1.0 CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-blind, Placebo Controlled Trial of 4-Hydroxytamoxifen Gel for Reducing Breast Tissue Density in Women with BI-RADS Breast Density Categories C or D
Study Number:	BHR-700-301
Study Phase:	Phase 3
Product Name:	BHR-700 (0.2% 4-Hydroxytamoxifen Gel)
IND Number:	59,081
EudraCT Number:	2017-002906-10 NCT Number: NCT03199963
Indication:	Reduction in Breast Tissue Density
Investigators:	Multicenter study conducted in approximately 25 centers
Sponsor:	BHR Pharma, LLC
Sponsor Contact:	[redacted]
Sponsor's Legal Representative:	[redacted]
Lead Investigator:	[redacted]
Medical Monitor:	[redacted]
CRO Contact:	[redacted]
Original Protocol:	19 April 2017
Amendment 1:	07 June 2017
Amendment 2:	01 August 2017
Amendment 3:	18 April 2018

CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary to BHR PHARMA, LLC. This information is being provided to you for the purpose of conducting a clinical study for BHR PHARMA, LLC. You may disclose the contents of this protocol to study personnel under your supervision who need to know the contents for the purpose, as well as to your Institutional Review Board(s) or Ethics Committee(s). The foregoing shall not apply to disclose required governmental regulations or laws; however, you will give prompt notice to BHR PHARMA, LLC of any such disclosure.

Any supplemental information that may be added to this document is also confidential and proprietary to BHR PHARMA, LLC and must be kept in confidence in the same manner as the contents of this protocol.

Any person who receives this protocol without due authorization from BHR PHARMA, LLC is requested to return it to BHR PHARMA, LLC or to promptly destroy it.

1.1 Sponsor Approval

A Randomized, Double-Blind, Placebo-Controlled Trial of 4-Hydroxytamoxifen Gel for Reducing Breast Tissue Density in Women with BI-RADS Breast Density Categories C or D

Version: 4.0 Amendment 3
Date: 18 April 2018

BHR PHARMA, LLC

[redacted]

1.2 Principal Investigator Agreement

A Randomized, Double-Blind, Placebo-Controlled Trial of 4-Hydroxytamoxifen Gel for Reducing Breast Tissue Density in Women with BI-RADS Breast Density Categories C or D

Version: 4.0 Amendment 3
Date: 18 April 2018

As an Investigator conducting this study, I agree:

- To assume responsibility for the proper conduct of the study at this site;
- To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by BHR PHARMA, LLC;
- Not to implement any deviations from or changes to this protocol without agreement from the Sponsor and prior review and the written approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard to the subject/subjects or for administrative aspects of the study (where permitted by all applicable regulatory requirements);
- That I am thoroughly familiar with the appropriate use of the investigational product, as described in this protocol, and any other information provided by the sponsor including, but not limited to the current study procedures or any equivalent documents provided by BHR PHARMA, LLC;
- That I am aware of, and will comply with Good Clinical Practice and all applicable regulatory requirements;
- To ensure that all persons assisting me with the study are adequately informed about the study procedures and study devices, and that they are qualified to perform their study-related duties and functions, as described in this protocol.

PRINCIPAL INVESTIGATOR

Name:

Signature Date

1.3 Study Synopsis

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Trial of 4-Hydroxytamoxifen Gel for Reducing Breast Tissue Density in Women with BI-RADS Breast Density Categories C or D
Development Phase:	Phase 3
Investigational Product (IP):	BHR-700, 4-Hydroxytamoxifen (afimoxifene) gel
Active Pharmaceutical Ingredient (API):	4-Hydroxytamoxifen (4-OHT)
Study Centers:	Multicenter study conducted in approximately 25 centers
Study Duration:	Up to 110 weeks per subject: 2 weeks screening, 52 weeks blinded treatment period with an optional 52 weeks open-label extension.
Study Objective	
Primary:	To determine the efficacy of 8 mg/day (4 mg/breast) of BHR-700 gel compared to placebo for reducing breast tissue density in women identified as having dense breast tissue upon analysis of screening mammography using the Food and Drug Administration (FDA)-cleared Cumulus 2D software.
Study Endpoints	
Primary:	The percentage reduction of mammographic breast tissue density on a follow-up mammogram compared to the baseline mammogram after 52 weeks of treatment.
Secondary:	Incidence and severity of adverse events (AEs) with special attention given to uterine abnormalities, cardiovascular events, thromboembolic events, and incidence of vasomotor symptoms (“hot flush”). Change in serum concentration of sex hormone binding globulin (SHBG). Change in serum concentration of: cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Change in serum concentration of Protein C-activity, Protein S-activity, Antithrombin 111 antigen, and Activated Protein C resistance (APCR). Change in serum concentration of select bone biomarkers CTx and BSAP. Plasma concentrations of the E and Z isomers of 4-OHT.
Study Design	
Methodology:	This is a multi-center, randomized, double-blind, placebo-controlled study in women identified as having dense breast tissue upon screening mammography. Subjects who give informed consent will have screening evaluations, including hormone measures of FSH, Estradiol, Estrone and LH to

	determine menopausal state. Some subjects may require a mammogram to be made at this stage because they do not have a mammogram that fulfills the necessary criteria (format or time period). Those subjects meeting entry criteria, will be stratified, based on their hormone levels, into pre/peri and post menopause groups and randomized within those groups 2:1 to receive either 8 mg/day (4 mg/breast) BHR-700 gel or placebo for up to 52 weeks. At the Principal Investigator's (PI) discretion, subjects may be allowed to reduce the dose to 4 mg/day (2 mg/breast) in cases of intolerance. Subjects will apply the gel to both breasts once per day. The first dose will be applied under the supervision of the PI/designee. Subsequent doses will be self-administered daily by the subject until she has completed 52 weeks of study drug administration. A diary will be kept by the subject to monitor compliance, the start and stop dates for the subject's last menstrual cycle and any breakthrough bleeding experienced excluding days of normal menses. Subjects who complete the double-blind phase of the study will be offered entry into an open-label follow-up period for an additional 52 weeks. While on treatment, subjects will be evaluated at Day 1 and every 13 weeks thereafter.
Number of Subjects:	A planned sample size of 330 women, identified as having dense breast tissue upon mammography, will be randomized to receive either BHR-700 gel or placebo (2:1 distribution). Considering an attrition rate of approximately 15%, the expectation is to have 272 evaluable women (4-OHT: 181 & Placebo: 91) who will have both baseline and 52 week measurements of percent mammographic density (MD) of the breast.
Inclusion Criteria:	1. Healthy women age 35 – 75 years with either heterogeneously dense (C) or extremely dense (D), breast tissue on 2D mammography, based on American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS©) fifth edition classification) in either breast within 3 months prior to randomization. Mammogram with BI-RADS final assessment category 1 or 2 (negative or benign findings). 2. If the woman is of childbearing potential, she must have a documented negative urine pregnancy test at time of screening and randomization and no plans to become pregnant for the duration of study participation. 3. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria:	1. Participants may not be receiving treatment with any investigational drug or investigational biologic within 30 days of randomization or at any time during the study. 2. Women with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to Tamoxifen. 3. Pregnant women are excluded from this study because the effects of 4-OHT gel on the developing human fetus at the recommended dose and route are unknown. 4. Pregnancy (independent of outcome) and/or lactation within 1 year prior to the screening mammogram. 5. Women with previous history of cancer (including invasive or intra-ductal breast cancer) except for non-melanoma skin cancer. 6. Women who have had a prior mastectomy (unilateral or bilateral), segmental mastectomy, reduction mammoplasty or breast augmentation including implants. 7. Women with surgical breast biopsy(s) performed within 3 years or core biopsy(s) performed within 1 year prior to randomization. 8. Women with an abnormal mammogram (BI-RADS final assessment category 3-probably benign, 4-suspicious, or 5-malignant findings). Women with BI-RADS 0 assessment (needs additional imaging evaluation) that are subsequently found to have negative (BI-RADS 1) or benign findings (BI-RADS 2), are NOT excluded. 9. Women with only synthetic 2D mammograms generated from 3D (tomosynthesis) are excluded as breast density measurements are not yet validated for synthetic mammograms. Women with combination 2D+3D mammograms are not excluded. 10. Women with active liver disease or thromboembolic disorder. 11. Women with skin conditions such as psoriasis, fungal infections, keloids etc., or tattoos and/or piercings, which in the opinion of the Investigator, would interfere with absorption of the IP. 12. Women who have had an abnormal gynecology exam within the last three years with clinically significant findings, such as secondary dysmenorrhea, polyps, or atypia, which in the opinion of the Investigator would interfere with the study. 13. Women who have received treatment with Selective Estrogen Receptor Modulators (SERMs) (e.g. tamoxifen, raloxifen) or aromatase inhibitors. 14. Women taking estrogen containing contraceptives or Hormone Replacement Therapy (HRT) must discontinue the treatment a minimum of 6 months prior to the screening mammogram. Progestin only contraceptives are permitted. 15. Women with a concurrent illness, disease or condition that, in the opinion of the Investigator, would limit their compliance with study requirements or place them at additional risk.

