg (1 mL) every other day, 10 mg (1 mL) daily, or 20 mg (2 mL) daily to an unaffected breast of healthy women at high risk for breast cancer for a duration of 4 weeks.

B. Dose Expansion Group

We will conduct an intervention of topical 1% bexarotene gel to an unaffected breast of healthy women at high risk for breast cancer for 4 weeks at the maximum tolerated dose (MTD) as determined during the dose escalation group phase to assess bexarotene concentration in the breast tissue.

1.2 Secondary Objectives

1. To detect bexarotene concentration in the serum at baseline and at 4 weeks of treatment.
2. To detect bexarotene concentration in the breast tissue at 4 weeks of treatment in the dose escalation group.
3. To investigate the effects of topical bexarotene on serum biomarkers we will determine the change from the baseline in:
 - i. Lipid Biomarkers (Total Cholesterol, triglycerides, LDL, HDL)
 - ii. Thyroid Function Biomarkers (Thyroid Stimulating Hormone (TSH), T4, T3)
 - iii. Calcium

1.3 Exploratory Objective (Dose Expansion Group)

To examine changes in gene expression associated with retinoid action.

2. BACKGROUND

2.1 Breast Cancer Prevention

Breast cancer is the most common malignancy among women in the US, and prevention of this disease is therefore a major public health concern. Chemoprevention with anti-estrogens, including tamoxifen, raloxifene, and exemestane, has been shown to reduce the incidence of hormone receptor (HR)-positive breast cancer. However, agents that can reduce the incidence of hormone receptor negative breast cancer are currently lacking.

2.2 Bexarotene

Retinoids are vitamin A analogues that have been shown to be involved in cell differentiation, growth, and apoptosis (1). They exert their effects by binding to two specific classes of receptors known as the retinoic acid receptors (RAR) and retinoic X receptors (RXR). Once activated, RARs and RXRs form heterodimers and function as transcription factors and subsequently bind to retinoic acid response elements (RARE) and regulate

gene expression regulating cell differentiation, growth, and apoptosis (2, 3). Retinoids are similar agents but only activate the RXR receptors without activating the RAR nuclear receptors. Bexarotene is a retinoid that has been studied extensively and is currently an FDA approved treatment for cutaneous T cell lymphoma (CTCL).

Oral bexarotene was evaluated in phase 2 and 3 clinical trials for refractory or persistent early stage CTCL. Duvic et al. randomized 58 patients to two doses of bexarotene at 6.5mg/m² per day and 650mg/m² per day which was later modified to 300mg/m² per day for at least 16 weeks or until progression. Responses of greater than 50% improvement in skin lesions were noted in 20% of patients at 6.5mg/m² and 54% of patients had a response at 300mg/m² and 67% of patients at doses greater than 300mg/m². Seventy-three percent of patients that crossed over from 6.5mg/m² to higher doses responded with the increased dose. Hypertriglyceridemia, hyperlipidemia, headache, and hypothyroidism were noted in a significant number of patients and were reversible with discontinuation of drug. Since increased toxicity was noted at dose level greater than 300mg/m², recommended dose is 300mg/m² in patients with refractory CTCL (4).

Bexarotene has been developed as a gel and has been evaluated in clinical trials in patients with early stage CTCL. Based on the positive results of these studies, topical bexarotene is currently an FDA approved drug for the treatment of CTCL. In phase I and II trials conducted by Breneman and colleagues, topical bexarotene was applied to the skin lesions directly at different concentration levels of 0.1%, 0.5%, and 1% bexarotene gel. Patients started at the lowest concentration and applied the gel to affected skin lesions daily and titrated to twice daily dosing after 2 weeks and were tolerating the medication. As patients were able to tolerate gel application, bexarotene concentration was increased to 0.5% and then 1% and applying gel up to 4 times daily if tolerated. Most patients were able to tolerate 1% gel at twice daily dosing. The total dosage each patient received depended on the size and the number of lesions. Bexarotene gel was well tolerated and the most frequent adverse events in 67 patients were rash (73%), pruritus (33%), and pain (24%) with most being mild to moderate in severity. Systemic concentrations of bexarotene were extremely low and systemic side effects noted with oral bexarotene such as hyperlipidemia, hypothyroidism, and hypertriglyceridemia were not detected when medication was applied topically(5). Bexarotene 1% gel was also evaluated in a Phase I/II trial for alopecia areata and was applied to half of participants' scalp to assess response. Out of 42 patients, 31 (73%) experienced some dermal irritation with only 4 patients experiencing grade 3 dermal irritation. Most common adverse event noted was mild erythema in the area of treatment that resolved with discontinuation of the drug (6).

2.3 Rationale

In preclinical mouse models that develop ER-negative breast cancers, bexarotene showed significant activity in delaying mammary tumor development. In p53-null mice, bexarotene was given at 10mg/kg and 100mg/kg by gastric gavage and a 75% reduction in mammary tumor development was found in virgin mice at the higher dose level (7). In mouse mammary tumor virus (MMTV)-ErbB2 transgenic mice, focal tumors develop at eight months. Similar to humans, (MMTV)-ErbB2 mice undergo a multistage process of mammary tumorigenesis that progresses from normal mammary tissue to hyperplasia, mammary intraepithelial neoplasia (MIN) and finally invasive cancer. Li and colleagues gave bexarotene at 100mg/kg by oral gavage for 2 to 4 months in MMTV-erbB2 transgenic mice starting at three months of age. They found that bexarotene prevented the development of premalignant mammary lesions such as hyperplasia and MIN that is similar to human ductal carcinoma in situ (8).

Based on these preclinical findings, oral bexarotene at 200mg/m² has been evaluated in women at high risk for breast cancer based on their genetic risk. Bexarotene was found to reduce cyclin D1 RNA expression in breast cells from postmenopausal women (9). A nonsignificant reduction in Ki-67 expression was also seen in these post-menopausal women. Significant systemic side effects such as hypertriglyceridemia, hypercholesterolemia, and hypothyroidism were also found and were reversible after discontinuation of the drug(9). These results demonstrated that bexarotene has a biological effect on breast cells in women at high risk of breast cancer.

In addition to repressing cyclin D1 in breast cancer cells, bexarotene has shown effects on cyclin D1 in lung cancer cell lines. Dragnev et al. showed that the combination of bexarotene 1-4 μ mol/L plus erlotinib 1-4 μ mol/L significantly decreased cyclin D1 expression in cyclin-E- and KRAS/p53-driven transgenic lung cancer cell lines. The combination of bexarotene 400mg/m² per day plus erlotinib 150mg daily was evaluated in early stage non-small cell lung cancer patients in a window of opportunity trial and significant decreases in cyclin D1 were noted as well as an induction of necrosis and inflammatory responses (10).

Topical Therapies in Chemoprevention

Uptake has been low in chemoprevention medications such as tamoxifen and raloxifene due to its systemic side effects of menopausal symptoms and blood clots. Topical creams applied directly to the breast could affect the breast tissue without leading to systemic side effects. Mauvais-Jarvis and colleagues evaluated trans-4-hydroxytamoxifen (4-OHT), an active metabolite of tamoxifen, by topical administration to the breast. They evaluated 4-OHT absorption through the skin and its metabolism. Topical 4-OHT was applied directly over the breast in patients with invasive breast cancer and subsequently underwent mastectomy for their tumor. Concentration of 4-OHT was evaluated in breast tissue cytosol as well as nuclear extract and plasma samples taken at the time of surgery. 4-OHT was detected in the cytosol as well as in the nuclear extract as early as 24 hours of application and decreased in concentration over time at 7 days after application. Plasma concentrations of 4-OHT was low but 4-OHT metabolites were present in the plasma but not detected in the breast tissue. This showed that topical application bypassed the first pass hepatic metabolism of the drug. Mauvais- Jarvis *et al.* also evaluated the topical application of 4-OHT on the breast versus the abdomen and found retention of the drug in the breast and delayed plasma concentrations of 4-OHT when compared to application on the abdomen (11).

Rouanet *et al.* evaluated 4-OHT in a pre-surgical trial of 55 postmenopausal women with invasive ER positive breast cancer. Patients applied 4-OHT for 2 to 3 weeks at various dose levels compared to another group receiving oral tamoxifen at 20mg/day. They found that tissue proliferation decreased as measured by Ki-67 levels between baseline and after treatment. There was a significant decrease in proliferation in the topical treatment arms with lower plasma concentrations of tamoxifen compared to oral treatment (12). Lee and colleagues evaluated 4-OHT in women with DCIS for 6 to 10 weeks prior to surgery. Women were randomized to either 4-OHT (4mg/day) or oral tamoxifen (20mg/day) and assessed change in Ki-67 in their DCIS lesions. Tissue concentration of drug was similar between 4-OHT and oral tamoxifen whereas systemic concentrations of 4-OHT were lower than oral tamoxifen. Changes in proliferation were also similar across both arms. No serious adverse events were noted with 4-OHT in this study. Bexarotene is similar to retinoids and thus more likely to have skin reactions than 4-OHT (13).

We hypothesize that topical bexarotene can be applied to the breasts as a chemoprevention agent with penetration to the breast tissue and without having high systemic levels of drug and subsequent side effects and toxicity as seen with oral bexarotene. Data from chemoprevention studies with topical tamoxifen support the concept of topical agents penetrating into the breast tissue and exhibiting biological activity in the tissue. Preclinical models have clearly shown the effect of bexarotene in reducing the incidence of estrogen receptor negative breast cancer. Based on this data, we propose a phase I study to evaluate topical bexarotene in women at elevated risk for developing breast cancer.

Rationale for including Alcohol and Tobacco Assessment Questionnaires

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline and (include follow-up timepoint), to determine the potential impact of tobacco and

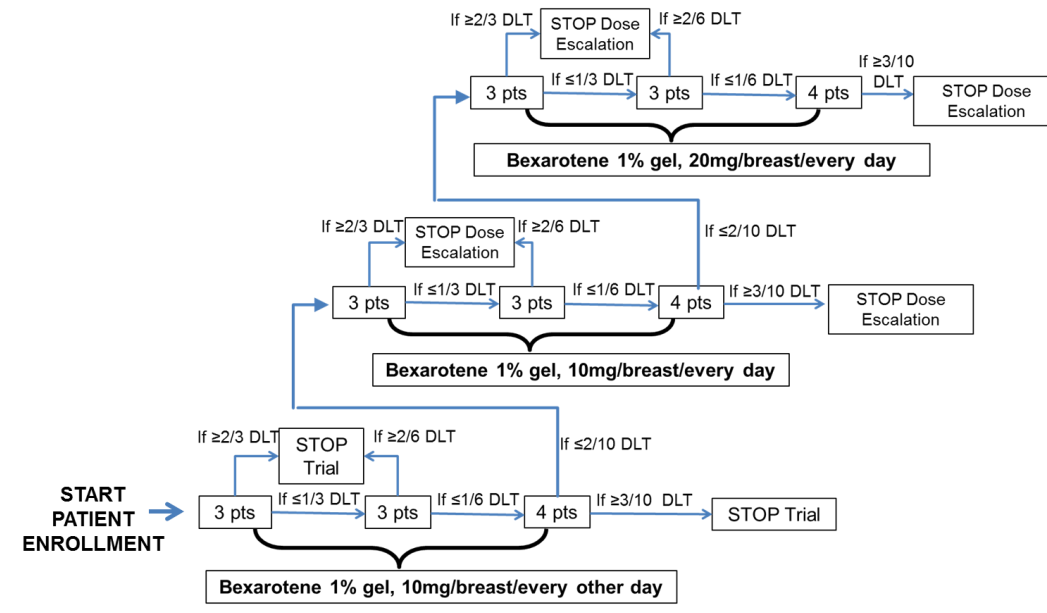
alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

A. Dose Escalation Group

We will recruit women at high risk for breast cancer to this phase I study. We will use topical bexarotene 1% gel and this will be applied to one unaffected breast for 4 weeks. Participants will be assigned to one of three different dose levels. Bexarotene gel volume is estimated to be 1ml for 1g of gel which contains 10mg of bexarotene. Therefore, the three dose cohorts will be 10mg (1ml) every other day, 10mg (1ml) daily, 20mg (2ml) daily. Dose Limiting Toxicity (DLT) is defined as a grade 2 skin adverse event that persists for at least 6 days or any grade 3 or greater adverse event possibly, probably, or definitely related to the study drug. In addition, a DLT will be a grade 2 skin adverse event that recurs and persists for at least 3 days. A conservative modification of the standard “3+3” design will be applied. The first three participants will be assigned to the lowest dose level. New cohorts of 3-4 participants will not be treated until toxicity has been evaluated for all current participants for 4 weeks. Group assignment algorithm is explained in Section 13.4 and dose escalation is illustrated in Figure 1. The Maximum Tolerated Dose (MTD) will be defined as the highest dose level with at most 2 participants with DLT in 10 participants treated.

