Abbreviated Clinical Study Report

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

Test Product: BHR700-4OHT Gel (BHR-700 [0.2% 4-Hydroxytamoxifen Gel])

Study Number: BHR-700-301

EudraCT Number: 2017-002906-10

IND Number: 59,081

Version: Final: 27 Aug 2021

1 TITLE PAGE

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
EudraCT Number:	2017-002906-10
IND Number:	59,081
Sponsor:	BHR Pharma, LLC 607 Herndon Parkway, Suite 110 Herndon, VA 20170, USA
Sponsor's Responsible Medical Officer:	Roland Gerritsen van der Hoop, MD, PhD 607 Herndon Parkway, Suite 110 Herndon, VA 20170, USA
Contract Research Organization:	Peachtree BioResearch Solutions, Inc. 4985 Lower Roswell Rd., Bldg. 100 Marietta, GA 30068 USA
Study Phase:	Phase 3
Test Product:	BHR700 (0.2% 4-Hydroxytamoxifen Gel) (BHR700-4OHT Gel)
Indication:	Reduction in breast tissue density
Protocol:	BHR-700-301
Study Initiation Date	Aug 2017
Early Termination Date:	19 Dec 2018
Report Version and Date:	Final: 27 Aug 2021

This study was performed in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

2 SYNOPSIS

Sponsor:

BHR Pharma, LLC

Name of Finished Investigational Product (IP)

BHR700-4OHT Gel

Name of Active Ingredient

BHR-700 (0.2% 4-Hydroxytamoxifen Gel)

Indication

Reduction in breast tissue density

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

EudraCT Number

2017-002906-10

IND Number

59,081

Study Phase:

Phase 3

Study Center(s)

Multi-center study conducted in 19 centers in the US, Spain, and Germany

Lead Investigator:

Jennifer A. Harvey, MD, FACR

Publication (References)

Not applicable

Study Period:

Aug 2017 (First Patient First Visit) to Apr 2019 (Last Patient Last Visit)

Date of Early Study Termination

19 Dec 2018

Objectives:

Primary objective:

To determine the efficacy of 8 mg/day (4 mg/breast) of 4-OHT delivered as 4 mL 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 2 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 gel 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 gel and placebo.
4. To describe the symptoms assessed by laboratory toxicity assessments: complete blood count (CBC) w/differential, 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 gel after 52 weeks of administration to the breasts such as adverse events (AEs) collection, effects on menstrual cycle, and laboratory values.
6. To determine whether 8 mg/day of 4-OHT gel will disrupt the menstrual cycle of premenopausal women.
7. To determine the plasma concentration of the E and Z isomers of 4-OHT gel after 13, 26, 52, 104 weeks of application of 4 mL BHR-700 gel to the breasts.

Methodology:

This was a multi-center, randomized, double-blind, placebo controlled study to evaluate in women identified as having dense breast tissue upon screening mammography.

Subjects were assessed as having mammographically dense breast based on the American College of Radiology [ACR] Breast Imaging Reporting and Data System [BI-RADS©] fifth edition classification).

Eligible subjects had screening evaluations, including hormone measures of follicle stimulating hormone, estradiol, estrone, and luteinizing hormone to determine menopausal state. Some subjects required a mammogram if they did not have a mammogram that fulfilled the necessary criteria (format or time period). Those subjects meeting entry criteria were stratified into pre/peri and post-menopause groups based on their hormone levels, and randomized within those groups 2:1 to receive either 8 mg/day (4 mg/breast) BHR-700 Gel (hereafter referred to as BHR700-4OHT Gel) or matching placebo gel for up to 52 weeks. At the Principal Investigator's (PI) discretion, subjects were allowed to reduce the dose to 4 mg/day (2 mg/breast) in cases of intolerance.

Subjects applied the gel to both breasts once daily. The first dose was applied under the supervision of the PI/designee. Subsequent doses were self-administered daily by the subject until she had completed up to 52 weeks of study drug administration. A diary was 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. While on treatment, subjects underwent periodic mammography to

assess breast tissue density. Subjects were evaluated on Day 1 and every 13 weeks thereafter (26 weeks, 39 weeks and 52 weeks).

The primary outcome measure was the comparison of reduction in breast density between BHR700-4OHT Gel and placebo treatment groups at 52 weeks. As the study was terminated early not all subjects reached the 52-week visit. Subjects who completed the double-blind phase of the study were offered entry into an open-label follow-up period for an additional 52 weeks.