Test Product, Dose, and Mode of Administration:	The BHR-700 gel formulation contains 2 mg/mL 4-OH tamoxifen (0.2%) in a clear, colorless, absorptive hydro-alcoholic gel base formulated to provide continuous release of 4-OH tamoxifen. The BHR-700 gel is supplied in a non-aerosol canister with a 1 mL fixed-dose pump. Two (2) fixed unit doses of BHR-700 gel will be applied daily to each breast. Each actuation dispenses 1 mL of gel. A total of 8 mg/day (4 mg/breast) of 4-OHT will be administered daily, unless dose reduction by the Investigator, is deemed necessary for reasons of tolerability. The placebo gel is identical in appearance and consistency to the BHR-700 gel. Treatment compliance will be monitored by the Investigator staff who will check subject diaries and weigh the IP canister(s) when dispensed and upon return.
Duration of Treatment:	Up to 52 weeks for primary efficacy assessment with an optional and additional 52 weeks of open-label treatment of BHR-700 gel.
Criteria for Evaluation	
Efficacy Measures:	Mammograms will be centrally analyzed. The reader will be blinded as to the treatment group (BHR-700 gel or placebo) and time point of each subject. Cumulus 2D will be the primary endpoint method with Volpara 3D as a secondary endpoint method.
Safety Measures:	Safety assessments will include evaluation of all AEs/serious adverse events (SAEs), with special attention given to uterine abnormalities, cardiovascular events, and thromboembolic events. Additional important safety parameters specific for this indication are: • Endometrial changes • Breast evaluation • Coagulation factors • Bone biomarkers • Changes in menstrual cycle; unexpected vaginal bleeding To address these safety parameters, subjects will undergo the following assessments: A bilateral mammogram with both the raw and processed 2D image DICOM files needs to be performed within 3 months prior to randomization. The same (make/model/serial number) mammography machine must be used for the Week 52 mammogram, and if the subject is participating in the Open-Label phase, the Week 104 mammogram. If the mammogram is older than 3 months but less than 18 months, or it cannot be provided in the format required for

	the study, the mammogram can be repeated to meet the study entry requirement after informed consent has been obtained. A clinical breast examination will be performed at Screening, Baseline (Study Day 1-Week 1) and Study Week 52. Coagulation factors will be measured prior to administration of study drug, Study Week 26 and Study Week 52. Changes in bone mineral density will be assessed by measurement of select bone biomarkers pre-dose and at Study Week 52. Serum concentration of sex hormone binding globulin (SHBG) will be measured pre-dose and at Study Week 52. Routine laboratory parameters (i.e., hematology and blood chemistry) will be measured at Screening, on Day 1 before administration of study drug, Study Week 26 and Study Week 52. Urine pregnancy tests will be performed on women of child bearing potential at Screening, Randomization, at each clinic visit and at any point during the study when pregnancy is suspected (i.e., missed cycle, skipped/failed birth control). AEs will be collected at each Study Visit beginning with the first dose of study drug (Study Day 1). During the trial, in a case of significant changes in bleeding pattern or other signs/symptoms which could be related to endometrial pathology, the Investigator will perform a uterine ultrasound followed by an endometrial biopsy if indicated.
Pharmacokinetic:	BHR-700 (E and Z isomers) plasma concentrations will be measured at Study Weeks 13, 26, 52, 78, and 104.

Statistical Methods:	**<u>Blinded Treatment Phase</u>** Primary Outcome Measure: • Comparison of the reduction in breast density between BHR-700 gel and placebo treatment groups at 52 weeks using the Cumulus method. Assuming a reduction from baseline of 6% on active and 2% on placebo, with a common standard deviation of 8%, a total of 272 subjects will achieve a power of 90% using a two sample, two-sided t-test at a significance level of < 0.01. Considering an attrition rate of approximately 15%, 330 subjects will be enrolled. Secondary Outcome Measures: • Comparison of breast density measurements (Cumulus and Volpara) • Laboratory parameters will be summarized in a descriptive fashion. • Incidence and severity of AEs will be compared between BHR-700 gel and placebo. **<u>Open-Label Treatment Phase</u>** Secondary Outcome Measures: • Comparison of breast density measurements (Cumulus and Volpara) • Laboratory parameters will be summarized in a descriptive fashion. • Incidence and severity of AEs will be compared between BHR-700 gel and placebo.

Table of Contents

List of Tables

2.0 BACKGROUND

2.1 Introduction

Breast cancer remains the most common type of cancer in women with an estimated 1.6 million cases per year worldwide. Studies have shown that women with dense breast tissue have a 2-6 fold increased risk of developing breast cancer, with only age or BRCA 1 and BRCA 2 gene mutation being associated with a higher increase in risk.[1] Mammographic density (MD) is heavily influenced by and inversely proportional to age, reflecting the relative decrease in glandular tissue and increase in fatty breast tissue associated with aging.[2]

Tamoxifen is an effective oral treatment for estrogen receptor-positive breast cancer. 17β-estradiol, at physiologic concentrations, is known to stimulate the proliferation of normal breast epithelial cells. Tamoxifen is an antiestrogen that inhibits estradiol effects through competitive binding to the estrogen receptor at or near the 17β-estradiol binding site resulting in cell-cycle arrest.[3,4,5] Studies of tamoxifen in the adjuvant and preventive setting have demonstrated that a decline in MD of approximately 10% is consistently associated with better outcomes. In a case-control analysis, Cuzick et al. observed that approximately 46% of tamoxifen-treated women experienced a ≥ 10% reduction in MD at 12−18 months and a 63% reduction in breast cancer risk when compared with all women on placebo treatment regardless of MD. In contrast, tamoxifen-treated women with a < 10% reduction in MD did not experience risk reduction compared to all women on placebo.[6]

Further retrospective analyses have reported that among women with estrogen receptor-positive breast cancer treated with tamoxifen, those whose mammographic density declined in the unaffected breast had a reduced risk of recurrence or death from breast cancer.[7,8]

2.2 Rationale

Despite the success of tamoxifen in reducing mammographic density in breast tissue and reducing the recurrence risk of new estrogen receptor positive tumors, the adverse event (AE) profile of oral administration makes it an unacceptable treatment to many women. Tamoxifen has been shown to increase the risk of endometrial cancer, thromboembolic events, vasomotor symptoms, arthralgia, and cataracts.

4-Hydroxytamoxifen (4-OHT) is a potent anti-estrogenic metabolite of tamoxifen with a much higher affinity for estrogen receptors than tamoxifen.[9,10,11,12] 4-OHT is produced by a step-wise synthetic process from the commercially available raw materials: anisole, 2-phenylbutyric acid chloride, 4-bromophenol, and 2-dimethylaminoethyl chloride: HCL. The crude 4-OHT is purified by recrystallization from methanol, resulting in two geometric isomers E and Z.

A topically applied formulation of 4-OHT is being developed with the aim of achieving concentrations of 4-OHT in the breast that are sufficiently high to be effective in treating breast disease, while avoiding first pass metabolism in the liver, therefore minimizing the potential for systemic AEs. The alcohol-based gel formulation solubilizes 4-OHT to allow topical administration and transdermal bioavailability. Studies to date indicate that the topical formulation of 4-OHT is absorbed through the skin into breast tissue with an order of magnitude higher than in plasma of 10:1. The breast tissue/plasma ratio is approximately 5:1 following oral administration of tamoxifen.

In vitro studies of 4-OHT gel formulation show linear systemic pharmacokinetics (PK) with much of the drug excreted in feces. Topical 4-OHT at doses up to 200µg/kg/day in two species was generally well tolerated, there were no clinical signs of toxicity; however, there were cases of weight loss, reduced uterus and ovary size, and changes seen in the genital tract.

In vivo, topical 4-OHT has been evaluated in clinical trials for cyclical breast pain and has been shown to be well tolerated. In a placebo-controlled study in cyclic mastalgia, patients were treated for 4 to 6 months. Headache and nasopharyngitis were the most common AEs seen in 15% and 2%, 20% and 11%, and 10% and 12% in patients on 2 mg/day, 4 mg day, and placebo, respectively.[13] 4-OHT and oral tamoxifen were studied in the neoadjuvant setting in 55 patients with invasive breast cancer; Ki-67, a prognostic parameter in breast cancer patients, was shown to decrease with both gel and oral treatments[14]. In a recent study of 26 women with Ductal Carcinoma In-Situ (DCIS), treatment of topical 4-OHT gel at 4 mg/day (2 mg to each breast) or oral tamoxifen at 20 mg/day for 6-10 weeks resulted in similar 4-OHT breast tissue levels and similar reductions in breast tumor cell proliferation[15]. However, systemic levels of 4-OHT were 5-fold lower with topical 4-OHT gel when compared to oral tamoxifen resulting in reduced effects on endocrine and coagulation parameters with transdermal delivery. The gel was well tolerated, with most AEs rated as mild and none as severe. The most commonly reported AEs were hot flushes (50% vs. 50%), breast pain (42% vs. 64%), fatigue (33% vs. 29%), and night sweats (25% vs. 43%).