Figure 1: Dose Escalation Schema for Bexarotene 1% gel



Bexarotene gel will be provided by Valeant pharmaceuticals and repackaged by DCP pharmacy in dose metered pumps for dispensing the correct dose for application. Participants will begin application of the gel to the upper outer and upper inner quadrants of one breast every other day for one week and then increase to daily for 3 weeks if they are assigned to daily dosing arm. If participants are assigned to every other day dosing, they will continue in this manner for the entire 4 weeks. Participants that are assigned to 20 mg (2ml) daily will first start with application of 10mg (1ml) to the breast every other day for 1 week, then increase to 10mg (1ml) daily for 1 week, and then increase to 20mg (2ml) daily for the remaining 2 weeks as long as it is tolerated. Participants can also participate in an optional core breast biopsy of the upper outer or inner quadrant at the end of study treatment and receive compensation for additional expenses associated with the biopsy, such as additional travel expenses, time missed from work or other expenses associated with the biopsy visit. All participants will need

to come in for clinic visits for toxicity assessment and blood collection. All participants will receive a follow-up phone call from the site investigator or designee 30 days \pm 7 days after completion of study drug to assess for any further AE and document resolution of any acquired AE during treatment.

As of Oct 2019, enrollment was completed to the first dose cohort and the second dose cohort was stopped early due to DLTs. No DLTs were experienced in the first dose cohort of 10 patients that applied 10mg of bexarotene to the breast every other day. In the second dose cohort, participants applied 10mg daily after tolerating application of every other day for one week. Four participants were enrolled in this cohort and 1 participant withdrew early due to adverse events unrelated to study drug. Two DLTs were noted in the remaining patients and thus enrollment was stopped at the second dose level. Therefore, no patients will be enrolled to the third dose level due to concerns for toxicity. MTD is 10mg/breast/every other day.

B. Dose Expansion Group

A dose expansion group of additional 10 participants will be enrolled and treated at the MTD to further evaluate safety and drug penetration into the breast tissue. There will be a ramp up to the desired dose similar to the ramp up schedule in the dose escalation group. At any time in the dose expansion cohort, if there are $\geq 30\%$ DLT among participants, the trial will be terminated. Assessment for dose limiting toxicities will occur continuously as participants are enrolled into the dose expansion group. This will be determined after the third and each successive participant until 10 participants are in the group. Participants in this group will receive treatment for 4 weeks and undergo the same schedule of events as the dose escalation group. All participants in the dose expansion cohort will have a core breast biopsy at end of treatment and receive compensation for additional expenses associated with the biopsy, such as additional travel expenses, time missed from work or other expenses associated with the biopsy visit. All participants will receive a follow-up phone call from the site investigator or designee 30 days \pm 7 days after completion of study drug to assess for any further AE and document resolution of any acquired AE during treatment.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

- 4.1.1 Participants must be at high risk as defined by a history of breast cancer (invasive or DCIS) and be at least 5 years out from diagnosis, or lobular carcinoma in situ (LCIS), or proliferative benign breast disease such atypical ductal hyperplasia (ADH), atypical lobular hyperplasia(ALH) or genetic test confirmation of BRCA 1/2 mutation carrier or have a breast cancer risk assessment $\geq 1.7\%$ in 5 years or a lifetime risk $\geq 20\%$.
- 4.1.2 No evidence of disease (in situ or invasive cancer that would normally be treated by resection) at trial entry as determined by the investigator. Diagnosis of invasive cancer must be at least 5 years prior to initiation on trial.
- 4.1.3 Female ≥ 18 years as breast cancer is extremely rare in women less than 18 years.
- 4.1.4 ECOG performance status ≤ 1 (Karnofsky $\geq 70\%$; see Appendix A)
- 4.1.5 Participants must have normal organ and marrow function as defined below:
 - Leukocytes $\geq 3,000$ /microliter
 - Absolute neutrophil count $\geq 1,500$ /microliter
 - Platelets $\geq 100,000$ /microliter
 - Total bilirubin within normal institutional limits
 - AST (SGOT)/ALT (SGPT) $\leq 1.5 \times$ institutional upper limit of normal (ULN)
 - Creatinine $\leq 1.5x$ institutional ULN

Hemoglobin	≥10 g/dL
TSH	within normal institutional limits
Triglycerides	≤300 mg/dl
Total Cholesterol	≤300 mg/dl

- 4.1.6 ≥ 6 months from all previous breast cancer treatment (including endocrine therapy).
- 4.1.7 Participants must have adequate accessible breast tissue as determined by the treating physician, consisting of one breast unaffected by invasive cancer, which has not been radiated. A history of benign core biopsy of this breast will be permitted.
- 4.1.8 Participants need to have had any breast imaging with a normal/benign (bi-rads 1 or 2) result within 180 days of Day 0 and no further routine breast imaging planned during the course of the study (4 weeks). Exception: if the mammogram result was a bi-rads 0 and the imaging work-up (ultrasound and/or MRI) result comes back normal/benign (bi-rads 1 or 2) before treatment initiation, then participant is eligible.
- 4.1.9 For women of childbearing potential; negative pregnancy testing within 72 hours prior to or on study visit #1 (Day 0) and willingness to use adequate contraception during the study intervention. OR Post-menopausal defined as any one of the following 1) prior hysterectomy, 2) absence of menstrual period for 1 year in the absence of prior chemotherapy or 3) absence of menstrual period for 2 years in women with a prior history of chemotherapy exposure who were pre-menopausal prior to chemotherapy. In women of childbearing potential, effective contraception must be used for one month prior to the initiation of therapy, during therapy, and for at least one month following discontinuation of therapy. It is recommended that two reliable forms of contraception be used simultaneously. If participants are interested in enrolling and have not met the requirement for contraception, they will be seen in the clinic in 1 month for re-evaluation once they have met this requirement and ensure all other eligibility criteria is met prior to dose assignment.
- 4.1.10 Willingness to comply with all study interventions and follow-up procedures including the ability to apply the study drug to the breast.
- 4.1.11 Ability to understand and the willingness to sign a written informed consent document.
- 4.1.12 Ability to avoid exposure of the treated breast area to sunlight and artificial ultraviolet light during the use of bexarotene gel.

4.2 Exclusion Criteria

- 4.2.1 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bexarotene gel, oral or topical retinoids.
- 4.2.2 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.
- 4.2.3 Pregnant, or had given birth, or nursed at any time during the last 12 months.
- 4.2.4 Women with a history of any cancer within the last 3 years, except for non-melanoma skin cancer. See 4.1.1 as history of breast cancer must be at least >5 years from diagnosis.

- 4.2.5 Prior bilateral breast surgery (mastectomy, segmental mastectomy, or breast augmentation surgery including breast implants or breast reductions) or combination of breast radiation and surgery involving both breasts.
- 4.2.6 Prior history or evidence of metastatic breast cancer
- 4.2.7 Prior history of histologically confirmed bilateral invasive breast cancer.
- 4.2.8 Current use or <6 months since use of SERMS or Aromatase inhibitors or any other investigational treatment for breast cancer prevention or therapy.
- 4.2.9 Skin lesions that disrupt the stratum corneum (eg. eczema, ulceration) or any breakdown of the skin.
- 4.2.10 Current use of a retinol containing agent or any retinoid analogue drug within the last 30 days.
- 4.2.11 Dietary Vitamin A intake $\geq 5,000$ IU/day (as determined by dietary supplementation)
- 4.2.12 Treatment with any investigational drug or investigational biologic within 30 days of initiating study treatment or during the study.
- 4.2.13 History of HIV or active hepatitis C.

4.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4.4 Recruitment and Retention Plan

Participants will be recruited for enrollment on this trial from the cancer prevention center, with particular attention to enhancing racial, ethnic and socioeconomic diversity. Prior to enrollment, the study will be discussed in detail with the participant, and possible toxicities will be presented. The informed consent document will be reviewed with the participant by the study physician or other medical staff authorized by the participating institution to obtain Informed Consent. Please refer to the study-specific Recruitment and Retention Plan for more details.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups/Gel Application

Participants will self-administer the bexarotene gel. Gel will be applied to one unaffected breast after freshly washed, either by washcloth, shower, or bath, preferably in the morning, (in order to minimize potential transfer to the partner at night). If morning shower is not possible, the subject will wash the one unaffected breast with a washcloth before gel application, to remove the prior day's dose. If a morning swim is planned, application

should be after the swim. No washing or immersion in water should occur for at least 4 hours following gel application. The gel should not be used near fire, flame or while smoking since it is flammable due to alcohol. Once dry, the gel is no longer flammable. Detailed instructions regarding application are in Appendix B and a demonstration of gel application will occur during the Baseline/Dose Assignment visit. The treated breast should be covered at all times to avoid transfer to other people and protect from natural or artificial sunlight; contact is permitted after the treated area has been washed with soap and water and washing is allowable after a minimum of 4 hours post-application.

Each bexarotene gel canister will contain 33 mL gel product and will be metered to dispense 10 mg of 1% bexarotene gel per pump. Cohorts 1 and 2 will receive 1 bexarotene gel canister containing 30 reliable doses. Cohort 3 will receive 2 bexarotene gel canisters containing 30 reliable doses each for a total of 60 reliable doses. The expansion cohort will receive either 1 or 2 bexarotene gel canisters depending on the maximum tolerated dose (MTD) as determined during the dose escalation group phase to assess bexarotene concentration in the breast tissue.

5.2 Gel Administration/Run-in Procedures

Each Bexarotene gel canister will contain 30 reliable doses of product metered to dispense 1mL per actuation, 1g of bexarotene gel per actuation. One gram of bexarotene gel contains 10mg of active bexarotene.

Participants in all dose levels will be instructed to apply the gel at 10mg (1 mL) every other day to one unaffected breast for the first 7 days of treatment. After the Day 8 phone call and confirmation that toxicity is at an acceptable range, participants assigned to 10mg/breast/daily will increase applications to daily. Participants assigned to 10mg/breast/every other day will continue to apply gel every other day. Participants assigned to 20mg/breast/daily will increase from 10mg (1mL) every other day to daily application for another 7 days. After the Day 15 visit and confirmation of acceptable toxicity, participants will increase to 20mg (2 mL) to the one unaffected breast daily for the remaining 2 weeks. All participants will continue to apply the gel to one unaffected breast as directed for a duration of 4 weeks. Participants in the dose expansion group will apply the gel with the same ramp up schedule as those in the dose escalation group for that dose level.

Participants will also receive moisturizing lotion [CeraVe] that can be applied to the breast to reduce and prevent redness that can be related from the study drug. CeraVe will be provided to all participants and they will be instructed to apply to the treated breast in the evening or at least 4 hours after application of study drug so it will not interfere with the absorption of study drug.

5.3 Contraindications

Participants are to avoid exposure of the treated breast skin to natural or artificial sunlight. This includes sunbathing or the use of tanning beds with the breasts exposed. Also, women who have dermatologic conditions causing the breakdown of skin should not use bexarotene gel.

5.4 Concomitant Medications

Women who are receiving endocrine therapy for breast cancer treatment or chemoprevention including tamoxifen, letrozole, anastrozole, fulvestrant, or exemestane at the time of screening will not be eligible. Participants may not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to bexarotene or retinoids. Participants must limit vitamin A intake to <5,000 IU/day. Participants should not concurrently use products that contain DEET (N,N-diethyl-m-toluamide), a common component of

insect repellent products. Otherwise, there are no restrictions on other medications, herbs, and vitamin and mineral supplements (other than study agents) while participating in the study.

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included.

5.5 Dose Modification

For any grade 1 adverse events or grade 2 adverse events that are not hypertriglyceridemia or skin related, no dose modifications will be made. For any grade 2 skin toxicity possibly, probably, or definitely related to study drug that persists for 3 days, drug will be held for 3 days. Participants at the lowest dose level will restart gel application at every 3 days dosing for 3 days (1 dose) and then increase back to every other day dosing. If grade 2 skin toxicity recurs and persists for 3 days, drug application will be discontinued and will be classified as a DLT. Participants in the second dose level (10mg daily) will hold for 3 days if toxicity is noted and resume at 10mg every other day for 4 days (2 doses) and then increase back to daily dosing. Participants at the highest dose level (20mg daily) will hold for 3 days and resume at 10mg daily for 3 days (3 doses) and then increase back to 20mg daily. Participants experiencing Grade 3 or Grade 4 toxicities of any attribution will be taken off study drug. Please see Table 1 for dose modification algorithm.