Safety assessments included evaluations of all AEs/serious adverse events (SAEs), vital signs, and laboratory studies, with special attention given to uterine abnormalities, cardiovascular events, and thromboembolic events. Additional important safety parameters assessed for this indication were: endometrial changes, breast evaluation, coagulation factors, bone biomarkers, changes in menstrual cycle; unexpected vaginal bleeding, SHBG level, plasma 4-OHT Z isomer levels, and tolerability of BHR700-4OHT Gel.

Number of subjects (planned and analyzed)

Planned: 330 women were to be randomized to receive either BHR700-4OHT Gel or placebo (2:1 distribution).

Analyzed: 223 subjects were enrolled, data from 222 subjects were analyzed.

Diagnosis and main eligibility criteria

Inclusion criteria:

1. Healthy women age 35 to 75 years with either heterogeneously dense (C) or extremely dense (D), breast tissue on 2D mammography, based on 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 was of childbearing potential, she had to 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.

Exclusion criteria:

1. Participants not 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 were excluded from this study because the effects of 4-OHT gel on the developing human fetus at the recommended dose and route were 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 were subsequently found to have negative (BI-RADS 1) or benign findings (BI-RADS 2), were NOT excluded.
9. Women with only synthetic 2D mammograms generated from 3D (tomosynthesis) were excluded as breast density measurements were not yet validated for synthetic mammograms. Women with combination 2D+3D mammograms were 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, could 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 could interfere with the study.
13. Women who had 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) had to discontinue the treatment a minimum of 6 months prior to the screening mammogram. Progestin only contraceptives were permitted.
15. Women with a concurrent illness, disease or condition that, in the opinion of the Investigator, could limit their compliance with study requirements or place them at additional risk.

Test product, dose, and mode of administration

BHR700-4OHT Gel formulation containing 2 mg/mL 4-hydroxytamoxifen (also referred to as 4-OH tamoxifen or 4-OHT) (0.2%) in a clear, colorless, absorptive, hydro-alcoholic gel base formulated to provide continuous release of 4-OHT. The BHR700-4OHT Gel was supplied in a non-aerosol canister with a 1 mL fixed-dose pump. Two fixed unit doses of BHR700-4OHT Gel were applied daily to each breast. Each actuation dispensed 1 mL of gel. A total of 8 mg/day (4 mg/breast) of BHR700-4OHT Gel were administered daily unless a dose reduction by the Investigator was deemed necessary for reasons of tolerability.

Reference therapy, dose and mode of administration

Placebo gel, identical in appearance and consistency to the BHR700-4OHT Gel.

Subjects applied 2 fixed unit doses of placebo gel daily to each breast. Each actuation dispensed 1 mL of gel.

Treatment compliance was monitored by the Investigator staff who checked subject diaries and weighed the IP canister(s) when dispensed and upon return.

Blinded kits:

BR#	Product Name	EMINENT Lot#
2017B0166	4-Hydroxytamoxifene Placebo Gel 88 G 1 EACH CAN	17B0166/67
2017B0167	4-Hydroxytamoxifene Active Gel 88 G 1 EACH CAN	17B0166/67
2018B0177	4-Hydroxytamoxifene Placebo Gel 88 G 1 EACH CAN	18B0177/78
2018B0178	4-Hydroxytamoxifene Active Gel 88 G 1 EACH CAN	18B0177/78

Open-label kits:

BR#	Product Name	EMINENT Lot#
2018B0203	4-Hydroxytamoxifene Active Gel 88 G 1 EACH CAN	18B0203
2018B0227	4-Hydroxytamoxifene Active Gel 88 G 1 EACH CAN	18B0227

Duration of treatment:

Subjects in both the BHR700-4OHT Gel and placebo treatment groups applied gel once daily for up to 52 weeks or until the study was terminated.

Criteria for evaluation

Efficacy measures:

The planned primary efficacy measure was analysis of mammographic breast density reduction from baseline in women with dense and extremely dense breasts as assigned by BI-RADS category C and D. Mammograms were centrally analyzed by a reader blinded as to the treatment group (BHR700-4OHT Gel or placebo) and time point of each subject. Cumulus 2D was the primary endpoint method with Volpara 3D as a secondary endpoint method.