To date, topical 4-OHT has been administered to > 450 pre-and post-menopausal women and has been shown to be safe and well tolerated with no clinically significant AEs reported to date following administration of doses of 0.25 mg/day, 0.5 mg/day, 1 mg/day, 2 mg/day, and 4 mg/day. The dose suggested for the present study is 8 mg/day, with the option of down titration to 4 mg/day in case of lack of tolerability. Even though breast tissue levels of 4-OHT were similar between 4 mg/day topical 4-OHT gel and 20 mg/day oral tamoxifen, the 8 mg/day dose was selected because there is another active metabolite (endoxifen) formed after oral tamoxifen

administration that is not seen after 4OHT gel topical administration[15]. The tolerability of 4 mg/day in the placebo controlled 6 months cyclic mastalgia study was excellent and therefore there is no reason to believe 8 mg/day would be associated with a large increase in side effects. An unblinded independent DSMB will monitor plasma levels of 4OHT and adverse events during the study to further ensure safety of the subjects.

BHR PHARMA, LLC has developed an investigational topical gel formulation of 4-OHT for the reduction of mammographic density in women at an increased risk for breast cancer. BHR-700 gel contains 4-Hydroxytamoxifen in an absorptive hydro-alcoholic gel base for topical administration to the breast(s). The active component of the topical gel is 4-OHT, a metabolite of tamoxifen with approximately 100 times the potency (as measured by binding affinity to estrogen receptors). The remaining components of the gel are pharmacologically inactive. The chemical structure of the two isomers (E and Z) of 4-OHT is shown in Figure 1 and Figure 2.

Figure 1. Chemical Structure of 4-OHT (4-Hydroxytamoxifen): E isomer

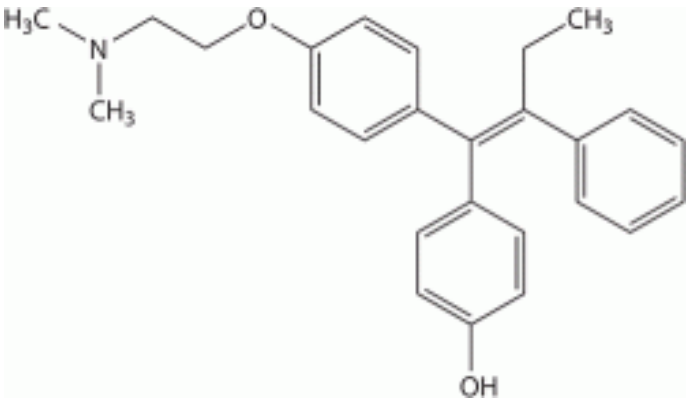
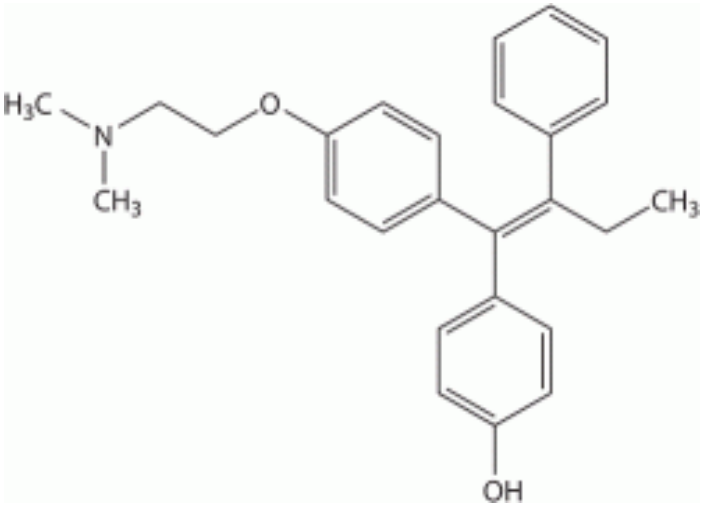


Figure 2. Chemical Structure of 4-OHT (4-Hydroxytamoxifen): Z isomer



Common Name:	4-Hydroxytamoxifen - (E) and (Z) isomers (50:50)
CAS Reg. No.:	68392-35-8
Chemical Name:	4-(1-[4-(Dimethylaminoethoxy)phenyl]-2-phenyl-1-butenyl)phenol; 4-OH Tamoxifen; cis/trans-4-Hydroxytamoxifen
Empirical Formula:	$C_{26}H_{29}NO_2$
Molecular Weight:	387.51

3.0 STUDY OBJECTIVES & PURPOSE

The overall purpose of this study is to evaluate whether daily application of 8 mg (4 mg/breast) of 4-OHT lowers breast density in women with mammographically dense breast tissue.

Primary Objective:

To determine the efficacy of transdermal administration of 8 mg/day (4 mg/breast) of 4-OHT delivered as 4 mLs BHR-700 gel compared to placebo for reducing breast tissue density in women identified as having dense breast tissue upon analysis of screening mammography using the Food and Drug Administration (FDA)-cleared Cumulus 2D software.

Secondary Objectives:

1. To compare the change in percent mammographic density from Baseline to the Week 52 mammogram in women applying 8 mg 4-OHT vs. placebo, using two breast density measurement methods (Cumulus versus Volpara).
2. To compare the percentage of women who underwent a change in BI-RADS category when comparing pre-and post-treatment measurements for recipients of 4-OHT and placebo.
3. To compare the percentage of women with a ± 10% absolute decrease in quantitative mammographic density (Cumulus) between baseline and 52 weeks, when comparing between the recipients of 4-OHT and placebo.
4. To describe the symptoms assessed by laboratory toxicity assessments complete blood count (CBC) w/diff, blood chemistry, coagulation factors, lipid panel, liver function tests, sex hormone binding globulin (SHBG), and bone biomarkers.
5. To determine the safety and tolerability of 8 mg/day of 4-OHT after 52 weeks of administration to the breasts such as AE collection, effects on menstrual cycle, and laboratory values.
6. To determine whether 8 mg/day of 4-OHT will disrupt the menstrual cycle of premenopausal women.
7. To determine the plasma concentration of the E and Z isomers of 4-OHT after 13, 26, 52, 78, and 104 weeks of application of 4 mL BHR-700 gel to the breasts.

4.0 STUDY DESIGN

This is a randomized, double blind, placebo-controlled study. Subjects will have been assessed as having mammographically dense breast (heterogeneously dense (C) or extremely dense (D), based on the American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS©) fifth edition classification) as described in Table 1, for eligibility.

Table 1. ACR BI-RADS© Breast Tissue Composition

Grade	Classification
A	The breasts are almost entirely fatty.
B	There are scattered areas of fibroglandular density.
C	The breasts are heterogeneously dense, which may obscure small masses.
D	The breasts are extremely dense, which lowers the sensitivity of mammography.

Approximately 330 subjects will be enrolled at approximately 25 sites located in the U.S. and Europe. Subjects who give informed consent will have screening evaluations, including hormone assessments of FSH, Estradiol, Estrone and LH to determine menopausal state. Those subjects meeting entry criteria, will be stratified, based on their hormone levels into either pre/peri or post-menopausal groups and randomized 2:1 within those groups to receive either 8 mg/day (4 mg/breast) 4-OHT or matching placebo for up to 52 weeks.

Subjects will apply the investigational gel to both breasts once per day. The first dose will be applied under the supervision of the Principal Investigator (PI) or designee. Subsequent doses will be self-administered at approximately the same time daily, after showering, by the subject until she has completed 52 weeks of study drug administration. There will be, in addition, an optional 52 weeks of open-label treatment for those subjects who choose to continue treatment. Subjects will capture daily gel administration in a diary to monitor compliance.

While on treatment, subjects will return to the clinic for study assessments, a review of AEs and to re-supply study gel at 13, 26, 39, weeks and at 52 weeks for those subjects who have agreed to take part in the open-label phase of the study. A schedule of study assessments is shown in Appendix 1.

During the study, in a case of significant changes in bleeding pattern or other signs/symptoms which could be related to endometrial pathology, the Investigator will perform a uterine ultrasound followed by an endometrial biopsy if indicated.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Inclusion Criteria

1. Healthy women age 35 – 75 years with either heterogeneously dense (C) or extremely dense (D) dense breast tissue on 2D mammography, based on ACR BI-RADS© fifth edition classification, within 3 months prior to randomization. Mammogram with BI-RADS final assessment category 1 or 2 (negative or benign findings).

2. If the woman is of childbearing potential, she must have a documented negative urine pregnancy test at the time of screening and randomization and no plans to become pregnant for the duration of study participation.

3. Ability to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

1. Participants may not be receiving treatment with any investigational drug or investigational biologic within 30 days of randomization or at any time during the study.

2. Women with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to Tamoxifen.

3. Pregnant women are excluded from this study because the effects of 4-OHT gel on the developing human fetus at the recommended dose and route are unknown.

4. Pregnancy (independent of outcome) and/or lactation within 1 year prior to the screening mammogram.

5. Women with previous history of cancer (including invasive or intra-ductal breast cancer) except for non-melanoma skin cancer.

6. Women who have had a prior mastectomy (unilateral/bilateral), segmental mastectomy, reduction mammoplasty or breast augmentation including implants.

7. Women with surgical breast biopsy(s) performed within 3 years or core biopsy(s) performed within 1 year prior to randomization.

8. Women with an abnormal mammogram (BI-RADS final assessment category 3 - probably benign, 4-suspicious, or 5-malignant findings). Women with BI-RADS 0 assessment (needs additional imaging evaluation) that are subsequently found to have negative (BI-RADS 1) or benign findings (BI-RADS 2), are NOT excluded.

9. Women with only synthetic 2D mammograms generated from 3D (tomosynthesis) are excluded as breast density measurements are not yet validated for synthetic mammograms. Women with combination 2D+3D mammograms are not excluded.