Table 1: Dose Modification Algorithm for Grade 2 Skin Adverse Events related to Bexarotene Gel

Dose Level	If Grade 2 Skin AE Persists for 3 Days	Dose Modification (If Skin AE resolves to \leq Grade 1)	If Grade 2 Skin AE Recurs and Persists for 3 Days
10mg/breast/every other day	Hold Study Drug for 3 days	Restart drug application at 10mg/breast/every three days for 3 days (1 dose) and then increase to original dose	Stop Drug
10mg/breast/daily	Hold Study Drug for 3 days	Restart drug application at 10mg/breast/every other day for 4 days (2 doses) and then increase to original dose	Stop Drug
20mg/breast/daily	Hold Study Drug for 3 days	Restart drug at 10mg/breast/ daily for 3 days (3 doses) and then increase to original dose	Stop Drug

Hypertriglyceridemia is a known systemic side effect with oral bexarotene formulation and will be monitored throughout the study. If grade 1 hypertriglyceridemia is noted, lipid profile will be continued to monitor weekly and at Day 22 blood specimen will be added for monitoring. If grade 2 hypertriglyceridemia is noted, drug will be held for 1 week and triglycerides will be rechecked. If normal, drug application will be resumed at the 1 dose level below. If triglycerides continue to be elevated or increase again, drug will be discontinued. If grade 3 hypertriglyceridemia is noted, drug will be discontinued and participant will be initiated on a statin. Triglycerides will be checked weekly until resolution and if elevation persists after 30 days, participant will be referred to their primary care physician for further management.

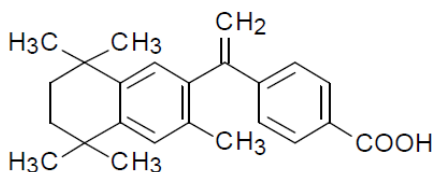
5.6 Adherence/Compliance

- 5.6.1 Participants will be considered compliant if they took 75% of their bexarotene gel dose.
- 5.6.2 The following methods will be used to monitor each participant's agent compliance:
- 1) Participants will be given a Gel Diary and instructed to initial it each time a dose is taken.
 - 2) Canisters will be weighed when released and also upon return.

6. PHARMACEUTICAL INFORMATION

6.1 Bexarotene (*IND #, NCI, Division of Cancer Prevention*)

Targretin® (bexarotene) 1% gel contains bexarotene and is intended for topical application. Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl] benzoic acid, and the structural formula is as follows:



Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of C₂₄H₂₈O₂. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP. Bexarotene gel is a clear gelled solution containing 1.0% (w/w) bexarotene in a base of dehydrated alcohol, USP, polyethylene glycol 400, NF, hydroxypropyl cellulose, NF, and butylated hydroxytoluene, NF.

Plasma concentrations of bexarotene were determined during clinical studies in patients with CTCL or following repeated single or multiple-daily dose applications of bexarotene gel 1% for up to 132 weeks. Plasma bexarotene concentrations were generally less than 5 ng/mL and did not exceed 55 ng/mL. However, only two patients with very intense dosing regimens (> 40% BSA lesions and QID dosing) were sampled. Plasma bexarotene concentrations and the frequency of detecting quantifiable plasma bexarotene concentrations increased with increasing percent body surface area treated and increasing quantity of bexarotene gel applied. The sporadically-observed and generally low plasma bexarotene concentrations indicated that, in patients receiving doses of low to moderate intensity, there is a low potential for significant plasma concentrations following repeated application of bexarotene gel. Bexarotene is highly bound (>99%) to plasma proteins. The plasma proteins to which bexarotene binds have not been elucidated, and the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene binding have not been studied. The uptake of bexarotene by organs or tissues has not been evaluated.

Four bexarotene metabolites have been identified in plasma following oral administration of bexarotene: 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. In vitro studies suggest that cytochrome P450 3A4 is the major cytochrome P450 responsible for formation of the oxidative metabolites and that the oxidative metabolites may be glucuronidated. The oxidative metabolites are active in in vitro assays of retinoid receptor

activation, but the relative contribution of the parent and any metabolites to the efficacy and safety of bexarotene gel is unknown.

The renal elimination of bexarotene and its metabolites was examined in patients with Type 2 diabetes mellitus following oral administration of bexarotene. Neither bexarotene nor its metabolites were excreted in urine in appreciable amounts.

6.2 Reported Adverse Events and Potential Risks

The safety of bexarotene gel has been assessed in clinical studies of 117 patients with CTCL who received bexarotene gel for up to 172 weeks. In the multicenter open label study, 50 patients with CTCL received bexarotene gel for up to 98 weeks. Patients in the CTCL trials were instructed to apply a generous layer of the gel to the CTCL lesion starting at every other day dosing and gradually applied more frequently up to two or four times a day. This area was variable by patient but resulted in a larger volume compared to this phase I trial in which the application is limited to 1ml of bexarotene gel to only one breast which is approximately 1% of the body surface area. The mean duration of therapy for these 50 patients was 199 days. The most common adverse events reported with an incidence at the application site of at least 10% in patients with CTCL were rash, pruritus, skin disorder, and pain. Adverse events leading to dose reduction or study drug discontinuation in at least two patients were rash, contact dermatitis, and pruritus.

Of the 49 patients (98%) who experienced any adverse event, most experienced events categorized as mild (9 patients, 18%) or moderate (27 patients, 54%). There were 12 patients (24%) who experienced at least one moderately severe adverse event. The most common moderately severe events were rash (7 patients, 14%) and pruritus (3 patients, 6%). Only one patient (2%) experienced a severe adverse event (rash). In the patients with CTCL receiving bexarotene gel, adverse events reported regardless of relationship to study drug at an incidence of $\geq 5\%$ are presented in Table 2 (5).

Table 2. Incidence of All Adverse Events* and Application Site Adverse Events with Incidence $\geq 5\%$ for All Application Frequencies of Bexarotene Gel in the Multicenter CTCL Study

Body System/Preferred Term	All Adverse Events N = 50 n (%)	Application Site Adverse Events N = 50 n (%)
Skin and Appendages		
Contact Dermatitis ¹	7 (14)	4 (8)
Exfoliative Dermatitis	3 (6)	0
Pruritus ²	18 (36)	9 (18)
Rash ³	36 (72)	28 (56)
Maculopapular Rash	3 (6)	0
Skin Disorder (NOS) ⁴	13 (26)	9 (18)
Sweating	3 (6)	0
Body as a Whole		
Asthenia	3 (6)	0
Headache	7 (14)	0
Infection	9 (18)	0
Pain	15 (30)	9 (18)
Cardiovascular		
Edema	5 (10)	0
Peripheral Edema	3 (6)	0

Hemic and Lymphatic		
Leukopenia	3 (6)	0
Lymphadenopathy	3 (6)	0
WBC Abnormal	3 (6)	0
Metabolic and Nutritional		
Hyperlipemia	5 (10)	0
Nervous		
Paresthesia	3 (6)	3 (6)
Respiratory		
Cough Increased	3 (6)	0
Pharyngitis	3 (6)	0

* Regardless of association with treatment

Includes Investigator terms such as:

¹ Contact dermatitis, irritant contact dermatitis, irritant dermatitis

² Pruritus, itching, itching of lesion

³ Erythema, scaling, irritation, redness, rash, dermatitis

⁴ Skin inflammation, excoriation, sticky or tacky sensation of skin; NOS = Not Otherwise Specified

Bexarotene 1% gel was also evaluated in a Phase I/II trial for alopecia areata and was applied to half of participants' scalp to assess response. Out of 42 patients, 31 (73%) experienced some dermal irritation with only 4 patients experiencing grade 3 dermal irritation. Most common adverse event noted was mild erythema in the area of treatment that resolved with discontinuation of the drug (6).

6.3 Availability

Bexarotene 1% gel will be supplied by Valeant Pharmaceuticals and will be repackaged in metered dose pumps by the Division of Cancer Prevention (DCP), NCI.

Each bexarotene gel canister will contain 30 reliable doses of product metered to dispense 1mL per actuation, 1g of bexarotene gel per actuation. One gram of bexarotene gel contains 10mg of active bexarotene.

Cohorts 1 and 2 will receive 1 bexarotene gel canister containing 30 reliable doses. Cohort 3 will receive 2 bexarotene gel canisters containing 30 reliable doses each for a total of 60 reliable doses.

The expansion cohort will receive either 1 or 2 bexarotene gel canisters depending on the maximum tolerated dose (MTD) as determined during the dose escalation group phase to assess bexarotene concentration in the breast tissue.

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each Organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior

approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF) or an institutionally-approved accountability system. The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility may be delegated to the site coordinator, institutional pharmacist or their designees. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant. Dr. Thomas or her representatives will be responsible for study agent accountability for participants at UT MD Anderson Cancer Center. DCP requirements for agent accountability and the required forms are available on the DCP website.

6.6 Packaging and Labeling

Bexarotene gel is packaged by NCI, DCP Repository.

Bexarotene gel is packaged in a container-closure system which consists of a pouch in a canister, a 1 mL pump, and a protective cap that covers the pump. A single actuation delivers 1mL of gel at 1g/mL. Each canister will have a label printed with the concentration and weight of gel, expiration date, protocol number and “Bexarotene 1% Gel” along with the statement “Caution: New Drug- Limited by Federal law (US) to investigational use”. Each canister is packaged in a carton with the sample label. Detailed instruction for gel application will be provided.” The canister will also have a bright label “DO NOT DISCARD- PLEASE RETURN TO CLINIC”.

6.7 Storage

All study drug must be stored in a secure limited-access area. Store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F) in accordance with labeled storage requirements. Avoidance of humidity and protecting from light is not necessary and packaging will provide this protection. Investigational labeling will include instructions to keep the product out of the reach of children.

6.8 Registration

Screening and Registration into the DMI Database:

Once informed consent has been signed, participants will be registered into the DMI database. The DMI database will assign a participant's PID upon completion of the registration process.

Screening/Registration into site-specific databases:

The DMI is the database of record for the study. Registration should occur per the procedures outlined above. If the site staff needs to enter study data into site-specific electronic databases per institutional requirements, they should do so in accordance with their institutional policies and procedures.

Appropriate CRFs must be completed for any participant who signs an informed consent. If a consented participant is a screen failure and deemed ineligible, the following CRFs must be completed: 1) the Registration CRF; 2) the Inclusion and Exclusion CRFs showing why the participant is ineligible, 3) the Off-Study CRF, 4) the Adverse Event CRF, 5) the Concomitant Medication CRF and 6) the Verification CRF. If no Adverse Event and/or Concomitant Medications were assessed by the time the participant is deemed ineligible, the "NONE" box will be checked to complete both CRFs. All participants who sign an informed consent must formally go off study. All participant registration information will be entered into DMI. If a participant experiences a serious Adverse Event during the screening process, a Serious Adverse Event (SAE) form must be completed.

6.9 Blinding and Unblinding Methods

This is not a blinded study. Participants and the PI's team will not be blinded to the dose of bexarotene gel.

6.10 Agent Destruction/Disposal

At the completion of investigation, all undispensed study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List". The Guidelines and form are available on the DCP website. Unused drug, that has been dispensed to participants, but that is returned unused by the participants, will be disposed of by the site staff following institutional guidelines after canisters have been weighed and the weights have been recorded.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Test	Baseline Testing/Prestudy Evaluation/ Registration (Within 30 days prior to or on Day 0)	Day 0	Day 1	Day 8 ±2 days Phone Call	Day 15 ±2 days	Day 28 ±2 days	Follow Up Call 30 days ± 7 days after Day 28
Informed Consent	X						
Registration	X						
Medical History	X					X	
Confirm Eligibility		X					
Dose assignment		X					
Baseline Symptom Assessment	X						
Concomitant Medications	X					X	X
Vitals	X				X	X	
Physical Exam	X						
Breast Exam	X				X	X	
Breast Cup Size	X						
Weight/ Height/ Last Menstrual Period ^a	X					X	
Routine Laboratory Tests ^b	X				X	X	
Pregnancy Test ^c	X	X				X	
Research Blood Sample ^d		X				X	
Breast Imaging ^e	X						
Dispense Study Agent ^f		X					
Start Study Medication			X				
Adverse Events/ Symptom Assessment				X	X	X	X
Dermatology Evaluation ^g					X	X	
Review Gel Diary		X		X	X	X	
Collect Study Agent						X	
Core Biopsy ^h						X	
Tobacco and Alcohol Use Assessment	X ⁱ					X ^j	
Telephone Contact				X			X

- a) Do not repeat height measurement and last menstrual period data collection after Baseline Testing.
- b) Routine laboratory tests include: CBC (hemoglobin, hematocrit, RBC, WBC, platelet count) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and CMP (Na⁺, K⁺, Cl⁻, CO₂ (bicarbonate), BUN, creatinine, glucose), liver function tests (ALT, AST, total bilirubin, Alk Phos, Albumin), triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), thyroid stimulating hormone (TSH), free T3 and free T4, and calcium.
- c) In women of child bearing potential a pregnancy test (urine or serum) must be done within 30 days prior to D0. Within 72 hours prior to or on Day 0 the pregnancy test (urine or serum) will be repeated and results must be known before starting study drug. If a urine pregnancy test is performed, the test must be done in the clinic or in the lab. Repeat pregnancy test will be done at the end of study as well.
 - If pregnancy test result is positive at Baseline (any time before Day 0), the participant is a Screen Failure.