Safety measures:

Safety assessments included evaluations of all AEs/SAEs, with special attention given to uterine abnormalities, cardiovascular events and thromboembolic events. Additional important safety parameters specific for this indication were:

- Endometrial changes
- Breast evaluation
- Coagulation factors
- Bone biomarkers
- Changes in menstrual cycle; unexpected vaginal bleeding
- SHBG level
- Plasma 4OHT-Z isomer levels
- Tolerability of BHR700-4OHT Gel

To address these safety parameters, subjects underwent the following assessments:

- A bilateral mammogram with both the raw and processed 2D image Digital Imaging and Communications in Medicine (DICOM) files needed to have been performed within 3 months prior to randomization. The same (make/model/serial number) mammography machine had to have been used for the Week 52 mammogram. If the mammogram was older than 3 months but less than 18 months or could not be provided in the format required for the study, the mammogram could be repeated to meet the study entry requirement after informed consent was obtained.
- A clinical breast examination was performed at Screening, Baseline (Study Day 1-Week 1), and Study Week 52.
- Coagulation factors were measured prior to administration of study drug, Study Week 26, and Study Week 52.
- Changes in bone mineral density were assessed by measurement of select bone biomarkers pre-dose and at Study Week 52.
- Serum concentrations of SHBG were measured pre-dose and at Study Week 52.
- Routine laboratory parameters (ie, hematology and blood chemistry) were measured at Screening, on Day 1 before administration of study drug, Study Week 26, and Study Week 52.
- Urine pregnancy tests were performed on women of childbearing potential at Screening, Randomization, and at each clinic visit and at any point during the study when pregnancy was suspected (ie, missed cycle, skipped/failed birth control).
- AEs were 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 performed a uterine ultrasound followed by an endometrial biopsy if indicated.

Statistical methods:

The study was terminated early; analyses were conducted using data available in the clinical database. Due to this lower-than-planned enrollment number, the statistical plan outlined in the protocol was not fully utilized. Data listings and summary tables were instead created, which captured data on the enrolled subjects in a descriptive manner.

Due to the early termination, this abbreviated clinical study report (CSR) focuses on the safety and pharmacokinetic/pharmacodynamic results.

SUMMARY - CONCLUSIONS

Efficacy results:

Since this study was early terminated for reasons other than safety, the analyses were limited to the available data. Of the 223 subjects randomized into the trial, 149 received BHR700-4OHT Gel and 73 received placebo gel.

Safety results:

With respect to safety results of the clinical study, the outcome was positive for the safety profile of BHR700-4OHT Gel, in keeping with the expected locally acting pharmacologic activity of BHR700-4OHT Gel and in contrast to the systemic adverse effects profile of the parent prodrug, oral tamoxifen. Of the 222 subjects in the safety population, 114 subjects experienced at least 1 AE, and 5 subjects experienced 1 SAE each. Out of the 5 reported SAEs, none of these events could be completely attributed to the study drug or procedures (2 SAEs were not related, 3 were possibly related).

Although the original planned safety analysis could not be completed due to the early termination of the trial, important safety and tolerability findings were retrieved from this study. The low number of

reported safety events during the trial is noteworthy. Overall, the AEs and SAEs were similar across the treatment and placebo groups.

The safety measures of the study are described below:

Endometrial changes occurred in a single subject who developed post-menopausal uterine bleeding in the open-label phase of the study, on a background of past medical history of post-menopausal bleeding, diagnosed in 2014 as benign. This subject (104-006) underwent endometrial biopsy; the pathology report revealed a diagnosis of endometrial adenocarcinoma.

No other subjects in the study underwent endometrial examination and biopsy.

Plasma levels of the pharmacologically active [Z] isomer of 4OHT were consistently low in all study subjects at relevant data collection timepoints during the trial. The data at 13 and 26 weeks showed plasma levels that were 3 times lower than levels found with 20 mg of oral tamoxifen. The levels at 52 weeks were less reliable as some patients discontinued treatment (due to study termination) prior to attending their end of study visit. Coagulation profile parameters were within the reference ranges for the majority of subjects with no overall clinically significant effects. SHBG levels, which are relevant for the estrogenic potential of BHR700-4OHT Gel, were not raised and did not show any clinically relevant changes.

No clinically significant changes in menstrual cycles occurred apart from the single case of post-menopausal bleeding discussed above.

Breast evaluation was unremarkable for most study participants.