10. Women with active liver disease or thromboembolic disorder.

11. Women with skin conditions such as psoriasis, fungal infections, keloids etc., or tattoos and/or piercings that in the opinion of the Investigator, would interfere with absorption of the investigational product.

12. Women who have had an abnormal gynecology exam within the last three years with clinically significant findings, such as secondary dysmenorrhea, polyps, or atypia, which in the opinion of the Investigator would interfere with the study.

13. Women who have received treatment with Selective Estrogen Receptor Modulators (SERMs) (e.g. tamoxifen, raloxifen) or aromatase inhibitors.

14. Women taking estrogen containing contraceptives or Hormone Replacement Therapy (HRT) must discontinue the treatment a minimum of 6 months prior to the screening mammogram. Progestin only contraceptives are permitted.

15. Women with a concurrent illness, disease or condition that, in the opinion of the Investigator, would limit their compliance with study requirements or place them at additional risk.

5.3 Dose Reduction

If a subject experiences toxicity that may make her want to stop taking study drug, the dose of study drug will be reduced by 50%, to 2 mg (1 pump actuation) to each breast. The reduced dose will be maintained for the duration of the study.

5.4 Early Withdrawal of Subjects

A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety. The primary reason for withdrawal must be recorded in the subject's medical record and on the withdrawal form in the Case Report Form (CRF). If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the CRF. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor before the subject stops administration of the study drug. If the study drug is discontinued, the final evaluations will be performed as completely as possible. Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination, date of stopping study drug, and the total amount of study drug administered must be recorded in the CRF and source documents.

5.5 Subject Replacement

Randomized subjects who do not complete the study for any reason will not be replaced.

6.0 TREATMENT OF SUBJECTS

Investigational product will only be shipped to Investigators who have provided BHR PHARMA, LLC (or an authorized representative) all required study documents, including Institutional Review Board (IRB) approval, have executed a clinical trial agreement (CTA), and have been approved by BHR PHARMA, LLC to begin the study. Study drug will be provided by BHR PHARMA, LLC (or authorized representative) as blind-labeled ready-to-use canisters containing 4-OHT gel or placebo.

6.1 Blinding and Unblinding

All Investigator site personnel will be blinded to treatment assignment. The Investigator (or designee) will be responsible for drug accountability and dispensing of the study drug.

In the case of an AE or serious adverse event (SAE) for which the Investigator must know a specific treatment allocation to ensure the subject's safety, unblinding of treatment assignment is permitted. Instructions for "breaking the blind" will be provided to the Investigator. It should be stressed that unblinding the treatment allocation is only allowed for safety concerns in an emergency. If time allows, the Investigator is encouraged to discuss the matter with the study Medical Monitor prior to "breaking the blind" whenever possible.

If possible, the relationship of the AE to the study drug should be assessed before the treatment code is broken. In all cases, the Medical Monitor must be notified within 24 hours after the code has been broken.

If the treatment assignment is unblinded, study drug will be discontinued and the subject's participation in the study will end.

6.2 Formulation, Packaging, and Labeling

BHR-700 [redacted]

BHR-700 [redacted] The placebo gel is identical in appearance and consistency to the BHR-700 gel. In this double-blind study, canisters will be labeled with a canister identifier and 'For Investigational Use Only'.

6.3 Investigational Product Storage

All study drug must be stored in a secure limited-access area, at controlled room temperature (20 – 25º C [68° to 77°F]; excursions are permitted to 15° to 30°C [59° to 86°F]) in accordance with labeled storage requirements. Subjects will be instructed to store the study drug at home at room temperature, and to avoid extreme heat or cold during transportation from the clinic to home. Investigational labeling will include instructions to keep the product out of the reach of children.

6.4 Dispensing

The Investigator (or designee) will only dispense the specific numbered canisters/study drug kit as allocated by an interactive, web-based tele-randomization system.

6.5 Dosage and Administration

The first dose of treatment will be applied under the supervision of the PI or designee at the clinical site. Thereafter, subjects will self-apply either BHR-700 gel or placebo as 2 fixed unit doses daily to each breast. The gel should not be applied to any other parts of the body, including the neck, abdomen, or genitals. It is advised to apply study drug in the morning after showering and to wash hands with soap and water after application. Night-time application is acceptable, but caution should be taken to limit transfer to other individuals. Application should occur approximately at the same time daily. A subject study drug administration guideline is provided in Appendix 2.

When a canister is used for the first time, it must be primed. To prime the canister, remove the cap from the canister and push the pump all the way down until gel is dispensed. Complete the priming process by pushing the pump all the way down an additional three (3) times. Do not use any gel that comes out while priming. Discard the gel by washing it down the sink to avoid accidental exposure to others. It is only necessary to prime the pump before the first dose is dispensed. Repeat priming each time a new canister is opened. After priming, the canister is ready to use. One complete press of the pump will deliver approximately the same amount of gel each time. The Investigator (or designee) will demonstrate this to each subject and will prime the study drug canister(s) prior to dispensing to the subject.

If a subject misses a dose by more than 12 hours, that dose should be noted as missed and the subject should wait for the next scheduled time before applying investigational product.

If a subject experiences toxicity that may make her want to stop taking study drug, the dose of study drug will be reduced by 50%, to 2 mg (1 pump actuation) to each breast. The reduced dose will be maintained for the duration of the study.

6.6 Investigational Product Administration Precautions

Following the initial application by the Investigator (or his/her designee) only the subject should apply the study drug. Others (such as the subject's family members) should not apply the study drug to the subject.

The subject should not make contact with the area of skin where the study drug was applied for at least 1 hour after the application. Subjects should not massage or rub in the gel and allow the gel to dry for 5 minutes before getting dressed.

If someone else is exposed to the study drug by direct contact with the study drug, that person should wash the area of contact with soap and water as soon as possible. The longer the study drug is in contact with the skin the greater the chance that the other person will absorb some of the study drug. **This is especially important for children.**

No skin-to-skin transfer studies with BHR-700 (4-OHT gel) have been conducted. However, a study conducted in women[16] with a FDA-approved product, EstroGel® (0.06% estradiol gel), using a similar formulation showed that skin-to-skin contact between treated and non-treated women 1 hour after application of the gel, neither resulted in a statistically significant or clinically important transfer of estradiol gel to the non-treated women nor was there subsequent absorption of estradiol by the non-treated women. Use of health and beauty products (lotions, creams, sunscreen, self-tanner, etc.) on the application site is allowed one (1) hour after application of the study gel.

6.7 Pregnancy and Nursing

The effects of 4-OHT gel on the developing human fetus at the recommended dose and route are unknown. For this reason, women of childbearing potential must agree to avoid pregnancy by using a reliable medically acceptable contraceptive method.

A woman is not considered to be of child bearing potential if she has:

a. Serum follicle-stimulating hormone (FSH) levels consistent with menopause and has had complete amenorrhea for at least 12 months prior to starting drug.
b. Documented surgical history of hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.

A woman of child bearing potential must use one of the following contraceptive methods throughout the study and for at least 90 days after completing the study:

a. Bilateral tube ligation performed 6 months or more prior to starting study drug.
b. Consistent monogamous relationship with a male partner who has had a medically proven vasectomy performed 6 months or more prior to starting study drug.
c. Intrauterine device (IUD) in place for at least 3 months before starting study drug.
d. Progestin-containing hormonal birth control (oral, transdermal, injectable, or implantable) used consistently and successfully for at least 3 months prior to starting study drug.
e. Double barrier contraception with spermicide, including a condom plus diaphragm or cervical cap. **Note:** Female condom should be used with male condom (as a double barrier method of contraception) due to risk of tearing.
f. Abstinence
   True abstinence, when this is in line with the preferred and usual lifestyle of the subject, is acceptable. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

There is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with 4-OHT gel. Therefore, it is required that breastfeeding be discontinued prior to the mother enrolling in this study (see also 5.2, exclusion criterion 4).

Procedure for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study, the event must be reported to the Medical Monitor upon receipt of information by the study staff. While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Any pregnancy will be followed through delivery for the observation of any SAEs. Fatalities and spontaneous abortions must be reported as SAEs.

6.8 Assessment of Compliance

Study drug compliance will be checked at each study visit. Subjects will be asked to capture daily gel administration in a diary and drug canisters will be weighed on release to the subject and on return. The canister weight will be recorded in grams. If the study drug is discontinued or interrupted, the reason(s) will be recorded. One or more extra canisters will be provided to cover loss. Subjects who are found to be non-compliant will be re-trained on study drug administration by the PI or designee.

6.9 Investigational Product Accountability

The Investigator will maintain accurate records of the disposition of all clinical drug supplies received during the study and the dates on which drug supplies were received from BHR PHARMA, LLC or authorized representative. At the conclusion of the study, any unused study gel will be destroyed by the site in accordance with their standard operating procedures (SOP), upon written authorization by BHR PHARMA, LLC and pursuant to applicable federal and state regulations or returned to BHR PHARMA, LLC or their designee.

6.10 Prior and Concomitant Medications

All medications, prescription and over-the-counter (OTC), administered or taken by the subject during the study are to be recorded on the concomitant medication form of the CRF. Information should be recorded for: name of drug, dose, route of administration, start and end dates, and indication.