- If pregnancy test result is positive on Day 0, do not dispense the study agent, take participant off-study, complete the Off-Study Case Report Form (CRF), follow the pregnancy to term and complete the Outcome of Pregnancy Case Report Form (CRF).
 - If a pregnancy is discovered after Day 0, instruct the participant to stop applying the gel, take participant off-study, complete the Off-Study CRF, follow the pregnancy to term and complete the Outcome of Pregnancy CRF.
- d) Research blood sample for serum bexarotene level.
- e) Participants need to have had any breast imaging with a normal/benign (bi-rads 1 or 2) result within 180 days of Day 0 and no further routine breast imaging planned during the course of the study (4 weeks). Exception: if the mammogram result was a bi-rads 0 and the imaging work-up (ultrasound and/or MRI) result comes back normal/benign (bi-rads 1 or 2) before treatment initiation, then participant is eligible.
- f) Participants must be instructed to apply the last dose of their study medication on the last day of the study (Day 28).
- g) Dermatology evaluation within 72 hours of study visit if participant experiences a grade 3 skin event or continues to have a persistent grade 2 skin event despite dose modification.
- h) The core biopsy at Day 28 is optional for dose escalation cohort participants. The biopsy is mandatory for participants in the dose expansion cohort at Day 28. If the participant is on aspirin, non-steroidal anti-inflammatory drugs or Vitamin E, she will be instructed to discontinue these 7 days prior to the end of treatment biopsy.
- i) See Appendix D “Alcohol and Tobacco Use Assessment Questionnaires – Baseline”.
- j) See Appendix E “Alcohol and Tobacco Use Assessment Questionnaires – Follow Up”.

7.2 Baseline Testing/Prestudy Evaluation

Days -30 to 0: Baseline Testing/Prestudy Evaluation/ Registration

The following procedures will be conducted during Baseline Testing or within 30 days prior to Day 0:

- Informed consent must be obtained prior to starting any further study procedures.
- Registration: Once informed consent has been signed, participants will be registered into the DMI database. The DMI database will assign a participant’s ID upon completion of the registration process. Participants will also be registered into site-specific registry databases as applicable.
- Medical history, to include a review of breast cancer history (if applicable) and previous medical history, previous surgeries, reproductive history, family history, demographic information, including age and race.
- Use of concomitant medications will be reviewed.
- Baseline symptom assessment.
- A physical examination to include vital signs (blood pressure, heart rate, respiratory rate) and breast exam. Breast cup size will be documented.
- Height, weight to calculate body mass index (BMI). The day of the last menstrual period will be recorded.
- Pre-study routine laboratory evaluations will include the following:
 - HEMATOLOGY: CBC (hemoglobin, hematocrit, RBC, WBC, platelet count) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
 - CHEMISTRY: Na⁺, K⁺, Cl⁻, CO₂, BUN, creatinine, glucose
 - Liver Function: ALT, AST, Tbili, Alk Phos, Albumin
 - Lipid profile, thyroid function tests, and calcium
- In women of child bearing potential, a pregnancy test (urine or serum) must be done within 30 days prior to D0. Within 72 hours prior to or on Day 0 the pregnancy test (urine or serum) will be repeated

and results must be known before starting study drug. If a urine pregnancy test is performed, the test must be done in the clinic or in the lab.

- If pregnancy test result is positive at Baseline (any time before Day 0), the participant is a Screen Failure.
 - If pregnancy test result is positive on Day 0, do not dispense drug, take participant off-study, complete the Off-Study Case Report Form (CRF), follow the pregnancy to term and complete the Outcome of Pregnancy Case Report Form (CRF).
 - If a pregnancy is discovered after Day 0, instruct the participant to stop taking drug, take participant off-study, complete the Off-Study CRF, follow the pregnancy to term and complete the Outcome of Pregnancy CRF.
- Participants need to have had any breast imaging with a normal/benign (bi-rads 1 or 2) result within 180 days of Day 0 and no further routine breast imaging planned during the course of the study (4 weeks). Exception: if the mammogram result was a bi-rads 0 and the imaging work-up (ultrasound and/or MRI) result comes back normal/benign (bi-rads 1 or 2) before treatment initiation, then participant is eligible.
 - Tobacco and Alcohol Use Assessment, using the Baseline questionnaires. See Appendix D “Alcohol and Tobacco Use Assessment Questionnaires – Baseline”. Refer to Appendix F for resources for alcohol and tobacco quitting. These resources can be given to individuals if there is concern about alcohol or tobacco dependence. It is not expected that investigators will refer individuals for assistance or that they will undertake the care of individuals for alcohol or tobacco dependence.
 - Confirm eligibility: At the completion of the screening period, eligibility must be confirmed. Only after eligibility is confirmed, eligible participants can be assigned to a dose level and scheduled for the on study tests and procedures.

Day 0

The following procedures will be conducted on Day 0:

- For women of childbearing potential a pregnancy test must be completed within 72 hours prior to or on Day 0. Either a serum or urine pregnancy test may be performed. If a urine pregnancy test is performed, the test must be done in the clinic or in the lab:
 - If pregnancy test result is positive on Day 0, do not dispense drug, take participant off-study, complete the Off-Study Case Report Form (CRF), follow the pregnancy to term and complete the Outcome of Pregnancy Case Report Form (CRF).
 - If a pregnancy is discovered after Day 0, instruct the participant to stop taking drug, take participant off-study, complete the Off-Study CRF, follow the pregnancy to term and complete the Outcome of Pregnancy CRF.
 - Study drug should be initiated on the second or third day of a normal menstrual period.
- Research Blood Sample for serum bexarotene concentration.
-
- Depending on the dose assignment, participants will receive:
 - Bexarotene 1 % gel 10mg/breast/every other day x 4 weeks
 - Bexarotene 1% gel 10mg/breast/daily x 4 weeks
 - Bexarotene 1% gel 20mg/breast/daily x 4 weeks
- Review guidelines for gel application with the participant.
- Review Gel Diary with the participant (see Appendix C). Provide instructions on use of diary.

All data will be captured on the appropriate eCRFs.

7.3 Evaluation During Study Intervention

Day 1

- Participants will initiate study agent on Day 1.

Day 8 \pm 2 days: Phone Call

- Participants will receive a phone call from the PI or designee for an assessment of adverse events. To assess skin toxicity please ask the participant non-leading questions such as “Have you noted any changes in the skin of your breast?” If the participant reports yes, then utilize the plain language guide (Appendix G) to ask more probing questions as needed. Refer to Table 3 for modified CTCAE for assessing skin toxicity of bexarotene gel applied to the breast skin.
- Gel diary will be reviewed.

Day 15 \pm 2 days

- Participants will return for an assessment of adverse events and breast exam. To assess skin toxicity please ask the participant non-leading questions such as “Have you noted any changes in the skin of your breast?” If the participant reports yes, then utilize the plain language guide (Appendix G) to ask more probing questions as needed. Refer to Table 3 for modified CTCAE for assessing skin toxicity of bexarotene gel applied to the breast skin. Gel diary will be reviewed. Vital signs will be measured. Routine blood sample will be obtained during the visit to evaluate for systemic toxicity.
- All skin AEs will be photographed by medical photography services.
- If Grade 3 adverse event is noted on exam, drug will be held and participant will be evaluated by dermatology within 72 hours of the study visit.

7.4 Evaluation at Completion of Study Intervention

Day 28 \pm 2 days

- Participants will return for an assessment of adverse events and breast exam. To assess skin toxicity please ask the participant non-leading questions such as “Have you noted any changes in the skin of your breast?” If the participant reports yes, then utilize the plain language guide (Appendix G) to ask more probing questions as needed. Refer to Table 3 for modified CTCAE for assessing skin toxicity of bexarotene gel applied to the breast skin. Medical history and concomitant medications will be reviewed. Gel diary will be reviewed and collected. Routine and research blood samples will be obtained during the visit. Pregnancy test will be repeated at this visit. The breast core biopsy will be scheduled at this visit for those participants in the dose escalation cohort who opt for the procedure and for all participants in the dose expansion cohort. Breast tissue will be evaluated for bexarotene concentration. Remaining study drug will be collected at this visit.
- Vital signs will be measured. Weight will be recorded.
- All skin AEs will be photographed by medical photography services.
- If Grade 3 adverse event is noted on exam, participant will be evaluated by dermatology within 72 hours of the study visit.

- Tobacco and Alcohol use assessment will be performed on Day 28, using the “Alcohol and Tobacco Use Assessment Questionnaires – Follow Up” questionnaires (see Appendix E).

7.5 Post-intervention Follow-up Period

All participants will receive a follow-up phone call from the site investigator or designee 30 days \pm 7 days after Day 28 study visit to assess for any further AE and document resolution of any acquired AE during treatment. If the AE has not resolved, then the participant will be scheduled for a follow up visit with their primary care provider for ongoing management of this AE. The use of concomitant medications will be recorded.

7.6 Methods for Clinical Procedures

Breast core biopsy (see also section 10):

The breast core biopsy (image guided) will not be performed prior to drug initiation in the dose escalation cohort, and is optional at Day 28. The breast core biopsy (image guided) is required of participants in the dose expansion group at Day 28. A 14-gauge needle will be used. Every effort will be made to collect 4 cores of tissue, with the minimum of 3 cores per participant. Refer to Section 10 for details of specimen management.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint: Toxicity and Safety

The primary objective of this study is to determine the safety and toxicity of topical 1% bexarotene gel application to the breasts of healthy women at high risk for breast cancer for duration of 4 weeks. Women with ADH, ALH, LCIS, breast cancer survivors (DCIS or invasive) \geq 5 years from their diagnosis, BRCA 1/2 mutation carriers, and women with elevated risk for breast cancer \geq 1.7% in 5 years or lifetime risk \geq 20% will be recruited. Three dose levels are considered (10mg every other day, 10mg daily, and 20mg daily). Dose Limiting Toxicity (DLT) is defined as a grade 2 skin adverse event that persists for at least 6 days or any grade 3 or greater adverse event possibly, probably, or definitely related to the study drug. In addition, a DLT will be a grade 2 skin adverse event that recurs and persists for at least 3 days. A conservative modification of the standard “3+3” design will be applied. The first cohort of 3 participants will be treated at the first dose level (10mg every other day). New cohorts of participants will not be treated until toxicity has been fully evaluated for all current participants for 4 weeks. We will add another 4 participants when only 1 or less participants experience DLT in 6 treated participants. We will only escalate dose to the next higher level when 20% or less of total participants experience a DLT. At any dose level, the algorithm is as follows:

- (1) If 0 or 1 out of 3 participants experience DLTs (\leq 1/3), an additional cohort of 3 participants will be treated at the same dose level. If total number of participants experiencing DLT at that dose level is 1 or less out of 6 (\leq 1/6), we will enroll another 4 at the same dose level.
- (2) If at any time 2 or more participants experience DLTs in 3 or 6 (\geq 2/3 or \geq 2/6) or 3 or more experience DLT in 10 participants (\geq 3/10), then the dose escalation will stop, and the next lower dose will be considered as the maximum tolerated dose (MTD).
- (3) In 10 participants at each dose level, if we observe 2 or less DLTs, a cohort of 3 will be treated at the next higher level. If 3 or more in 10 participants experience DLT, we will stop accrual to that level and above, and claim the regimen as to be too toxic for that level or above.

MTD is defined the highest dose level with at most 2 participants with DLTs in 10 participants treated.

Once MTD is identified, we will enroll another 10 participants into MTD and these participants will have mandatory biopsies before and after 4 weeks of treatment. We will continuously monitor aggregate DLTs in these participants together with the 10 participants treated during the dose escalation part of the study. If at any time the posterior probability of observing a DLT rate of at least 20% exceeds 70%, i.e., $\Pr(\text{DLT rate} \geq 0.20 | \text{Data}) > 70\%$, given the prior of the DLT rate of beta (0.2, 0.8), we will stop the trial and claim the dose is too toxic. Given the above rule, the boundaries for early stopping due to excessive DLT are Total Number of Participants with DLTs/Total Number of Participants $\geq 4/11\sim 14$, $5/15\sim 19$, and $6/20$. Combining with the boundaries during dose escalation phase, i.e., stop accrual at the dose level if Total Number of Participants with DLTs/Total Number of Participants $\geq 2/3$, $2/6$, $3/10$, $4/11\sim 14$, $5/15\sim 19$, and $6/20$, the early stopping probability for this level will be 15%, 51%, 82% if the true DLT rate is 0.10, 0.20, and 0.30, respectively.

Given that there are 3 dose levels and 10 participants enrolled at each level, and 10 additional participants at MTD, it is anticipated that 40 participants will be enrolled and treated and up to 40 will be evaluable at the end of this study.