Bone biomarkers data did not suggest any clinically significant safety changes in the BHR700-4OHT Gel treatment arm. Routine hematology and biochemistry were unremarkable, as were lipids. Upon analysis of all the safety parameters, BHR700-4OHT Gel was well tolerated and similar degrees of vasomotor symptoms or reproductive system symptoms were observed across treatment groups.

The 149 subjects in the BHR700-4OHT Gel group experienced a total of 358 AEs, and the 73 subjects in the placebo group experienced a total of 178 AEs. There were 3 subjects with laboratory abnormalities assessed as clinically significant by the Investigator and reported as AEs (elevated AST and ALT, low Protein S and elevated hemoglobin).

From the start of the clinical trial in Aug 2017 until data cutoff , Besins Healthcare, as Sponsor of the clinical trial, received 5 reported SAEs for 5 of the 222 subjects in the safety population. Of these 5 reported serious events, 2 SAEs (Intraductal proliferative breast lesion and Invasive ductal breast carcinoma) were assessed by the Investigator and the Sponsor as unrelated to BHR700-4OHT Gel and therefore have no impact on the safety profile of the IP. Three SAEs (Endometrial adenocarcinoma; Invasive ductal breast carcinoma; and Pulmonary embolism) were initially classified as possible suspected unexpected adverse drug reactions. However, as there were other potential causes for these events, they could not be fully contributed to BHR700-4OHT Gel and were subsequently classified as ‘possibly related’ to the study drug.

The study was terminated early due to a change in clinical development strategy for BHR700-4OHT Gel to pursue focus on a “cancer prevention” indication rather than on “breast density reduction” alone. As such it was determined that the healthy population enrolled in the BHR-700-301 study, which was not stratified by being at high risk of breast cancer, was not optimal for pursuit of a “cancer prevention” indication for 4-OHT Gel. The Sponsor understands that a high-risk population represents the most clinically meaningful cohort for further development strategy. Mammographic breast density reduction in women at high risk of developing breast cancer may be an important strategy to modify breast cancer risk. The optimal population should include women at high risk of developing breast cancer, according to risk assessment models that

incorporate mammographic breast density as well as other non-modifiable risk factors (such as Tyrer Cuzick).

CONCLUSION

4-OHT (4-hydroxytamoxifen) is an active metabolite of prodrug tamoxifen. Tamoxifen is licensed for prevention of estrogen receptor-positive breast cancer in women at high risk of developing breast cancer. The therapeutic and pharmacological rationale for BHR700-4OHT Gel therapy in women with high mammographic breast density and who are also at elevated risk of developing breast cancer, is based on the premise that reduction of mammographic breast density is a risk reduction strategy for these women. When the minimal reported events that can be completely contributed to BHR700-4OHT are considered, the product presents an safe, practical strategy for breast cancer prevention for these women.

Although the study was terminated early, the safety results demonstrated that BHR700-4OHT Gel was very well tolerated, as seen with the high compliance in the study and low number of reported AEs. Plasma 4OHT [Z] isomer levels remained consistently low in study subjects supporting the scientific rationale that 8 mg of transdermal BHR700-4OHT Gel systemic absorption is low when compared to systemic absorption of the parent compound and prodrug, oral tamoxifen. As a reference, plasma levels of [Z]isomer of 4OHT with 20 mg of tamoxifen are generally 3 times higher. The anti-estrogen type AEs associated with systemic tamoxifen therapy are well cited reasons for women not adhering to tamoxifen therapy, coupled with the known risks of SAEs.

Three women reduced their treatment dose from 8 mg per day to 4 mg per day, allowed at the discretion of the Investigator.

Overall, there was a very low rate of AEs and AEs such as vasomotor type symptoms were no more frequent than in the placebo group. With regards to the non-serious AEs reported during the clinical trial, approximately 70% of those AEs that were associated with subjects receiving BHR700-4OHT and 74% of those subjects receiving placebo were deemed unrelated to study treatment. Only 5% of AEs reported by the BHR700-4OHT Gel group and 2.8% of AEs in the placebo group were thought to be ‘probably related’ to study treatment. This also indicates a positive safety profile for the IP.

Of the 5 reported SAEs, 3 were deemed possibly related (2 in the blind phase, 1 in the open-label phase) but could not be determined as related as there were other factors that could also have been possible causes of these events. Concerning the reported SAEs, 5 reported SAEs for 222 subjects over the reporting period of the trial is extremely low and shows the safety and tolerability of BHR700-4OHT Gel.