Any therapeutic or surgical procedure performed for concurrent conditions through the end of the study, should be recorded, including the date, description of the procedure, and clinical findings.

6.11 Prohibited Concomitant Medications/Therapies

Investigational drugs or therapies should not be used at any time during the study because of their potential to confound the results. The following drugs or therapies are prohibited during the study because of their potential to confound the results:

- Application of prescription or OTC topical drug products (including but not limited to: gel, patch, cream, ointment, lotion, or spray) to the study drug application site(s), i.e., on the breast(s).
- Prescription or OTC treatments that are known/suggested to have an estrogenic or anti-androgenic effect including SERMs and aromatase inhibitors.

7.0 STUDY PROCEDURES

7.1 Screening (Within 30 days prior to randomization)

Subjects who fulfill the Inclusion and Exclusion criteria and who have signed an Informed Consent Form will receive a Physical Examination including a breast exam. Relevant medical history will be recorded. Subjects will also be asked to complete a questionnaire on their menstrual cycle as shown in Appendix 3. Measurements of vital signs, including height and weight and laboratory measurements including hematology, blood chemistry, and hormones will be performed. A urine pregnancy test will be performed on women of child bearing potential.

A bilateral mammogram with both the raw and processed 2D image DICOM files needs to be performed within 3 months prior to randomization. The same (make/model/serial number) mammography machine must be used for the Week 52 mammogram and if the subject is participating in the Open-Label phase, the Week 104 mammogram. If the mammogram is older than 3 months but less than 18 months, or it cannot be provided in the format required for the study, the mammogram can be repeated to meet the study entry requirement after informed consent has been obtained.

7.2 Study Day 1 (Week 1): Baseline

Prior to dosing, the Inclusion/Exclusion criteria and Informed Consent will be reaffirmed with each subject.

Any changes that are found since the Screening Visit will be evaluated for an update to medical history and a focused Physical Examination will be performed at the Investigator's discretion. Measurements of vital signs, including weight and laboratory measurements including hematology, blood chemistry, coagulation factors, hormones, and bone biomarkers will be performed. A urine pregnancy test will be performed on women of child bearing potential.

Subjects will be stratified into pre/peri or post-menopausal groups and will be randomized to receive either 8mg/day (4mg/breast) BHR-700 gel or placebo. Each subject will be given a non-aerosol canister with a 1mL fixed dose pump. The subject will apply two (2) actuations ("squirts") of gel containing either: 2mg 4-OHT per 1 mL or placebo for daily application to each breast. The first dose will be applied under the supervision of the PI or designee.

A study drug kit, containing 6 canisters of study treatment, which is sufficient for 13 weeks of dosing, will be dispensed to each subject and a diary will be provided to capture dosing compliance. Subjects will be advised to call the clinic in between scheduled telephone calls and clinic visits if they experience AEs. Additional canisters may be assigned to avoid missing a dose due to lost or damaged canisters.

7.3 Blinded Phase Visits

- **Study Week 1: Telephone Call (+/- 1 day)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 4: Telephone Call (+/- 1 day)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 8: Telephone call (+/- 1 day)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application and query for any AEs.

- **Study Week 13: (+/- 2 weeks)**

Subjects will return to the clinic for study assessments. Vital signs including weight will be measured and the use of any concomitant medications and AEs recorded. A blood sample for PK measurements of 4-OHT isomers E and Z will be taken. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. Treatment canisters, sufficient for 13 weeks dosing, will be dispensed.

- **Study Week 19: Telephone Call (+/- 2 weeks)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 26: (+/- 2 weeks)**

Subjects will return to the clinic for study assessments. Vital signs including weight will be measured and the use of any concomitant medications and AEs recorded. Laboratory measurements will be performed and will include hematology, blood chemistry, and coagulation factors. A blood sample for PK measurements of 4-OHT isomers E and Z will be taken. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. Treatment canisters, sufficient for 13 weeks dosing, will be dispensed.

- **Study Week 32: Telephone Call (+/- 2 weeks)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 39: (+/- 2 weeks)**

Subjects will return to the clinic for study assessments. Vital signs including weight will be measured and the use of any concomitant medications and AEs recorded. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. Treatment canisters, sufficient for 13 weeks dosing, will be dispensed.

- **Study Week 45: Telephone Call (+/- 2 weeks)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 52: (+/- 2 weeks) – End of Blinded Phase and End of Study Visit**

Subjects will return to the clinic for study assessments. A Physical Examination including a breast exam will be performed, vital signs, height and weight will be measured and AEs and the use of any concomitant medications will be recorded. Laboratory measurements will be performed and will include hematology, blood chemistry, coagulation factors, hormones and bone biomarkers. PK measurements of 4-OHT isomers E and Z will be taken. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. A mammogram will be performed.

Subjects will be offered the opportunity to participate in the Open-Label-Extension Phase of the study. Informed consent will be obtained from those subjects choosing to continue in the Open-Label-Extension Phase. Open-labeled study drug will be dispensed to those subjects who have agreed to administer the BHR-700 gel for an additional 52 weeks.

7.4 Open-Label Phase Visits

- **Study Week 1 (53): Telephone call (+/- 1 day)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 4 (56): Telephone Call (+/- 1 day)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 8 (60): Telephone call (+/- 1 day)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 13 (65): (+/- 2 weeks)**

Subjects will return to the clinic for study assessments. Vital signs including weight will be measured and the use of any concomitant medications and AEs recorded. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. Treatment canisters, sufficient for 13 weeks dosing, will be dispensed.

- **Study Week 19 (71): Telephone Call (+/- 2 weeks)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 26 (78): (+/- 2 weeks)**

Subjects will return to the clinic for study assessments. Vital signs including weight will be measured and the use of any concomitant medications and AEs recorded. Laboratory measurements will be performed and will include hematology, blood chemistry, and coagulation factors. A blood sample for PK measurements of 4-OHT isomers E and Z will be taken. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. Treatment canisters, sufficient for 13 weeks dosing, will be dispensed.

- **Study Week 32 (84): Telephone Call (+/- 2 weeks)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 39 (91): (+/- 2 weeks)**

Subjects will return to the clinic for study assessments. Vital signs including weight will be measured and the use of any concomitant medications and AEs recorded. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. Treatment canisters, sufficient for 13 weeks dosing, will be dispensed.

- **Study Week 45 (97): Telephone Call (+/- 2 weeks)**

During this visit, the site will call the subject and review the subject's dosing compliance, product application, and query for any AEs.

- **Study Week 52 (104): (+/- 2 weeks) End of Open-Label Phase and End of Study Visit**

Subjects will return to the clinic for study assessments. A Physical Examination including a breast exam will be performed, vital signs, height and weight will be measured and AEs and the use of any concomitant medications will be recorded. Laboratory measurements will be performed and will include hematology, blood chemistry, coagulation factors, hormones, and bone biomarkers. PK measurements of 4-OHT isomers E and Z will be taken. A urine pregnancy test will be performed on women of child bearing potential. Treatment canisters will be weighed and the diary checked for study compliance. A mammogram will be performed.

8.0 ASSESSMENTS OF SAFETY

8.1 Adverse Event Collection and Reporting

- **Adverse Event Collection**

AEs will be captured for the duration of the study. The reporting period begins with the first dose of study drug (Study Day 1) and ends at Week 52 and Week 104. The Adverse Events eCRF must be completed for all reported AEs and SAEs.

For this study, an AE is defined as: "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

AEs may also be reported spontaneously at any time. Details of any adverse or unexpected events, signs, and symptoms will be collected including details of onset, resolution, frequency, severity (as defined below), seriousness, relationship to the drug, effect on the study drug, treatments administered, and outcome. Any AE will be followed, whenever possible, until it returns to the baseline condition or becomes stable with no further change expected.

8.2 Reporting of Adverse Events

- **Diagnoses vs. Signs/Symptoms**

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values if not constituting AEs themselves) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE.

- **Laboratory Values**

Changes in laboratory values may be considered AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported as an AE.

- **Pre-existing Conditions**

Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of….").

- **Preplanned Surgeries or Procedures**

Preplanned procedures (surgeries or therapies) that were scheduled prior to the start of an AE are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

- **Elective surgeries or procedures**

Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents.

- **Overdose**

Cases of drug overdose without manifested side effects are NOT considered AEs.

8.3 Assessment of Adverse Event Severity

The following guidelines for rating severity of adverse events should be used.

Mild:

Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study medication.

Moderate:

Discomfort enough to cause interference with usual activities; the study medication may have been interrupted.

Severe:

Incapacitating with inability to do work or do usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may have been stopped, and treatment for the event may be required.

The term "severe" is often used to describe the intensity of a specific event, as in mild, moderate or severe myocardial infarction; the event itself however, may be of relatively minor medical significance, such as severe headache. This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The Investigator must decide whether each AE meets the definition of an SAE.

8.4 Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening. Life-threatening, in the definition of serious, refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires hospitalization (> 24 hours) or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

- Is considered medically significant by the Investigator or requires intervention to prevent any one of the outcomes above. Medically significant are those events considered important in the Investigator's opinion that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

All SAEs will be captured for the duration of the study. The reporting period begins with the first dose of study drug (Study Day 1) and ends at Week 52 and Week 104. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intermittent illness.

Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. Death should usually be reported as the outcome of a specific SAE. Reports for hospitalization of elective procedures do not need to be reported as SAEs if there are no precipitating signs/symptoms or worsening of a pre-existing condition that necessitated the procedure. However, SAEs must be reported for any complications resulting from a procedure that prolonged the hospitalization.

- **SAE Reporting**

The SAE Form should be completed *within 24 hours of the Investigator/Site learning of the event* and sent as a PDF by email to a secure safety email box. On receipt, the SAE form will be disseminated to:

<u>For U.S. Centers</u>

<u>For European Centers</u>

For each SAE, the Investigator and Sponsor will independently assess whether there is a reasonable possibility that the event may have been caused by the study drug ("drug-related"). The Sponsor will evaluate each drug-related SAE to determine if the event was unexpected. If the SAE is assessed to be both drug-related and unexpected, the Sponsor or designee will notify all Investigators, and will report it to the appropriate regulatory authorities as required by applicable local regulations. The Sponsor or designee will report SAEs, including narratives, to the U.S. FDA and local regulatory authorities as required by 21 CFR 312.32 and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice. The Investigator is responsible for notifying his/her respective IRB.

8.5 Laboratory Tests

Laboratory tests (hematology and blood chemistry) will be performed by a central laboratory. Laboratory tests will be performed at screening, at pre-dose, at Week 26 and Week 52. For those subjects who have elected to continue open-label treatment for a further 52 weeks, laboratory tests will also be performed at Week 78 and Week 104. The Investigator will assess all abnormal lab values for clinical significance; if categorized as AEs, they will be collected and recorded similarly to other AEs. All clinically significant abnormal lab values will be followed until resolution. If resolution is not seen, a justification as to the cause for such an abnormality, such as due to an underlying pre-existing condition, associated co-morbidity, etc., will be recorded.

The following laboratory assessments will be performed for this study:
Hematology, Blood Chemistry, Coagulation factors, Hormones, and Bone biomarkers.

Any residual biological samples will be destroyed after test results are confirmed by the respective testing laboratory. No samples will be retained for future testing.

8.6 Physical Examination

A Physical Examination (PE) including a breast exam will be performed at screening, pre-dose on Day 1 (only if the subject has reported any changes since the Screening Visit), and Week 52. For those subjects who have elected to continue open-label treatment for a further 52 weeks, a PE will also be performed at Week 104. A breast exam and mammogram will be performed at Week 104 for those subjects who have elected to continue open-label treatment for a further 52 weeks. Any significant findings present prior to the first dose of study drug (Study Day 1) must be reported on the PE CRF. Significant findings made after the first dose of study drug which meet the definition of an AE must be recorded on the AE CRF. The PE will include an assessment of all body systems.

8.7 Vital Signs

The measurement of Vital Signs and weight will be made at screening, pre-dose and at weeks 13, 26, 39, and 52. For those subjects who have elected to continue open-label treatment for a further 52 weeks, Vital Signs will also be performed at weeks 65, 78, 91, and 104. Any significant findings present prior to the first dose of study drug (Study Day 1) must be reported on the Vital Signs CRF. Sitting vital signs to be measured are: heart rate (beats/minute), respiration rate (breaths/minute), systolic and diastolic blood pressure (mmHg), and body temperature. Height will also be measured at pre-dose, week 52 and week 104 for those who elect to continue open-label treatment

8.8 Mammogram

A bilateral mammogram with both the raw and processed 2D image DICOM files needs to be performed within 3 months prior to randomization. The same (make/model/serial number) mammography machine must be used for the Week 52 and if the subject is participating in the Open-Label phase, the Week 104 mammogram. If the mammogram is older than 3 months but less than 18 months, or it cannot be provided in the format required for the study, the mammogram can be repeated to meet the study entry requirement after informed consent has been obtained. Assuming the original mammogram has been made within 3 months before the date of randomization, the BI-RADS classification of this original mammogram will be used to assess and demonstrate the eligibility of the subject on inclusion criterion 1, a BI-RADS assessment C or D. The repeat mammogram will be used for determining the baseline density measurements, but not for re-assessment and/or confirmation of the BI-RADS criterion.

The mammography report must also be obtained. The breast density classification of C (heterogeneously dense) or D (extremely dense) should be recorded in the subject's study chart.

9.0 STATISTICAL ANALYSIS

9.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will give a detailed description of the summaries and statistical methodologies for analyses that will be performed and clearly describe when these analyses will take place. Should any inconsistencies exist between the analyses described in this section and the analyses described in the more detailed SAP, the SAP will take precedence.

Blinded Treatment Phase

Primary Outcome Measure:

- A comparison of reduction in breast density between BHR-700 gel and placebo treatment groups at 52 weeks using the Cumulus method**.**

Secondary Outcome Measures:

- Comparison of the reduction in breast density as calculated with the Volpara method and the Cumulus method.
- Laboratory parameters will be summarized in a descriptive fashion.
- Incidence and severity of AEs will be compared between BHR-700 gel and placebo.

Open-Label Treatment Phase

Secondary Outcome Measures:

- Comparison of the reduction in breast density as calculated with the Volpara method and the Cumulus method.
- Laboratory parameters will be summarized in a descriptive fashion.
- Incidence and severity of AEs will be compared between BHR-700 gel and placebo.

9.2 Sample Size

Assuming a reduction from baseline of 6% on active and 2% on placebo, with a common standard deviation of 8%, a total of 272 subjects will achieve a power of 90%, using a two sample, two-sided t-test at a significance level of < 0.01. Considering an attrition rate of 15%, 330 subjects are planned for enrollment in this study.

9.3 Analysis by Study Period (Blinded Phase / Open-Label Phase)

Study data will be cleaned and monitored prior to lock of the study database following the last subject exiting the blinded phase of the study. An analysis will be done on this data and results reported and described in a study report. An additional analysis will be done at the end of the study when the database has been monitored and cleaned, following the exit of the last subject from the open-label portion of the study. These analyses will be described in the study SAP.

9.4 Mammographic Density Assessments

Mammographic density will be measured using a 2D image (A "synthesized" 2D image created from a 3D image cannot be used). Both the processed and raw 2D image files will be sent for analysis by a central reader. The reader will be blinded as to the treatment group (BHR-700 or placebo) of each subject and the time point of each mammogram. The primary method used for analysis will be Cumulus 2D with Volpara 3D used as the secondary endpoint method.

9.5 Data Management

An electronic data capture (EDC) system will be used to collect the background information, safety and efficacy data from each subject. This information will be used for statistical analysis. The study datasets will be created from data from the EDC system including laboratory data information. Data queries will be generated and resolved according to the pre-specified data cleaning plan. In addition, range checks, plausibility and consistency checks will be performed to assess consistency, accuracy, and completeness of the data collected. Standard SAS datasets will be generated from the final study database for analysis. A complete audit trail of all corrections will be made and kept as a part of EDC database.

Although there is no reason to assume concerns about safety or tolerability of the test drug, a DSMB will be set up to review and evaluate unblinded data (plasma levels of 4OHT and adverse events data) to ensure subject safety and study integrity.

9.6 Study Populations

Three analysis populations will be defined and analyzed:

1. Intent-to-treat (ITT) population will contain all subjects who are randomized into the study. All efficacy parameters will be analyzed using the ITT population. In the case of a subject who was randomized but did not take the study drug, the analysis will be done for this subject using the randomized treatment.
2. Per-protocol population will contain all ITT subjects who do not have any major protocol deviation. The major protocol deviations will be described in the SAP and identified by BHR PHARMA, LLC before the database is locked.
3. Safety population will contain all subjects who receive at least one dose of study drug. All safety parameters will be analyzed using safety population.

9.7 Handling of Missing and Incomplete Data

The SAP will describe how to handle missing efficacy data. Missing date or time for the safety date will be imputed. The SAP will include all detailed imputation rules.

9.8 Methodology and Conventions

Safety and efficacy data will be summarized and presented by treatment group and time point in summary tables. Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

When the actual treatment received by a subject is different from the randomized treatment assigned, the subject will be analyzed per the randomized treatment for the efficacy parameters (using the ITT population); while she will be analyzed per actual treatment that was taken for the safety parameters (using the safety population).

Unless otherwise stated, all statistical tests will be two-sided hypothesis tests performed at the 5% level of significance for main effects and all confidence intervals will be two-sided 95% confidence intervals.

10.0 REGULATORY AND PROCEDURAL REQUIREMENTS

10.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. This study will be conducted in compliance with GCP and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

10.2 Institutional Review Board

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for following the regional law where the study is to be conducted to obtain written approval for the clinical study protocol (including all substantial protocol amendments), the subject informed consent, informed consent updates, subject recruitment procedures (e.g., advertisements), and any other information to be provided to subjects from an IRB that complies with the local regulatory requirements.

Written approval of the study must be obtained from the IRB prior to the study being implemented (i.e., shipment of clinical supplies to the Investigator or screening of subjects). Copies of the approval documentation will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the designated study documentation files.
The Sponsor (or an authorized representative) or the Investigator (according to national provisions) will submit written reports of the clinical study status to the IRB annually, or more frequently if requested by the IRB. A final study notification should be forwarded to the IRB within 90 days after the study has completed, or in the event of premature termination of the study within 15 days, with the rationale for study termination clearly explained. Copies of all clinical study status reports (including termination) will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

In accordance with national provisions and the rules of FDA, or applicable national or state laws, the Sponsor (or an authorized representative) will inform all participating IRBs and applicable national authorities of all SAEs or other safety-related information, which occur during the clinical study as appropriate.