Skin Toxicity

CTCAE criteria will be utilized to grade adverse events. Skin adverse events are expected to be the most common in this study. Bexarotene is similar to retinoids and retinoid dermatitis is very common and can be managed with temporarily withholding drug and restarting at a decreased frequency until tolerated by the individual. Dose modifications for each dose level have been defined in Section 5.5 to guide management of participant experiences of an adverse event

CTCAE criteria for skin will be modified (Table 3) for this study as adverse events are expected to be localized to the breast area. This modified criteria was also utilized by Talpur *et al.* when they evaluated bexarotene 1% gel on the scalp of participants with alopecia areata (6). Please see Table 3 for modified CTCAE criteria. Use plain language when talking to the participant about skin AEs. Refer to Appendix G for a plain language guide to support both phone and in-person assessments of skin application AEs.

Participants will be shown how much area of their breast is considered 25% of the treated area so they can clearly describe their symptoms and the extent of the affected area. They will also be instructed to draw around reddened areas so they can clearly see if an area is expanding or improving and relay that information to the study team.

Table 3: Modified CTCAE for assessing skin toxicity of bexarotene gel applied to the breast skin. These assessments will be made on the breast skin (application site).

	Grade 1	Grade 2	Grade 3	Grade 4
Dry Skin	No erythema or pruritus	With erythema or pruritus	With erythema and pruritus	-
Pain of Skin	Mild pain	Moderate Pain	Severe Pain	-
Photosensitivity	Painless erythema	Mild to Moderate Pain with erythema	Erythema with blistering or skin breakdown	Erythema with ulceration
Pruritus	Mild, requiring topical intervention	Intense, with changes from	Intense, constant, limiting ADL or	-

		scratching, oral intervention needed	sleep, oral steroids needed	
Rash, maculopapular	Macules or papules <25% of treated area, with or without symptoms (pruritus, burning, tightness)	Macules or papules >25% of treated area, with or without symptoms (pruritus, burning, tightness), limiting instrumental ADL	Macules or papules >25% of the treated area, with or without symptoms (pruritus, burning, tightness), limiting self care ADL	-
Urticaria	Asymptomatic or mild symptoms, not requiring therapy	Moderate, limited local therapy needed, limiting instrumental ADL	Urticarial lesions covering >30% of application site; oral or IV intervention indicated	-

8.2 Secondary Endpoints

8.2.1 Markers of Systemic Toxicity: Based on data from oral bexarotene in women at high risk for breast cancer, bexarotene alters lipid levels, thyroid function, and calcium levels. Therefore, serum biomarkers to be tested will be Total Cholesterol, triglycerides, LDL, HDL, TSH, free T4, free T3, and calcium. Evaluation and changes in these biomarkers will be done at baseline, 15, and Day 28 visits.

8.2.2 Bexarotene Concentration: Bexarotene concentration will be determined using LC-MS/MS (5500 or similar; AB SCIEX, Foster City, CA) according to methods developed and qualified at IIT Research Institute (IITRI) for the study.

8.2.3 Effect of Bexarotene on Tissue Markers:

- i. One of the four cores collected from the core biopsies from post treatment (all dose expansion cohort participants and optional for dose escalation group) will be formalin-fixed and paraffin embedded (FFPE) for future histological analysis. These cores will be stored for future use.
- ii. One of the four cores collected from the core biopsies post treatment will be placed in RNALater and utilized for future biomarker analysis such as gene expression of RNA biomarkers.

8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, AE or SAE including a DLT, inadequate agent supply, noncompliance, concomitant medications, medical contraindication, or became pregnant. Participants experiencing Grade 3 or Grade 4 toxicities of any attribution will be taken off study drug. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants that receive agent but withdraw without initiating treatment will be replaced and will not be followed or evaluable for DLTs.

8.4 Off-Study Criteria

Participants may go ‘off-study’ for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility (including screen failure), and pregnancy.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

Section 8 outlines our primary and secondary endpoint biomarkers. The primary endpoint measurement will be done by assessing toxicity and adverse events using modified CTCAE criteria and standard clinical methods. CTCAE criteria for skin will be modified (Table 3) for this study as adverse events are expected to be localized to the breast area. This modified criteria was also utilized by Talpur *et al.* when they evaluated bexarotene 1% gel on the scalp of patients with alopecia areata (6). For secondary endpoints, again, we choose methods that have been previously published, either by our group or other investigators, that are widely available, practical, and financially preferable.

9.2 Comparable Methods

The methodologies described above are those previously used (see details above), and the resulting data will be able to be compared to existing data.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

10.1.1 Bexarotene concentration analysis in the serum and breast tissue will be performed in Dr. Miguel Muzzio’s laboratory at IITRI.

10.1.2 Thyroid function tests, lipid profile, calcium, and all standard labs will be performed at UT MD Anderson Outpatient Laboratory as MD Anderson is the only site participating in the study.

10.2 Collection and Handling Procedures

Blood collection:

Peripheral blood will be obtained by venipuncture at baseline, Day 15, and at Day 28 visits. Blood will be collected for bexarotene concentration and other biomarkers mentioned in section 8.2.1 and 8.2.2. Fasting for the blood draws for lipid analysis is recommended but is not mandated.

For the purpose of tracking samples: All cryovials will be labeled to identify all sample vials. Blood specimen for bexarotene level will be collected in 4mL Li- Heparin tubes such as BD 367884 Plasma Tube, 60 USP Units

of Lithium Heparin (spray-coated) or similar. Specimen will be centrifuged at 1000G for 15 min at -4degrees Celsius. Plasma will be separated and aliquoted to 0.5-1.0 ml/tube in at least 2 vials. Plasma specimens will be stored in a secure -80 degree Celsius freezer (range -70 °C to -80 °C)

Breast Core Biopsy (see also section 7.6):

The breast core biopsy (image guided) will not be performed prior to treatment initiation in the dose escalation cohort and is optional at Day 28. The breast core biopsy (image guided) is required of participants in the dose expansion group at Day 28. A 14-gauge needle will be used. Every effort will be made to collect 4 cores of tissue, with the minimum of 3 cores per participant at each time point.

Planned usage of core biopsies is shown in Table 4.

Core biopsy specimens #1 and 2 will be fresh frozen in liquid nitrogen for bexarotene concentration using LC-MS/MS (5500 or similar; AB SCIEX, Foster City, CA).

Core biopsy specimens #3 will be fixed in formalin and embedded in a single paraffin block. One H&E slide will be prepared for adequacy and histological assessment. Tissue will be considered adequate for research assays if the H&E stained slide from the block demonstrates at least one terminal duct lobular unit (TDLU) in the tissue core. Usually each terminal duct lobular unit contains 200 to 2500 cells. If no terminal duct lobular units are seen, deeper sections from the tissue block will be obtained.

Core biopsy specimens #4 will be placed immediately into RNAlater. Each biopsy sample will be placed in (1) prefilled cryovial and then stored in a secure 4 degree Celsius refrigerator (range of 4-6 °C) for a minimum of 24 hours and up to 7 days. The cryovials will then be removed from the refrigerator and placed in a secure -80 degree Celsius freezer (range -70 °C to -80 °C). Core #2 will be used for exploratory gene expression analysis.

Table 4. Planned use of core tissue biopsies:

Core	Preparation	Analyses
1-2	Fresh frozen	Bexarotene concentration using LC-MS/MS (5500 or similar; AB SCIEX, Foster City, CA)
3	Formalin fixed, paraffin-embedded	Used to make 5 slides and then used for histological evaluation at to rule out cancer and stored for future use.
4	RNAlater at 4C then transferred to -80°C (range -70°C to -80°C) freezer	Exploratory gene expression analysis

10.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

At the completion of the study, all plasma specimens and tissue specimens for bexarotene concentration will be shipped to Miguel Muzzio at IITRI for analysis. Samples will be sent to:

Miguel Muzzio
 Analytical Chemistry Division

IIT Research Institute
10 West 35th Street, 8E9-1
Chicago, IL 60616
Tel: 312.567.4909
Fax: 312.567.4466
Email:MMuzzio@iitri.org

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term (Include at application site, if applicable)
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date

- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc.*

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs

SAEs should be reported to the following 3 entities: 1) NCI DCP, 2) DCP's regulatory contractor CCSA, and 3) MDACC, the CLO. Detailed reporting instructions are provided below. In addition, the site will follow the IRB requirements for SAE reporting.

11.2.2.1 SAEs will be reported on the DCP SAE Report Form found at <http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia>.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

Marjorie Perloff, MD
Division of Cancer Prevention
National Cancer Institute
9609 Medical, Rm 5E544
Rockville, MD 200850
Office Tel (240)276-7097
Cell (240)731-1772
Email: perloffm@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 Contact the Consortium Lead Organization (CLO) PI, Dr. Powel Brown, or designee by phone, fax or email listed on the protocol face page within 24 hours of knowledge of the event. The same information reported to the DCP Medical Monitor should be provided to the CLO PI or designee via email, phone or fax within 24 hours of knowledge of the event.

11.2.2.4 Written SAE reports should be forwarded to DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com within 48 hours of learning of the event using the fillable PDF SAE Report Form.

11.2.2.5 The CLO PI, Dr. Brown, or designee must be copied on the email sent to DCP's Regulatory Contractor CCS Associates, Inc.

11.2.2.6 Valeant Drug Safety (drugsafety@valeant.com) and Ali Hussain (Ali.Hussain@valeant.com) should be copied on the email sent to DCP's Regulatory Contractor CCS Associates, Inc.

11.2.2.7 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.8 The Site will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. SAEs related to the study agent will be followed until resolved.

12. STUDY MONITORING

12.1 Data Management

This study will report clinical data using the Data Management Initiative (DMI) web-based application managed by the Consortium Biostatistics and Data Management Core. Data Management Initiative (DMI) infrastructure has been developed in the Division of Quantitative Sciences (DQS), MD Anderson Cancer Center. This infrastructure supplies integrated database and software services for web-based data collection, randomized treatment assignment, reporting, query, data download, and data quality management. The DMI will be the database of record for the protocol and subject to NCI and FDA audit. All DMI users will be trained to use the DMI system and will comply with the instructions in the protocol-specific "DMI User Manual" as well as applicable regulatory requirements such as 21 CFR; Part 11. Data management procedures for this protocol will adhere to the Data Management Plan (DMP) on file at the DCP for contract HHSN261201200034I.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). The study will utilize electronic CRF (e-CRF) only, which will be viewed as screens in the DMI application. Site staff will enter data into the e-CRF in DMI. CRF amendments will be submitted to the DCP Protocol Information Office for review and approval. Approved changes will be programmed into the DMI database by the Consortium Biostatistics and Data Management Core.

12.3 Source Documents

Source documentation will include only those documents containing original forms of data, including clinic charts, shadow files, hospital charts, and physician notes. Data recorded directly on the CRFs designated as source documents (*i.e.*, no prior written or electronic record of data) will be considered source data. All other data recorded on the CRFs will not be considered source documentation.

12.4 Data and Safety Monitoring Plan

The Data and Safety Monitoring Plan for the MD Anderson Consortium is on file at the DCP. This study will be monitored by the MDACC Data and Safety Monitoring Board (DSMB), the data and safety monitoring board of record for this study. The DSMB reports to the President, or his designee, as the on-campus representative of The University of Texas Board of Regents. It oversees the data and patient safety issues for clinical trials that originate at MD Anderson; that are coordinated or analyzed by MD Anderson and are not being monitored by any other DSMB; or have been designated as requiring DSMB monitoring at the request of the IRB, the CRC, or institution. The primary objectives of the DSMB are to ensure that patients' rights pertaining to participation in a research study are protected, and that patients' interests are prioritized over the interests of the scientific investigation. Responsibilities include:

- (a) Review interim analyses of outcome data (prepared by the study statistician or other responsible person at the time points defined in the study) approved by the IRB and additional time points as determined by the DSMB, and to recommend, if necessary, whether the study needs to be changed or terminated based on these analyses;
- (b) Determine whether, and to whom, outcome results should be released prior to the reporting of study results;
- (c) Review interim toxicity data and efficacy of treatment;
- (d) Review major research modifications proposed by the investigator or appropriate study committee prior to implementation (*e.g.*, termination, dropping an arm based on toxicity results from the study or results of other studies, increasing target sample size).

Refer to the Data and Safety Monitoring Plan for the MD Anderson Consortium on file at the DCP for further details.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc.*), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned

destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s) supplied by DCP, NCI, used in this protocol, is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Valeant Pharmaceuticals North America LLC (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Prevention. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator@ contained within the terms of award, apply to the use of Agent(s) in this study:

12.7.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If an individual participating on the study or participant’s family member requests a copy of this protocol, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from the DCP website.

12.7.2 For a clinical protocol where there is an Investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-party Data").

12.7.3 NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

12.7.4 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

12.7.5 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

12.7.6 Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

12.7.7 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators of Collaborator's wish to contact them.

12.7.8 Any manuscripts reporting the results of this clinical trial must be provided to DCP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days (or as specified in the CTA) from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator(s) for courtesy review

as soon as possible and preferably at least three days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to the Protocol Information Office at NCI_DCP_PIO@mail.nih.gov.