Considering this and the very small number of reported SAEs received over the duration of the study, BHR700-4OHT Gel shows a positive safety profile and showed no new signals during the trial.

Overall, the results indicate that the benefit-risk profile of BHR700-4OHT Gel remains positive and has not changed during the conduct of the trial. The clinical trial was not terminated early due to safety concerns and no significant actions were taken during the conduct of the trial for safety reasons by Besins Healthcare as the Sponsor of the clinical trial.

Date of the report: 27 Aug 2021

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

4-OHT	4-Hydroxytamoxifen
ACR	American College of Radiology
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BI-RADS	Breast Imaging Reporting and Data System
CBC	complete blood count
COPD	chronic obstructive pulmonary disease
CRF	case report form
CSR	clinical study report
CT	computed tomography
DCIS	ductal carcinoma in situ
DICOM	Digital Imaging and Communications in Medicine
GCP	Good Clinical Practice
GYN	gynecology
HbgA1c	glycated hemoglobin
HRT	hormone replacement therapy
IB	Investigator's brochure
ICH	International Conference on Harmonization
IP	investigational product
ITT	intention to treat
MCH	mean cell hemoglobin
MCV	mean corpuscular volume
MD	mammographic density
MedDRA	Medical Dictionary for Regulatory Activities
PE	pulmonary embolism
PI	Principal Investigator
PK	pharmacokinetic
PT	preferred term
PTT	prothrombin time
SAE	serious adverse event
SERM	selective estrogen receptor modulators
SHBG	sex hormone binding globulin
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
US/USA	United States of America

5 ETHICS

Not applicable for the abbreviated clinical study report (CSR). Refer to Section 10.1 of Protocol version 4.0 in Appendix 16.1.1.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Not applicable for the abbreviated CSR. Refer to Section 10 of Protocol version 4.0 in Appendix 16.1.1.

7 INTRODUCTION

7.1 Breast Tissue Density and Breast Cancer

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 to 6-fold increased risk of developing breast cancer, with only age or BRCA1 and BRCA2 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. At physiologic concentrations, 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 MD declined in the unaffected breast had a reduced risk of recurrence or death from breast cancer.[7,8]

7.2 Rationale for the Study

Despite the success of tamoxifen in reducing MD in breast tissue and reducing the recurrence risk of new estrogen receptor-positive tumors, the 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 stepwise 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 2 geometric isomers, E and Z.

A topically applied formulation of 4-OHT has been 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 the 4-OHT gel formulation show linear systemic pharmacokinetics (PK) with much of the drug excreted in feces. Topical 4-OHT at doses up to 200 µg/kg/day in 2 species was

generally well tolerated, and 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 with 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% with 4-OHT vs. 50% with oral tamoxifen), breast pain (42% vs. 64%), fatigue (33% vs. 29%), and night sweats (25% vs. 43%).

Prior to this study, topical 4-OHT Gel had been administered to >450 pre-and post-menopausal women, with that number now increased to >600 with the inclusion of subjects in the BHR-700-301 4WARD study 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 was 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 the 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 4-OHT gel topical administration.[15] The tolerability of 4 mg/day in the placebo controlled 6 month cyclic mastalgia study was excellent and therefore there was no reason to believe 8 mg/day would be associated with a large increase in side effects. An unblinded independent data and safety monitoring board monitored plasma levels of 4-OHT and AEs during the study to further ensure safety of the subjects.

The Sponsor has developed an investigational topical gel formulation of 4-OHT for the reduction of MD in women at an increased risk for breast cancer. BHR700-4OHT 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 structures of the 2 isomers (E and Z) of 4-OHT are shown in Figure 1 and Figure 2.