10.3 Subject Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent from the subject prior to initiating any study procedures. All consent documentation must be in accordance with

applicable regulations and GCP. Each subject is requested to sign the subject Informed Consent Form after the subject has received an explanation of what the study involves, including but not limited to, the following: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (Consent Form) must be given to the subject.

10.4 Advisory Board

An Advisory Board, composed of experts in the field of Breast Cancer, will provide scientific and clinical leadership for this study in consultation with BHR PHARMA, LLC.

10.5 Investigator Obligations

The PI agrees to conduct the clinical study in compliance with this protocol which was approved by the IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol (Page 3) to confirm this agreement.

10.6 GCP Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6(R2) (NOV 2016) and the applicable regulatory requirements. Copies of these guidelines are available at www.ich.org and will be provided to the site by BHR PHARMA, LLC upon request.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the *curriculum vitae* for the Investigator, sub-investigator(s), and essential study staff, as appropriate, will be provided to BHR PHARMA, LLC (or designee) before starting the study.

10.7 Protocol Adherence and Investigator Agreement

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

It is the Investigator's responsibility to communicate with their IRB to ensure accurate and timely information is provided at all phases during the study. The appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB must be informed of study completion.

10.8 Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from the Sponsor or designee, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. The governing IRB/ will be informed of all protocol changes issued by the Sponsor by the Investigator in accordance with the IRBs established procedure.

10.9 Monitoring of the Study

Site visits and inspections will be conducted by the Sponsor or designee at regular intervals in accordance with FDA and ICH guidelines. The Investigator will permit representatives of the Sponsor's monitoring team, Ethics Committee, FDA, or local health authority auditors to inspect facilities and records relevant to this study.

11.0 FINANCIAL DISCLOSURE

Under the applicable regulations, the Sponsor is required to submit to FDA a list of clinical Investigators who conducted the clinical studies and certify and/or disclose certain financial arrangements as follows:

1. Certification that no financial arrangements with an Investigator have been made where study outcome could affect compensation; that the Investigator has no proprietary interest in the tested product; that the Investigator does not have a significant equity interest in the Sponsor of the covered study; and that the Investigator has not received significant payments of other sorts; and/or
2. Disclosure of specified financial arrangements and any steps taken to minimize the potential for bias.

Disclosable Financial Arrangements:

1. Compensation made to the Investigator in which the value of compensation could be affected by study outcome. This requirement applies to all covered studies, whether ongoing or completed as of February 2, 1999.

2. A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright, or licensing agreement. This requirement applies to all covered studies, whether ongoing or completed as of February 2, 1999.
3. Any equity interest in the Sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. This requirement applies to all covered studies, whether ongoing or completed;
4. Any equity interest in a publicly held company that exceeds $50,000 in value. These must be disclosed only for covered clinical studies that are ongoing on or after February 2, 1999. The requirement applies to interests held during the time the clinical Investigator is carrying out the study and for 1 year following completion of the study; and
5. Significant payments of other sorts, which are payments that have a cumulative monetary value of $25,000 or more made by the Sponsor of a covered study to the Investigator or the Investigators' institution to support activities of the Investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical Investigator is carrying out the study and for 1 year following completion of the study. This requirement applies to payments made on or after February 2, 1999.

In consideration of participation in the study, BHR PHARMA, LLC, will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

11.1 Documentation and Retention of Records

- **Case Report Forms**

Data collection for this protocol will be accomplished using EDC. Therefore, the term CRF refers to an electronic data record.

CRFs are required and must be completed for each randomized subject. It is the Investigator's responsibility to ensure the accuracy and completeness of the data reported on the subject's CRF. CRFs should be completed in a timely fashion to support the study timelines.
Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and status. The Investigator or designee should complete and the Investigator should verify the source documents as the information is collected. Completed CRFs must be submitted for each subject. The Investigator will retain a copy of all completed source documents.

- **Recording, Access, and Retention of Source Data**

Source data to be reviewed during this study may include, but is not limited to: subject's medical file, original laboratory reports, radiology reports, and histology and pathology reports. All key data must be recorded in the subject's medical records.
The Investigator must permit authorized representatives of BHR PHARMA, LLC, the respective national, local, or foreign regulatory authorities, the IRB, auditors, and interested commercial parties to inspect facilities and records relevant to this study.

The monitor, auditors, IRB, or regulatory inspectors, may check the CRF entries against the source documents. The consent form will include a statement by which the subjects allow the monitor/auditor/inspector from BHR PHARMA, LLC or its representatives, national, or local regulatory authorities or the IRB access to source data (e.g., subject's medical file), which substantiate information recorded in the CRFs.

As described in the ICH GCP Guidelines, 'essential documents', including CRFs, source documents, consent forms, laboratory test results, and study drug inventory records, should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with BHR PHARMA, LLC. The Investigator must obtain written permission from BHR PHARMA, LLC prior to the destruction of any study document.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the U.S. FDA in accordance with the U.S. Code of Federal Regulations 21 CFR 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

11.2 Disclosure of Data

Individual subject's medical information obtained because of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers. If results of this study are reported in medical journals or at meetings, the subject's identity will remain confidential. Medical information may be provided to the subject's personal physician, at the subject's request, or to other appropriate medical personnel responsible for the subject's welfare.

Data generated because of this study are to be available for inspection on request by FDA/local health authority auditors, the sponsor's monitors, and by the IRBs. If the FDA or other regulatory agency should schedule an inspection, the Medical Monitor should be advised immediately.

11.3 Publication

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor.

Publications or presentations based on the study may not be made until the study is completed, unless so decided by the Sponsor. Once the Sponsor or designee publishes the final report and main study manuscript, or if publication has not occurred within 18 months after completion of the study (final database lock), an Investigator may individually publish or present information on this study, preferably providing the manuscript to the Sponsor for review prior to publication. The Clinical Trial Agreement between the Investigator and the Sponsor may provide additional terms regarding publication or presentation based on the study.

12.0 REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D, Global cancer statistics, CA Cancer J Clin 2011; 61:69-90
2. Checka CM, Chun JE, Schnabel FR, et al: The relationship of mammographic density and age; implications for breast cancer screening. Am J Roentgenol 2012 198; W292-295
3. Jordan VC. Molecular mechanisms of antiestrogen action in breast cancer. Breast Cancer Research and Treatment 1994; 31:41-52
4. Gallo MA, Kaufman D. Antagonistic and agonistic effects of tamoxifen: significance in human cancer. Seminars in Oncology. 1997. 24: S1-71; S1-80
5. Linares-Cruz G, Fournier S, Lalardrie JP, Lignieres B. Human breast dynamics during menstrual cycle. Anticancer Research, 1998; 18:3813-3892
6. Cuzick J, Warwick J, Pinney E Et al. Tamoxifen-induced reduction in MD and breast cancer risk reduction. JNCI 2011 103; 9:744-752
7. Li J, Humphreys K, Eriksson L, et al. Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. J Clin Oncol 2013, 31: 2249-2256
8. Nyante SJ, Sherman ME, Pfieffer RM, et al. Prognostic significance of mammographic density change after initiation of tamoxifen for ER-positive breast cancer. J Natl Cancer Inst.2015, 107
9. Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, Gustafsson A. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Encrinology 1997; 138:863-870
10. Coezy E, Borgna JL, Rochefort H, Tamoxifen and metabolites in MCF7 cells: correlation between binding to estrogen receptor and inhibition of cell growth. Cancer Research 1982; 42:317-323
11. Malet C, Gompel A, Spritzer P, Bricout N, Yaneva H, Mowszowiez I, Kuttenn F, Mauvais-Jarvis P. Tamoxifen and hydroxytamoxifen isomers versus estrodial effects on normal human breast cells in culture. Cancer Research 1988. 48: 7193-7199
12. Lonning PE, Lien EA, Lundgren S, Kvinnsland S. Clinical pharmacokinetics of endocrine agents used in advanced breast cancer 1992. Clin Pharmacokinetics 1992; 22:327-358
13. Mansel R, Goyal A, Nestour EL, et al; Phase 11 trial of 4-OHT gel for cyclical mastalgia. Breast Cancer Res Treat 2007106:389-397
14. Rouanet P, Linares-Cruz G, Dravet F Et al. Neoadjuvant percutaneous 4-OHT decreases breast tumoral cell proliferation. J Clin Oncol 2005 23: 2980-2987
15. Lee O, Page K, Ivancic, et al. Transdermal 4-OHT vs Tamoxifen in women with DCIS. Clinical Cancer Research 2014; 20:3672-3682

16. Zumbrunnen TL, Meuwsen I, de Vries M, Brennan JJ. The effect of washing and the absence of interindividual transfer of Estradiol Gel. Am J. Drug Delivery 2006 4(2): 89-95