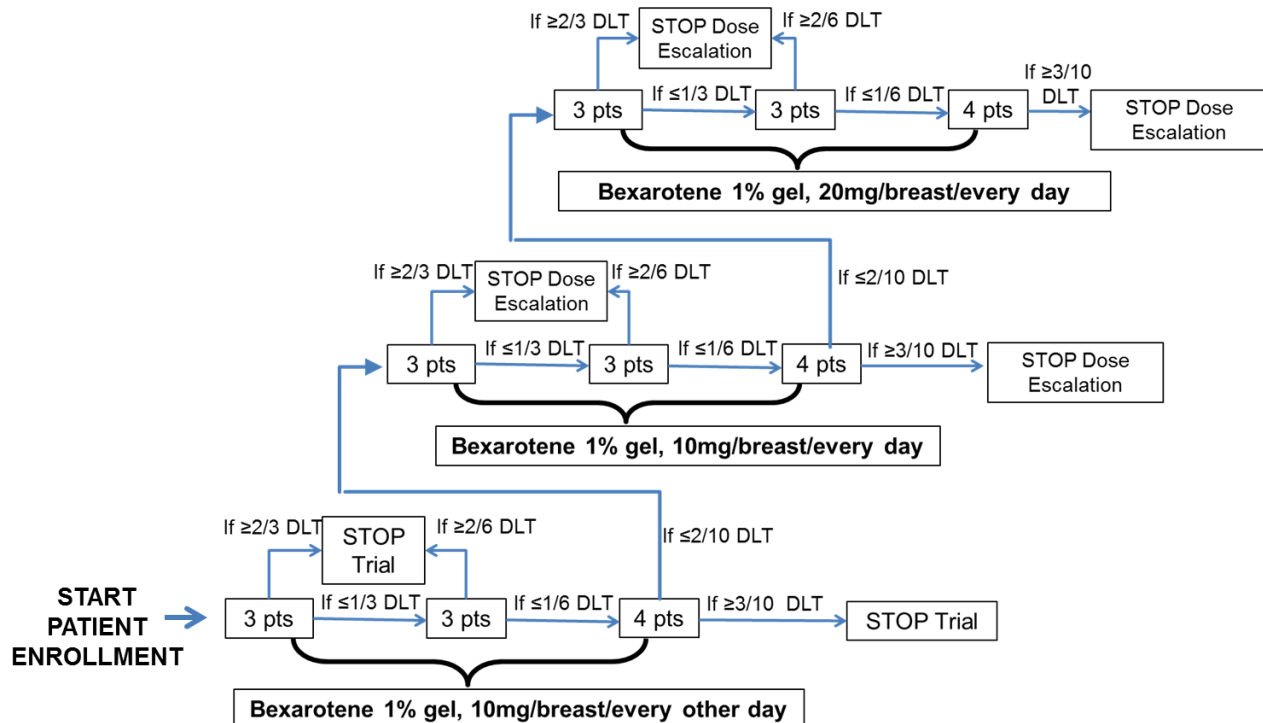
The Protocol Information Office will forward manuscripts to the DCP Project Officer for distribution to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This is a phase I study to evaluate the safety and toxicity of bexarotene 1% gel in healthy women at elevated risk for breast cancer. A phase I dose escalation trial was designed to test the safety of three different dose levels and ensure the lowest dose level is safe prior to enrollment into the second dose level and so forth. Please see Figure 1 for the dose escalation schema. DLT is defined as a grade 2 skin adverse event that persists for at least 6 days or any grade 3 event or greater adverse event possibly, probably, or definitely related to the study drug. In addition, a DLT will be a grade 2 skin adverse event that recurs and persists for at least 3 days. The MTD will be defined as the highest dose level with at most 2 DLTs in 10 participants treated. A dose expansion group of additional 10 patients will be accrued at the MTD for the same treatment duration of 4 weeks with required baseline and post treatment biopsies to understand safety, toxicity, and penetration of bexarotene into the breast tissue.

Figure 1: Dose Escalation Schema for Bexarotene 1% gel



13.2 Randomization/Stratification

A conservative modification of the standard “3+3” design will be applied. The first three participants will be assigned to the lowest dose level. New cohorts of 3-4 participants will not be treated until toxicity has been evaluated for all current participants for 4 weeks. Group assignment algorithm is explained in Section 13.4.

13.3 Accrual and Feasibility

Treatment will be initiated in 10 participants per group up to 40 participants. Participants found eligible but who withdraw without initiating treatment will be replaced and will not be followed or evaluable for DLTs. We plan to screen (consent) 60 participants to enroll (initiate treatment in) up to 40 participants. Our estimated screen out rate after consent prior to study participation is approximately 25%. We anticipate accrual of approx. 3 participants per month. Since accrual is done in groups of 3-4 participants, there will be a 4 week hold in accrual to assess for toxicity in the currently enrolled participants. Assuming that all dose levels are maximally accrued to, there will be 9 months of intentional hold on accrual to assess for safety and toxicity. Therefore, it will take approximately 21 months to complete accrual to the three dose levels and an additional 4 months to accrue to the dose expansion cohort.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective of this study is to determine the safety and toxicity of topical 1% bexarotene gel application to the breasts of healthy women at high risk for breast cancer for a duration of 4 weeks. Women with ADH, ALH, LCIS, breast cancer survivors (DCIS or invasive) ≥ 5 years from their diagnosis, BRCA 1/2 mutation carriers, and women with elevated risk for breast cancer $\geq 1.7\%$ in 5 years or lifetime risk $\geq 20\%$ will be recruited. Three dose levels are considered (10mg every other day, 10mg daily, and 20mg daily). Dose Limiting Toxicity (DLT) is defined as a grade 2 skin adverse event that persists for at least 6 days or any grade 3 or greater adverse event possibly, probably, definitely related to the study drug. In addition, a DLT will be a grade 2 skin adverse event that recurs and persists for at least 3 days. A conservative modification of the standard “3+3” design will be applied. The first cohort of 3 participants will be treated at the first dose level (10mg every other day). New cohort of participants will not be treated until toxicity has been fully evaluated for all current participants for 4 weeks. We will add another 4 participants when only 1 or less participants experience DLT in 6 treated participants. We will only escalate dose to the next higher level when 20% or less of total participants experience DLT. At any dose level, the algorithm is as follows:

- (1) If 0 or 1 out of 3 participants experience DLTs ($\leq 1/3$), an additional cohort of 3 participants will be treated at the same dose level. If total number of participants experiencing DLT at that dose level is 1 or less out of 6 ($\leq 1/6$), we will enroll another 4 participants the same dose level.
- (2) If at any time 2 or more participants experiences DLTs in 3 or 6 participants ($\geq 2/3$ or $\geq 2/6$) or 3 or more participants experience DLT in 10 participants ($\geq 3/10$), then the dose escalation will stop, and the next lower dose will be considered as the maximum tolerated dose (MTD).
- (3) In 10 participants at each dose level, if we observe 2 or less DLTs, a cohort of 3 participants will be treated at the next higher level. If 3 or more in 10 participants experience DLT, we will stop accrual to that level and above, and claim the regimen as to be too toxic for that level or above.

MTD is defined the highest dose level with at most 2 participants with DLTs in 10 participants treated.

Once MTD is identified, we will enroll another 10 participants into MTD and these participants will have mandatory biopsies before and after 4 weeks of treatment. We will continuously monitor aggregate DLTs in these participants together with the 10 participants treated during the dose escalation part of the study. If at any time the posterior probability of observing a DLT rate of at least 20% exceeds 70%, i.e., $\Pr(\text{DLT rate} \geq 0.20 \mid \text{Data}) > 70\%$, given the prior of the DLT rate of beta (0.2, 0.8), we will stop the trial and claim the dose is too toxic. Given the above rule the boundaries for early stopping due to excessive DLT are Total Number of Participants with DLTs/Total Number of Participants $\geq 4/11\sim 14$, $5/15\sim 19$, and $6/20$. Combining with the boundaries during dose escalation phase, i.e., stop accrual at the dose level if Total Number of Participants with DLTs/Total Number of Participants $\geq 2/3$, $2/6$, $3/10$, $4/11\sim 14$, $5/15\sim 19$, and $6/20$, the early stopping probability for this level will be 15%, 51%, 82% if the true DLT rate is 0.10, 0.20, and 0.30, respectively.

Given that there are 3 dose levels and 10 participants enrolled and treated at each level, and 10 additional patients at MTD, it is anticipated that 40 participants will be treated and up to 40 will be evaluable at the end of this study.

At the end of the study, the toxicity data will be summarized for each dose level using frequency tabulation. The compliance of treatment application for each dose level will be presented using descriptive statistics.

13.5 Secondary Objectives, Endpoints, Analysis Plans

Secondary Objectives:

1. To detect bexarotene concentration in the serum at baseline and at 4 weeks of treatment.
2. To detect bexarotene concentration in the breast tissue at 4 weeks of treatment in the dose escalation group.
3. To investigate the effects of topical bexarotene on serum biomarkers
We will determine the change from the baseline in:
 - i. Lipid Biomarkers (Total Cholesterol, triglycerides, LDL, HDL)
 - ii. Thyroid Function Biomarkers (Thyroid Stimulating Hormone (TSH), T4, T3)
 - iii. Calcium

These measurements will be summarized using mean, standard deviation and median (range) for continuous variables at each time point. Wilcoxon rank-sum test may be used to examine the difference of continuous variables between participants' characteristics groups. Participants' demographic characteristics will be compared between different dose levels by Wilcoxon rank-sum and Fisher's exact test for continuous and categorical variables, respectively. In order to explore the changes over time, values of bexarotene concentration and biomarkers in serum will be plotted as functions of time (baseline, week 1, week 2, and week 4). Linear mixed effect model will be applied to model the biomarker change over time for all participants. Appropriate transformation and regression model will be used to ensure the model fit. Estimated bexarotene concentration mean in the breast tissue at 4 weeks will be calculated along with a 95% confidence interval. Other statistical methods may be applied when appropriate.

13.6 Reporting and Exclusions

Every reasonable attempt will be made to recover any missing data. If any data for the primary efficacy measure remains missing then the change of the primary endpoint for will not be calculated and the participant will not be evaluable for the primary endpoint. However any available data from other time points will be included in the repeated measure analysis.

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of bexarotene gel. The grade, attribution, onset and resolve date of all toxicities will be recorded and summarized for each dose level at the end of the study.

13.8 Evaluation of Response

All participants included in the study must be assessed for response to intervention, even if there are major protocol deviations or if they are ineligible.

All of the participants who met the eligibility criteria (with the possible exception of those who did not receive study agent) will be included in the main analysis. All conclusions regarding secondary efficacy measures requiring breast biopsies will be based on eligible participants selecting this option.

Subanalyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of intervention, major protocol violations, etc.). However, subanalyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported. For all measurements of response, the 95% confidence intervals should also be provided.

13.9 Interim Analysis

There is continual interim analysis in a modified 3+3 design for this study.

13.10 Ancillary Studies

No additional ancillary studies are planned.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in “Protection of Human Research Subjects” for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator’s Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented.

Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the CLO and reviewed for completeness and accuracy. Once the CLO has received complete and accurate documents from the Site, the CLO will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:

Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Place, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:

regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the CLO for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

Participants will not be responsible for non-standard of care costs of this study. Study agent will be provided at no cost to the participant. Participants in the dose escalation cohort who choose to participate in an optional core breast biopsy at the end of study treatment will receive compensation for additional expenses associated with the biopsy, such as additional travel expenses, time missed from work or other expenses associated with the biopsy visit. All participants in the dose expansion cohort will have a core breast biopsy at end of treatment and will receive compensation for additional expenses associated with the biopsy, such as additional travel expenses, time missed from work or other expenses associated with the biopsy visit. If, as a result of participation in this study, an individual experiences injury from known or unknown risks of the research procedures as described in the informed consent, immediate medical care and treatment, including hospitalization, if necessary, will be available. No monetary compensation is available for the costs of medical treatment for an injury, thus, the participant will be responsible for the costs of such medical treatment, either directly or through their medical insurance and/or other forms of medical coverage.