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

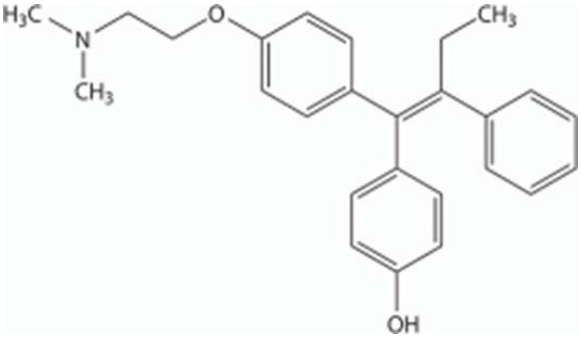
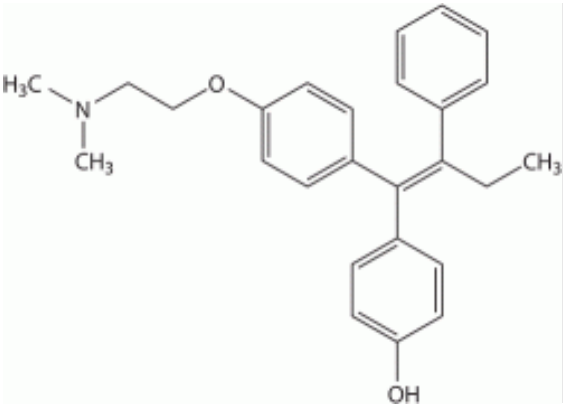


Figure 2 Chemical Structure of 4-OHT (4-Hydroxytamoxifen): Z Isomer



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: C26H29NO2

Molecular Weight: 387.51

7.3 Rationale for Early Study Termination

The study was terminated early due to a change in clinical development strategy for BHR700-4OHT Gel to pursue focus on a “cancer prevention” indication rather than on “breast density reduction” alone. As such, it was determined that the healthy population, not stratified by being at high risk of breast cancer enrolled in the BHR-700-301 study was not optimal for pursuit of a “Cancer Prevention” indication for 4-OHT Gel.

The Sponsor understands that a high-risk population represents the most clinically meaningful cohort for further development strategy. Mammographic breast density reduction in women at high risk of developing breast cancer may be an important strategy to modify breast cancer risk. The optimal population should include women at high risk of developing breast cancer,

according to risk assessment models that incorporate mammographic breast density as well as other non-modifiable risk factors (such as Tyrer Cuzick).

8 STUDY OBJECTIVES AND ENDPOINTS

Not applicable for the abbreviated CSR. Refer to the Protocol v4.0 in Appendix 16.1.1 and the Statistical Analysis Plan in Appendix 16.1.9.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a multi-center, randomized, double-blind, placebo controlled study to evaluate whether daily application of 4-OHT delivered as 4 mL BHR-700 Gel (hereafter referred to as BHR700-4OHT Gel) lowers breast density in women identified as having dense breast tissue upon screening mammography.

Approximately 330 healthy subjects aged 35 to 75 years with either heterogeneously dense (C) or extremely dense (D) dense breast tissue on 2D mammography were to be enrolled at approximately 25 sites located in the US and Europe.

Subjects who gave informed consent had screening evaluations to determine menopausal state that included hormone measures of follicle stimulating hormone, estradiol, estrone, and luteinizing hormone. Some subjects underwent a mammogram if they did not have a mammogram that fulfilled the necessary criteria (format or time period).

Subjects were 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

ACR BI-RADS=American College of Radiology [ACR] Breast Imaging Reporting and Data System (Fifth edition)
Source: Appendix 16.1.1 (Protocol v4.0)

Eligible subjects were stratified into pre/peri and post-menopause groups based on their hormone levels, and randomized within those groups 2:1 to receive either 8 mg/day (4 mg/breast) BHR700-4OHT Gel or placebo gel for up to 52 weeks. In cases of intolerance, subjects were allowed to reduce the dose to 4 mg/day (2 mg/breast) at the Investigator's discretion.

The BHR700-4OHT Gel was supplied in a non-aerosol canister with a 1 mL fixed-dose pump. Subjects applied 2 fixed unit doses of BHR700-4OHT Gel or placebo gel daily to each breast. Each actuation dispensed 1 mL of gel. For subjects in the BHR700-4OHT Gel treatment group, a total of 8 mg/day (4 mg/breast) of BHR700-4OHT Gel was administered daily unless a dose reduction by the Investigator was deemed necessary for reasons of tolerability. The placebo gel was identical in appearance and consistency to the BHR700-4OHT Gel.

Subjects applied the gel to both breasts once daily. The first dose was applied under the supervision of the Investigator/designee. Subsequent doses were to be self-administered daily by the subject until she had completed 52 weeks of study drug administration. A diary was kept by the subject to monitor compliance, start and stop dates for the subject's last menstrual cycle, and any breakthrough bleeding experienced excluding days of normal menses.

Treatment compliance was monitored by the Investigator staff; subject diaries were checked and IP canister(s) weighed when dispensed and returned.