APPENDIX 1. SCHEDULE OF STUDY ASSESSMENTS AND PROCEDURES

Study Assessment or Procedure	Screen	Week 1 - Day 1		Week 13	Week 26	Week 39	Week 52	Week 13	Week 26	Week 39	Week 52/104
		Pre-Dose	Hour 0	Blinded Phase				Open-Label Phase			
Informed Consent	X	Affirm									
Inclusion/Exclusion	X	Affirm					Affirm[1]				
Demographics	X										
Limited Medical History	X	Review					Review[1]				
PE / Body Systems Review	X	X[2]					X				X
Height	X						X				X
Vital Signs and weight	X	X		X	X	X	X	X	X	X	X
AEs				X	X	X	X	X	X	X	X
Con Meds & Procedures	X	X		X	X	X	X	X	X	X	X
Randomization		X									
Mammogram	X						X				X
Dispense Study Drug: (BHR-700 Gel/Placebo)			X	X	X	X	X[1]	X	X	X	
Study Drug compliance: (weigh canisters/check diaries)		X		X	X	X	X	X	X	X	X
Laboratory Tests (hematology and blood chemistry)	X	X			X		X		X		X
Urine Pregnancy Tests for women of child bearing potential	X	X		X	X	X	X	X	X	X	X
Coagulation Factors: (Protein C and S activity, Antithrombin 111 antigen, and APCR.)		X			X		X		X		X
Hormones: (FSH, Estrodial, Estrone and LH)	X						X				X
Hormones (SHBG)		X					X				X
Biomarkers: Bone (CTx and BSAP)		X					X				X
PK assessment (plasma 4-OHT E & Z isomers)				X	X		X		X		X
Menstrual Cycle Questionnaire	X										

1-Assessments performed *ONLY* if the subject chooses to participate in the Open-Label Extension Phase.
2-Only if the subject has reported any changes since the Screening Visit.

APPENDIX 2. SUBJECT INSTRUCTIONS FOR USE

BHR-700 [redacted]

BHR-700 [redacted]

The clear, colourless gel provides delivery of 4-Hydroxytamoxifen through the skin of the breast(s).

BHR-700 gel is for topical use only. Do not swallow.

For Investigational Use, Only

PRECAUTIONS:

1. **BHR-700 is flammable until dry. Do not apply BHR-700 gel near fire, flame or heat.**
2. Be sure to follow your doctor's instructions carefully throughout the course of the study.
3. Inform your doctor about **any** new medicine you take during the study (including dose(s), duration and reason), or any change(s) to medicines you take regularly.
4. Inform your doctor about any unusual symptoms or side effects occurring during the study.

INSTRUCTIONS FOR USE:

Step 1. Applying BHR-700 gel

Do not allow other people to apply BHR-700 to your skin for you.
Apply BHR-700 gel once daily preferably in the morning
Apply BHR-700 gel once daily at the same time of day.

- Apply BHR-700 gel to clean, dry breast(s) after your bath or shower.
- Remove the cap from the canister. Hold the canister in one hand and place the palm of your other hand under the pump to catch the gel; see Figure A. Be sure to press down completely on the pump and release it completely to dispense one dose of gel. Repeat to dispense prescribed dose.

Figure A

- Using your hand, apply the BHR-700 gel. Spread the gel as thinly as possible – avoid contact with the nipple. Do not massage or rub in BHR-700 gel. Allow the gel to dry for 5 minutes* before you get dressed (BHR-700 gel is colorless and will not stain your clothing). Use the **same** application method every time you apply the gel.

* If it takes more than 5 minutes for the gel to air-dry or a sticky residue remains on your skin after 5 minutes, you need to spread the gel over a larger area of the breast(s).

Step 2. After applying BHR-700 gel

- Replace the cap on top of the canister after each BHR-700 gel application to protect the pump.
- Wash your hands right away with soap and water after applying the BHR-700 gel.
- Avoid water activities (i.e., swimming) after you apply the BHR-700 gel. If not possible, try to wait at least one (1) hour after applying the BHR-700 gel before participating in the water activity.
- Do not apply transdermal patches (i.e., nicotine patch) to your breast(s) at any time during the study.
- Use of health and beauty products (lotions, creams, sunscreen, self-tanner, etc.) on the application site is allowed one (1) hour after application of the study gel.

RECOMMENDATIONS:

- The following precautions are recommended to minimize potential transfer of the BHR-700 gel to other individuals (i.e. your child, your sexual partner, or other persons):
    - Wash your hands immediately after gel application.
    - Cover the application site with clothing after the gel has dried.
    - Skin contact is permitted AFTER the application area (breasts) has been washed.
    - In the event that unwashed or unclothed skin to which study gel has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.
- If you forget to apply a dose, do not double the next dose to "catch up." If you have a study visit scheduled that day, tell the study staff about your missed dose and they will instruct you on what to do. If you do not have a study visit scheduled that day, contact your Study Coordinator about your missed dose.

STORAGE:

- Keep BHR-700 gel at room temperature 68°F to 77°F (20°C to 25°C).
- Keep out of the reach of children.
- Avoid exposure to extreme heat or cold during transportation from the clinic to home.

REMEMBER TO: Bring the study drug canister with you to each clinic visit.

This is very important for the conclusion of the study:

After completing treatment, be sure to give all of the unused study gel back to your Doctor. Do Not throw out your unused study gel.

APPENDIX 3. MENSTRUAL HISTORY QUESTIONNAIRE

Menstrual History Questionnaire

1. How old were you when you started having menstrual periods?
Age: _____ 1a. If you cannot remember your exact age, were you:

☐ Younger than 10 ☐ 16 or older
☐ 10-12 yrs old ☐ Don't Know
☐ 13-15 yrs old

2. At present which statement best describes your menstrual cycle?

☐ I'm still having regular periods: The date of my last period was: ___/___/_____
☐ My periods are irregular: The date of my last period was: ___/___/_____
☐ I'm pregnant, or my last pregnancy ended within the past 2 months, or I'm breast feeding

☐ My periods have stopped on their own. (I've had menopause.)
☐ I've had menopause, but now have periods because I am taking hormones.
☐ I've had an operation (surgery) which stopped my periods.
If your menstrual periods ceased because of surgery, what did you have removed?
☐ One ovary only ☐ Uterus only
☐ Both ovaries ☐ Uterus and one ovary
☐ Uterus and both ovaries
☐ Don't know
☐ I've taken medication which has stopped my periods.
If your periods stopped because of medication, which medication were you taking? Medication name: _____

☐ I"ve had chemotherapy which has stopped my periods.
☐ I've had radiation therapy which has stopped my periods.
☐ Other: _____

3. If your menstrual periods have stopped, how old were you when your menstrual periods stopped? (Please provide us with the age at which your menstrual periods stopped regardless of why they have stopped – naturally, due to surgery, medication, chemotherapy, or radiation therapy. If your periods have stopped, but you now have periods because of taking hormones, answer with the age at which your periods first stopped.)

Were you: ☐ Younger than 20 ☐ 45-49 yrs old
☐ 20-29 yrs old ☐ 50-54 yrs old
☐ 30-39 yrs old ☐ 55 – 59 yrs old
☐ 40-44 yrs old ☐ 60 or older

OR ☐ My menstrual periods have not stopped.

4. If your menstrual periods have stopped, how old were you when you first experienced symptoms of menopause such as hot flashes or night sweats?

_____ Years old ☐ Did not experience symptoms
☐ Don't Know

OR ☐ My menstrual periods have not stopped.

P:\FERNALD\Questionnaires\2007 Menstrual History Questionnaire.doc

All women should answer the next two questions, whether they currently have menstrual periods or not.

5. When you are (were) having regular menstrual cycles, how many days are (were) there between periods? _____ Days between periods

For how many days do (did) you have your period? _____ Days

6. Between the ages of 18 and 40, excluding times when you may have been on the pill, pregnant, or nursing, which of the following statements BEST describes your menstrual periods? They are (were)...

- ☐ Nearly always regular, that is, you could usually predict when you would start bleeding to within two or three days
- ☐ Fairly Regular
- ☐ Irregular
- ☐ Don't Know

P:\FERNALD\Questionnaires\2007 Menstrual History Questionnaire.doc

APPENDIX 4. LABORATORY ASSESSMENTS

BLOOD CHEMISTRY
ALAT (SGPT)
ALBUMIN
ALKALINE PHOSPHATASE
ASAT (SGOT)
UREA NITROGEN
CALCIUM
CARBON DIOXIDE (CO2)
CHLORIDE
CHOLESTEROL, TOTAL
HDL
LDL-CHOL CALCULATION
CREATININE
BILIRUBIN, DIRECT
GLUCOSE
LACTIC DEHYDROGENASE
POTASSIUM
SODIUM
BILIRUBIN, TOTAL
PROTEIN, TOTAL SERUM
TRIGLYCERIDES

HEMATOLOGY WITH % DIFFERENTIAL
HEMATOCRIT
HEMOGLOBIN
WHITE CELL COUNT
BASOPHILS
EOSINOPHILS
LYMPHOCYTES
MONOCYTES
NEUTROPHIL, SEGS
TOTAL NEUTROPHILS
RED CELL COUNT
PLATELET COUNT

BONE BIOMARKERS
BONE CTx
BONE BSAP

HORMONES
FOLLICLE STIMULATING HORMONE (FSH)
LUTEINIZING HORMONE (LH)
SEX HORMONE BINDING GLOBULIN (SHBG)
ESTRADIOL
ESTRONE

COAGULATION FACTORS
PROTEIN C ACTIVITY
PROTEIN S ACTIVITY
ANTITHROMBIN III ANTIGEN
ACTIVATED PROTEIN C RESISTANCE (APCR)