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APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

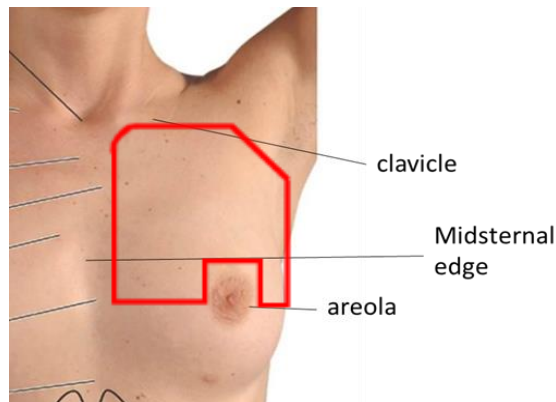
Karnofsky Performance Scale

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Appendix B

GEL APPLICATION INSTRUCTIONS

1. Flammable: do not apply near fire, flame or heat, or while smoking
2. Apply the gel to your breast after bathing, preferably in the morning and at approximately the same time each day. Apply approximately 30 minutes after bathing when breast is completely dry.
3. To apply, remove the cap from the bottle. When you use the bottle for the first time, you must prime it by pressing the pump fully several times until gel is dispensed (point the spout toward a sink or wastebasket and do not use the first dose, which may be incorrect).
4. Once the bottle is primed, hold it in one hand and place the palm of your other hand under the pump to catch the gel. Be sure to press down completely on the pump and release it completely to dispense one dose of gel.
5. Apply **one dose of gel to one breast** (dosage is indicated on the bottle label). Do not apply more or less than one dose to the breast. If you are assigned to the 20mg dose level (which requires two (2) pumps), be sure to release the pump completely between both actuations (pumps). Application of gel will always be to only one breast and the same breast each time. Do not alternate doses between breasts.
6. If you accidentally pump more than is needed, please discard this dose and try again to get the correct dose. If you do discard pumped doses, please record this on your Gel Diary.
7. Spread the gel evenly over the upper outer and upper inner quadrant of your breast, without rubbing. Start from above the areola and spread outwards to below the clavicle and up to the midsternal edge which is the midline of your chest. Avoid spreading the gel in the nipple and areola area of the breast. Avoid spreading the gel below the nipple or underneath the breast. Please see diagram below.



8. Wash your hands immediately after applying the gel.
9. Allow the gel on your breast to air dry for 2 minutes and then immediately cover with clothing (the gel is colorless and will not stain your clothing). Do not expose your bare breasts to sunlight or ultraviolet light (tanning beds) at any time while on the study.
10. Do not apply any other cream, lotion or moisturizer to your breast immediately after application of the study drug.
11. Do not wash your breast or immerse in water (bath, swim) for at least 4 hours following application of the

gel. If this is not possible, delay application of the gel that day until after immersion, and be sure to follow all the above instructions. If you regularly swim in the morning, it is better to apply the gel afterwards, after your shower.

12. After use, replace the cap on the bottle.

RECOMMENDATIONS:

1. Be sure to apply **after bathing or showering, each day** during the study and preferably in the morning.
2. You may use CeraVe moisturizing cream, a moisturizer that will be supplied to you, to apply to the same breast that you are applying the study gel. CeraVe moisturizing cream can be used in the evening or at least 4 hours after study gel application so it will not interfere with absorption. CeraVe moisturizing cream can be applied daily to help with any skin redness.
3. If you forget to apply a dose, do not double the dose to “catch up”.

If you are applying the gel **daily**: If your next dose is scheduled within the next 12 hours, it is best just to wait; if it is more than 12 hours until your next dose, apply the dose you missed and resume your normal dosing after that.

If you are applying the gel **every other day**: If your next dose is scheduled within the next 24 hours, it is best just to wait; if it is more than 24 hours until your next dose, apply the dose you missed and resume your normal dosing after that.

4. For the duration of the study, avoid contact between the application area and the skin of other individuals (i.e. your child, your sexual partner, or other persons). If necessary, skin contact is allowable after the breast has been washed. As noted above, you must wait at least 4 hours following application before washing the application area, otherwise, delay application until after washing and contact.
5. Avoid using sprays containing DEET (i.e. bug spray) to the treated area and limit vitamin A intake to <5000 IU per day.
6. Do not ingest or swallow the gel. For external use only.
7. Please note the first and last day of use on the bottle label.
8. If the pump doesn't come back up correctly or if there's no gel delivered when you press down on the pump, notify your doctor immediately. A replacement bottle will be shipped to you.
9. After the end of study treatment, be sure to take back to your doctor **all** the gel bottles you have been given (even if empty or not used). **This is very important for the success of the study.**
10. If any ulcerations, blisters or open areas start please notify the research team the next day for guidance.

STORAGE INSTRUCTIONS:

1. Keep your gel bottles in a cool room temperature- 59°F to 77°F.
2. Keep the gel bottles out of the reach of children.

APPENDIX C

Bexarotene Gel Diaries

Bexarotene Gel Diary [IRB Protocol #:]

Group 1

PID: _____

Amount of Agent Provided: Number of Canisters _____

Total Daily Dose: 10mg applied to one breast, **every other day**

Pump actuations: Push the Pump 1 time

Breast to Apply Gel: Right OR Left

Number of Canisters Returned: _____

Visit#: _____

INSTRUCTIONS:

1. Complete the diary daily.
2. If you miss an application, do not take an extra application to “make up” for the missed application.

If your next dose is scheduled within the next 24 hours, it is best just to wait; if it is more than 24 hours until your next dose, apply the dose you missed and resume your normal dosing after that.
3. If you accidentally pump more than is needed for one breast, please discard this dose and try again to get correct dose. If you do discard pumped doses, please record this on your Gel Diary.
4. Do not discard the gel canister. Bring the canister and this diary to your next appointment.
5. Store the study gel at home at room temperature and avoid extreme heat or cold during transportation from the clinic to home.
6. If you experience any concerning side effects or changes in the texture of your skin (e.g., skin feels like sandpaper), call _____ (insert name of Study Coordinator or Study Nurse) at _____ (insert telephone number) or the study doctor, Dr. Parijatham Thomas at 713-745-8040 for guidance.

Bexarotene Gel Diary Group 1 Continued

Please Bring this Sheet and Empty Canister to Your Next Visit

	Day	Date	R or L Breast, OR Did not apply	Initials	Did you experience any symptoms, if "Yes" list below List # of discarded pumps of gel here
Week 1 Apply 1 pump to the breast every other day	1		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	2		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	3		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	4		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	5		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	6		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	7		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
Week 2 Apply 1 pump to the breast every other day	8		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	9		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	10		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	11		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	12		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	13		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	14		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
Week 3 Apply 1 pump to the breast every other day	15		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	16		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	17		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	18		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	19		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	20		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	21		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		

	Day	Date	R or L Breast, OR Did not apply	Initials	Did you experience any symptoms, if "Yes" list below List # of discarded pumps of gel here
Week 4 Apply 1 pump to the breast every other day	22		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	23		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	24		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	25		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	26		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	27		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	28		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	29		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	30		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		

Participant's Signature: _____

Date: _____

Reviewer's Signature: _____

Date: _____

Comments:

Bexarotene Gel Diary [IRB Protocol #: _____]

Group 2

PID: _____

Amount of Agent Provided: Number of Canisters _____

Total Daily Dose:

Week 1: 10mg applied to one breast, **every other day**
Push the Pump 1 time

Weeks 2-4: 10mg applied to one breast, **every day**
Push the Pump 1 time

Breast to Apply Gel: Right OR Left

Number of Canisters Returned: _____

Visit#: _____

INSTRUCTIONS:

1. Complete the diary daily.
2. If you miss an application, do not take an extra application to “make up” for the missed application.

If you are applying the gel daily: If your next dose is scheduled within the next 12 hours, it is best just to wait; if it is more than 12 hours until your next dose, apply the dose you missed and resume your normal dosing after that.

If you are applying the gel every other day: If your next dose is scheduled within the next 24 hours, it is best just to wait; if it is more than 24 hours until your next dose, apply the dose you missed and resume your normal dosing after that.

3. If you accidentally pump more than is needed for one breast, please discard this dose and try again to get correct dose. If you do discard pumped doses, please record this on your Gel Diary.
4. Do not discard the gel canister. Bring the canister and this diary to your next appointment.
5. Store the study gel at home at room temperature and avoid extreme heat or cold during transportation from the clinic to home.
6. If you experience any concerning side effects or changes in the texture of your skin (e.g., skin feels like sandpaper), call _____ (insert name of Study Coordinator or Study Nurse) at _____ (insert telephone number) or the study doctor, Dr. Parijatham Thomas at 713-745-8040 for guidance..

Bexarotene Gel Diary Group 2 Continued
Please Bring this Sheet and Empty Canister to Your Next Visit

	Day	Date	R or L Breast, OR Did not apply	Initials	Did you experience any symptoms, if "Yes" list below List # of discarded pumps of gel here
Week 1 Apply 1 pump to the breast every other day	1		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	2		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	3		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	4		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	5		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	6		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	7		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
Week 2 Apply 1 pump to the breast every day	8		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	9		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	10		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	11		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	12		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	13		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	14		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
Week 3 Apply 1 pump to the breast every day	15		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	16		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	17		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	18		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	19		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	20		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	21		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		

	Day	Date	R or L Breast, OR Did not apply	Initials	Did you experience any symptoms, if "Yes" list below List # of discarded pumps of gel here
Week 4 Apply 1 pump to the breast every day	22		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	23		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	24		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	25		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	26		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	27		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	28		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	29		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	30		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		

Participant's Signature: _____

Date: _____

Reviewer's Signature: _____

Date: _____

Comments:

Bexarotene Gel Diary [IRB Protocol #: _____]

Group 3

PID: _____

Amount of Agent Provided: Number of Canisters _____

Total Daily Dose:

Week 1: 10mg applied to one breast, **every other day**
Push the Pump 1 time

Week 2: 10mg applied to one breast, **every day**
Push the Pump 1 time

Weeks 3-4: 20mg applied to one breast, **every day**
Push the Pump **2 times**

Breast to Apply Gel: Right OR Left

Number of Canisters Returned: _____

Visit#: _____

INSTRUCTIONS:

1. Complete the diary daily.
2. If you miss an application, do not take an extra application to “make up” for the missed application.

If you are applying the gel daily: If your next dose is scheduled within the next 12 hours, it is best just to wait; if it is more than 12 hours until your next dose, apply the dose you missed and resume your normal dosing after that.

If you are applying the gel every other day: If your next dose is scheduled within the next 24 hours, it is best just to wait; if it is more than 24 hours until your next dose, apply the dose you missed and resume your normal dosing after that.
3. If you accidentally pump more than is needed for one breast, please discard this dose and try again to get correct dose. If you do discard pumped doses, please record this on your Gel Diary.
4. Do not discard the gel canisters. Bring the canisters and this diary to your next appointment.
5. Store the study gel at home at room temperature and avoid extreme heat or cold during transportation from the clinic to home.
6. If you experience any concerning side effects or changes in the texture of your skin (e.g., skin feels like sandpaper), call _____ (insert name of Study Coordinator or Study Nurse) at _____ (insert telephone number) or the study doctor, Dr. Parijatham Thomas at 713-745-8040 for guidance.

Bexarotene Gel Diary Group 3 Continued

Please Bring this Sheet and Empty Canisters to Your Next Visit

	Day	Date	R or L Breast	Initials	# of pumps	Did you experience any symptoms, if "Yes" list below List # of discarded doses here
Week 1 Apply 1 pump to the breast every other day	1				___ or <input type="checkbox"/> Did not apply	
	2				___ or <input type="checkbox"/> Did not apply	
	3				___ or <input type="checkbox"/> Did not apply	
	4				___ or <input type="checkbox"/> Did not apply	
	5				___ or <input type="checkbox"/> Did not apply	
	6				___ or <input type="checkbox"/> Did not apply	
	7				___ or <input type="checkbox"/> Did not apply	
Week 2 Apply 1 pump to the breast every day	8				___ or <input type="checkbox"/> Did not apply	
	9				___ or <input type="checkbox"/> Did not apply	
	10				___ or <input type="checkbox"/> Did not apply	
	11				___ or <input type="checkbox"/> Did not apply	
	12				___ or <input type="checkbox"/> Did not apply	
	13				___ or <input type="checkbox"/> Did not apply	
	14				___ or <input type="checkbox"/> Did not apply	
Week 3 Apply 2 pumps to the breast every day	15				___ or <input type="checkbox"/> Did not apply	
	16				___ or <input type="checkbox"/> Did not apply	
	17				___ or <input type="checkbox"/> Did not apply	
	18				___ or <input type="checkbox"/> Did not apply	
	19				___ or <input type="checkbox"/> Did not apply	
	20				___ or <input type="checkbox"/> Did not apply	
	21				___ or <input type="checkbox"/> Did not apply	

	Day	Date	R or L Breast	Initials	# of pumps	Did you experience any symptoms, if "Yes" list below List # of discarded doses here
Week 4 Apply 2 pumps to the breast every day	22				_____ or <input type="checkbox"/> Did not apply	
	23				_____ or <input type="checkbox"/> Did not apply	
	24				_____ or <input type="checkbox"/> Did not apply	
	25				_____ or <input type="checkbox"/> Did not apply	
	26				_____ or <input type="checkbox"/> Did not apply	
	27				_____ or <input type="checkbox"/> Did not apply	
	28				_____ or <input type="checkbox"/> Did not apply	
	29				_____ or <input type="checkbox"/> Did not apply	
	30				_____ or <input type="checkbox"/> Did not apply	

Participant's Signature: _____

Date: _____

Reviewer's Signature: _____

Date: _____

Comments:

Bexarotene Gel Diary [IRB Protocol #:]

Dose Expansion Group

PID: _____

Amount of Agent Provided: Number of Canisters _____

Total Daily Dose: 10mg applied to one breast, **every other day**

Pump actuations: Push the Pump 1 time

Breast to Apply Gel: Right OR Left

Number of Canisters Returned: _____

Visit#: _____

INSTRUCTIONS:

1. Complete the diary daily.
2. If you miss an application, do not take an extra application to “make up” for the missed application.