While on treatment, subjects underwent periodic mammography to assess breast tissue density. Safety assessments included evaluations of all AEs/serious adverse events (SAEs), vital signs, and laboratory studies, with special attention given to uterine abnormalities, cardiovascular events, and thromboembolic events. Additional important safety parameters assessed for this indication were: endometrial changes, breast evaluation, coagulation factors, bone biomarkers, changes in menstrual cycle; unexpected vaginal bleeding, sex hormone binding globulin (SHBG) level, plasma 4-OHT Z isomer levels, and tolerability of BHR700 4OHT Gel.

Study assessments were performed at Day 1 and every 13 weeks thereafter (ie, at Weeks 13, 26, and 39, and at 52 weeks for those subjects who agreed to take part in the open-label phase). In the event of significant changes in bleeding pattern or other signs/symptoms which could be related to endometrial pathology, the Investigator was to perform a uterine ultrasound followed by an endometrial biopsy, if indicated.

Subjects who completed the double-blind phase of the study were offered entry into an open-label follow-up period for an additional 52 weeks.

A schedule of study assessments is shown in Table 2.

Table 2 Schedule of Study Assessments and Procedures

Study Assessment or Procedure	Screening	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 (BHR700-4OHT Gel/Placebo)			X	X	X	X	X[1]	X	X	X	
Study Drug compliance (weight canister/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 childbearing 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, Estradiol, Estone, 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										

APCR=activated protein C resistance; BSAP=bone-specific alkaline phosphatase; FSH=follicle stimulating hormone; LH=luteinizing hormone; PE=physical examination; SHBG=sex hormone binding globulin

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.

9.2 Discussion of Study Design, Including the Choice of Control Groups

Not applicable to the abbreviated CSR. Refer to Section 4.0 of Protocol version 4.0 in Appendix 16.1.1.

9.3 Selection of Study Population

Not applicable to the abbreviated CSR. Refer to Section 5.0 of Protocol version 4.0 in Appendix 16.1.1.

9.4 Treatments

Not applicable to the abbreviated CSR. Refer to Section 6.0 of Protocol version 4.0 in Appendix 16.1.1.

9.5 Efficacy and Safety Variables

Not applicable to the abbreviated CSR. Refer to Section 9.4 (Mammographic Density Assessments) of Protocol version 4.0, and Section 8.0 (Assessments of Safety) of Protocol version 4.0 in Appendix 16.1.1.

9.6 Data Quality Assurance

Not applicable to the abbreviated CSR. Refer to Protocol version 4.0 in Appendix 16.1.1.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

Not applicable to the abbreviated CSR. Refer to Section 9.0 of Protocol version 4.0 in Appendix 16.1.1, and the SAP in Appendix 16.1.9.

9.8 Changes in the Conduct of the Study or Planned Analyses

The first subject was enrolled into this study under Protocol version 2, Amendment 1, dated 07 Jun 2017. The protocol was subsequently amended twice. A summary of the key changes made during amendments 1 through 3 is provided in Table 3. The final protocol and amendment change histories are provided in Appendix 16.1.1.

Table 3 Summary of Protocol Amendments

Protocol Version	Date	Key Changes Made
Version 2, Amendment 1	07 Jun 2017	Not applicable
Version 3, Amendment 2	01 Aug 2017	Administrative; Clarification
Version 4, Amendment 3	18 Apr 2018	Administrative; Clarification

Source: Appendix 16.1.1

This study was terminated early after 223 subjects had been enrolled. The Sponsor made the decision to suspend enrollment due to the assessment that the study population was not optimal to demonstrate the most meaningful therapeutic benefit of BHR700-4OHT Gel in the reduction of mammographic breast density in women with dense breasts categorized as BI-RADS C and D, *and* at high risk of developing breast cancer.

Mammographic breast density reduction in women at high risk of developing breast cancer may be an important strategy to modify breast cancer risk. The optimal population should include women at high risk of development breast cancer, according to risk assessment models that incorporate mammographic breast density as well as other non-modifiable risk factors (such as Tyrer Cuzick). Of the 223 subjects, data from 222 who received at least 1 application of blinded study drug were analyzed.

It was determined that high mammographic breast density is associated with the development of breast cancer. As a modifiable risk factor, it is seen as a potentially important parameter in breast cancer reduction strategies in women at high risk of developing breast cancer. Breast density reduction alone in healthy women not stratified by high risk for developing breast cancer (as per risk prediction models) may not be the optimal research question at this stage of the overall BHR700-4OHT Gel development program. As the study was terminated early, data available for analysis were limited and did not allow any substantive conclusions to be drawn.