If your next dose is scheduled within the next 24 hours, it is best just to wait; if it is more than 24 hours until your next dose, apply the dose you missed and resume your normal dosing after that.
3. If you accidentally pump more than is needed for one breast, please discard this dose and try again to get correct dose. If you do discard pumped doses, please record this on your Gel Diary.
4. Do not discard the gel canister. Bring the canister and this diary to your next appointment.
5. Store the study gel at home at room temperature and avoid extreme heat or cold during transportation from the clinic to home.
6. If you experience any concerning side effects or changes in the texture of your skin (e.g., skin feels like sandpaper), call _____ (insert name of Study Coordinator or Study Nurse) at _____ (insert telephone number) or the study doctor, Dr. Parijatham Thomas at 713-745-8040 for guidance.

Bexarotene Gel Diary: Dose Expansion Group (Continued)

Please Bring this Sheet and Empty Canister to Your Next Visit

	Day	Date	R or L Breast, OR Did not apply	Initials	Did you experience any symptoms, if "Yes" list below List # of discarded pumps of gel here
Week 1 Apply 1 pump to the breast every other day	1		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	2		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	3		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	4		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	5		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	6		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	7		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
Week 2 Apply 1 pump to the breast every other day	8		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	9		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	10		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	11		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	12		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	13		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	14		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
Week 3 Apply 1 pump to the breast every other day	15		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	16		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	17		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	18		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	19		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	20		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	21		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		

	Day	Date	R or L Breast, OR Did not apply	Initials	Did you experience any symptoms, if "Yes" list below List # of discarded pumps of gel here
Week 4 Apply 1 pump to the breast every other day	22		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	23		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	24		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	25		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	26		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	27		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	28		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	29		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		
	30		<input type="checkbox"/> R <input type="checkbox"/> L <input type="checkbox"/> Did not apply		

Participant's Signature: _____

Date: _____

Reviewer's Signature: _____

Date: _____

Comments:

APPENDIX D

Alcohol and Tobacco Use Assessment Questionnaires – Baseline

ALCOHOL ASSESSMENT – BASELINE

REGISTERING INSTITUTION _____	PARTICIPANT ID _____	VISIT TYPE _____	VISIT DATE (MM/DD/YYYY) ____ / ____ / _____
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Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?
 Yes
 No **(End)**
 Refused **(End)**
 Don't know/Not sure
2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage?
_____ (Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)
 Week
 Month
 Year
 Refused
 Don't know/Not sure
3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?
_____ (Enter the average number of drinks per day)
 Refused
 Don't know/Not sure
4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?
_____ (Enter the number of days you had 5 or more drinks, or enter 0 if none.)
 Refused
 Don't know/Not sure
5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?
 Yes
 No
 Refused
 Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?

- Within the past month (0 to 1 month ago)
- Between 1 and 3 months (1 to 3 months ago)
- Between 3 and 6 months (3 to 6 months ago)
- Between 6 and 12 months (6 to 12 months ago)
- Between 1 and 5 years (1 to 5 years ago)
- Between 5 and 15 years (5 to 15 years ago)
- More than 15 years ago
- Don't know/Not sure
- Never drank regularly

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average?

_____ (Enter the number of drinks a day)

- Refused
- Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly?

_____ years

- Refused
- Don't know/Not sure

9. At what age did you begin drinking regularly?

_____ years of age

- Refused
- Don't know/Not sure

10. What type(s) of alcohol do you drink? (Mark ALL that apply)

- Wine
- Liquor
- Beer
- Wine cooler

Signature of Individual Completing This Form _____ Date ____ / ____ / ____
(MM/DD/YYYY)

Name of Individual Completing This Form (please print) _____

TOBACCO ASSESSMENT – BASELINE

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
_____	_____	_____	____ / ____ / _____

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?

- Yes
 No → **Skip to Section B**
 Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette (even one or two puffs)?

_____ Years old

3. How old were you when you first began smoking cigarettes regularly?

_____ Years old

Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.

_____ Years (If you smoked less than one year, write "1.")

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

6. Do you NOW smoke cigarettes?

- Everyday
 Some days
 Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette?

- Within 30 minutes
 After 30 minutes

8. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

- I smoked a cigarette today (at least one puff)
- 1-7 days → Number of days since last cigarette _____
- Less than 1 month → Number of weeks since last cigarette _____
- Less than 1 year → Number of months since last cigarette _____
- More than 1 year → Number of years since last cigarette _____
- Don't know/Don't remember

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes?

- Yes
- No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?

- Every day → Number of times per day _____
- Some days → Number of days _____ per Week Month Year

11. Which of the following products have you ever used regularly?

Check all that apply

- Cigarettes
- E-cigarettes or other electronic nicotine delivery system
- Traditional cigars, cigarillos or filtered cigars
- Pipes
- Hookah
- Clove cigarettes or kreteks
- Bidis
- Smokeless tobacco, like dip, chew, or snuff
- Snus
- Paan with tobacco, gutka, zarda, khaini
- Other, Please specify: _____

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

- Within the past month (0 to 1 month ago)
- Between 1 and 3 months (1 to 3 months ago)
- Between 3 and 6 months (3 to 6 months ago)
- Between 6 and 12 months (6 to 12 months ago)
- Between 1 and 5 years (1 to 5 years ago)
- Between 5 and 15 years (5 to 15 years ago)
- More than 15 years ago
- Don't know/Not sure
- Never used other forms of tobacco regularly

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker?

- Yes
- No

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors?

- Yes
- No

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors?

- Yes
- No

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?

- Yes In total, for about how many years? _____ If less than 1, write "1."
- No

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?

- Yes → In total, for about how many years? _____ If less than 1, write "1."
- No

Signature of Individual Completing This Form _____ Date ____/____/_____
(MM/DD/YYYY)

Name of Individual Completing This Form (please print) _____

APPENDIX E

Alcohol and Tobacco Use Assessment Questionnaires – Follow Up

ALCOHOL ASSESSMENT – FOLLOW UP

REGISTERING INSTITUTION _____	PARTICIPANT ID _____	VISIT TYPE _____	VISIT DATE (MM/DD/YYYY) ____ / ____ / _____
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Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. During the past 30 days, did you drink any alcoholic beverages?

- Yes
- No **(End)**
- Refused **(End)**
- Don't know/Not sure

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?

_____ (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.)

- Week
- Month
- Refused
- Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?

_____ (Enter the average number of drinks you had per day.)

- Refused
- Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day?

_____ Number of times

- None
- Do not know/Not sure

Signature of Individual Completing This Form _____ Date ____ / ____ / ____
(MM/DD/YYYY)

Name of Individual Completing This Form (please print) _____

TOBACCO ASSESSMENT – FOLLOW UP

REGISTERING INSTITUTION	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
_____	_____	_____	____ / ____ / _____

1. Do you NOW smoke cigarettes?

- Everyday
- Some days
- Not at all → **Skip to Question 3.**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

3. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

- I smoked a cigarette today (at least one puff)
- 1-7 days → Number of days since last cigarette _____
- Less than 1 month → Number of weeks since last cigarette _____
- Less than 1 year → Number of months since last cigarette _____
- More than 1 year → Number of years since last cigarette _____
- Don't know/Don't remember

4. Since your last visit, have you used other forms of tobacco, not including cigarettes?

- Yes
- No (**End**)

5. How often do you/did you use other forms of tobacco?

- Every day → Number of times per day _____
- Some days → Number of days _____ per Week Month Year

6. Since your last visit, which of the following products have you used? **Check all that apply**

- Cigarettes
- E-cigarettes or other electronic nicotine delivery system
- Traditional cigars, cigarillos or filtered cigars
- Pipes
- Waterpipe
- Hookah
- Clove cigarettes or kreteks
- Bidis
- Smokeless tobacco, like dip, chew, or snuff
- Snus
- Paan with tobacco, gutka, zarda, khaini
- Other, Specify _____

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

- Within the past month (0 to 1 month ago)
- Between 1 and 3 months (1 to 3 months ago)
- Between 3 and 6 months (3 to 6 months ago)
- Between 6 and 12 months (6 to 12 months ago)
- Between 1 and 5 years (1 to 5 years ago)
- Between 5 and 15 years (5 to 15 years ago)
- More than 15 years ago
- Don't know/Not sure
- Never used other forms of tobacco regularly

The following instructions pertain to questions 8 - 10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment

- Smoked every day
- Smoked some days
- Did not smoke at all
- Don't know/not sure
- Not applicable

9. After the end of study treatment

- Smoked every day
- Smoked some days
- Did not smoke at all
- Don't know/not sure
- Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic

- Smoked every day
- Smoked some days
- Did not smoke at all
- Don't know/not sure
- Not applicable (This is my first visit to this clinic)

Signature of Individual Completing This Form _____ Date ____ / ____ / ____
(MM/DD/YYYY)

Name of Individual Completing This Form (please print) _____

APPENDIX F

Resources for tobacco and alcohol quitting

National and local resources to help with alcohol abuse and alcoholism

NIAAA's online guide *Treatment for Alcohol Problems: Finding and Getting Help* is written for individuals, and their family and friends, who are looking for options to address alcohol problems. It is intended as a resource to understand what treatment choices are available and what to consider when selecting among them. <https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm>

Other resources:

National Institute on Alcohol Abuse and Alcoholism www.niaaa.nih.gov
301-443-3860

National Institute on Drug Abuse www.nida.nih.gov
301-443-1124

National Clearinghouse for Alcohol and Drug Information www.samhsa.gov
1-800-729-6686

Substance Abuse Treatment Facility Locator www.findtreatment.samhsa.gov
1-800-662-HELP

Alcoholics Anonymous (AA) www.aa.org
212-870-3400 or check your local phone directory under "Alcoholism"

Moderation Management www.moderation.org
212-871-0974

Secular Organizations for Sobriety www.sossobriety.org
323-666-4295

SMART Recovery www.smartrecovery.org
440-951-5357

Women for Sobriety www.womenforsobriety.org
215-536-8026

Al-Anon Family Groups www.al-anon.alateen.org
1-888-425-2666 for meetings

Adult Children of Alcoholics www.adultchildren.org
310-534-1815

National and local resources to help with quitting smoking

NCI's Smokefree.gov offers science-driven tools, information, and support that has helped smokers quit. You will find state and national resources, free materials, and quitting advice from NCI.

Smokefree.gov was established by the [Tobacco Control Research Branch](#) of NCI, a component of the National Institutes of Health, in collaboration with the Centers for Disease Control and Prevention and other organizations.

Publications available from the Smokefree.gov Web site include the following:

- [Clearing the Air: Quit Smoking Today](#) for smokers interested in quitting.
- [Clear Horizons](#) for smokers over age 50.
- [Forever Free™](#) for smokers who have recently quit.
- Forever Free for Baby and Me™, in [English](#) and [Spanish](#), for pregnant smokers who have recently quit.
- [Pathways to Freedom: Winning the Fight Against Tobacco](#) for African American smokers.

NCI's **Smoking Quitline at 1-877-44U-QUIT (1-877-448-7848)** offers a wide range of services, including individualized counseling, printed information, referrals to other resources, and recorded messages. Smoking cessation counselors are available to answer smoking-related questions in English or Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m., Eastern time. Smoking cessation counselors are also available through [LiveHelp](#), an online instant messaging service. LiveHelp is available Monday through Friday, 8:00 a.m. to 11:00 p.m., Eastern time.

Your state has a toll-free telephone quitline. Call **1-800-QUIT-NOW (1-800-784-8669)** to get one-on-one help with quitting, support and coping strategies, and referrals to resources and local cessation programs. The toll-free number routes callers to state-run quitlines, which provide free cessation assistance and resource information to all tobacco users in the United States. This initiative was created by the [Department of Health and Human Services](#). For more information about quitlines, [speak to an expert](#) on the Smokefree.gov Web site.

APPENDIX G

Plain Language Guide for Assessing Skin Application AEs

Utilize this guide for assessing Skin Application AEs during the Day 8 phone call and Day 15 and Day 28 visits. To assess skin toxicity please ask the participant non-leading questions such as “Have you noted any changes in the skin of your breast?” If the participant reports yes, then utilize the plain language guide below to ask more probing questions as needed.

1. Is your breast skin dry from gel application? If yes, is it red or itchy?
2. Do you have pain on your breast skin? If yes, how severe?
3. Is your skin itchy from gel application? If yes, how severe? Are you taking any medicine for it?
4. Do you have rash on your breast skin? If yes, how big is the affected area? Are you taking any medicine for it? Can you please send us a picture of your rash?
5. Do you have hives on the breast skin where you have applied the gel? If yes, how big is the affected area? Are you taking any medicine for it?