Due to the early termination, this abbreviated CSR focuses on the safety and PK/pharmacodynamic results.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

A summary of subject disposition for subjects in the blinded phase is presented in Section 14.1 (Table 1 [TDS01a]), and for the open-label phase in Section 14.1 (Table 57 [TDS01b]).

A total of 223 subjects were enrolled in this study; 222 subjects were randomized to the study treatment groups as follows:

- BHR700-4OHT GEL: n=149
- Placebo: n=74

A total of 222 subjects received ≥1 application of gel (BHR700-4OHT Gel or placebo). Subject disposition in the blinded phase is summarized in Table 4.

In the blinded phase, 15 subjects (6.7%) discontinued the study due to AEs, and 163 subjects (73.1%) discontinued study treatment due to early termination of the study by the Sponsor (for administrative reasons).

Table 4 Disposition of Subjects in the Blinded Phase – All Subjects

	BHR700-4OHT Gel Group N (%)	Placebo Group N(%)	Total N (%)
Enrolled (Intention to treat [ITT] population)	149	74	223
Safety population (received ≥1 gel application)	149 (100%)	73 (98.6%)	222 (99.6%)
Completed blinded phase through 52-week visit/End of study	16 (10.7%)	8 (10.8%)	24 (10.8%)
Discontinued:	133 (89.3%)	66 (89.2%)	199 (89.2%)
Adverse event	10 (6.7%)	5 (6.8%)	15 (6.7%)
Lost to follow-up	9 (6.0%)	2 (2.7%)	11 (4.9%)
Withdrawal by subject	5 (3.4%)	5 (6.8%)	10 (4.5%)
Other: Sponsor discontinued study*	109 (73.2%)	54 (73.0%)	163 (73.1%)
Pregnancy	0	0	0
Death	0	0	0

*Study was terminated early by the Sponsor for administrative reasons
Source: Section 14.1 (Table 1: [TDS01a])

A total of 13 subjects entered the open-label phase (Table 57 [TDS01b]); 7 of these subjects had received BHR700-4OHT in the blinded phase, 6 had received placebo. All subjects in the open-label phase discontinued the study prematurely, 12 discontinued due to the early termination of the study by the Sponsor, and 1 subject withdrew due to an AE.

Details of discontinued subjects are presented for the blinded phase and the open-label phase in Appendix 16.2.4 Listing 1 (LDS01a) and Listing 26 (LDS01b), respectively.

10.2 Demographic Characteristics

Demographic characteristics of the ITT population are presented for the blinded phase and the open-label phase in Appendix 16.2.4 Listing 2 (LDM01a) and Listing 27 (LDM01b), respectively; summaries are presented in Section 14.1 Table 2 (TDM01a) and Table 58 (TDM01b), respectively.

Subject demographics for subjects in the blinded phase are summarized in Table 5. The 2 treatment groups were balanced at baseline.

Subjects were aged between 37 and 75 years and the majority were White, and Not Hispanic or Latino.

Table 5 Subject Demographics (Blinded Phase)

	BHR700-4OHT Gel Group (n=149)	Placebo Group (n=74)	Total (N=223)
Age (year)			
N	149	74	223
Mean (SD)	54.2 (9.23)	56.2 (9.63)	54.9 (9.39)
Median	54.0	56.0	55.0
Min, Max	37, 75	40, 75	37, 75
Ethnicity, n (%)			
Not Hispanic or Latino	136 (91.3%)	66 (89.2%)	202 (90.6%)
Hispanic or Latino	12 (8.1%)	8 (10.8%)	20 (9.0%)
Unknown	1 (0.7%)	0	1 (0.4)
Race, n (%)			
White	132 (88.6%)	65 (87.8%)	197 (88.3%)
Black or African American	11 (7.4%)	7 (9.5%)	18 (8.1%)
Asian	2 (1.3%)	1 (1.4%)	3 (1.3%)
Native Hawaiian/Pacific Islander	1 (0.7%)	0	1 (0.4%)
Other	1 (0.7%)	1 (1.4%)	2 (0.9%)
Unknown	2 (1.3%)	0	2 (0.9%)

Source: Table 2 (TDM01a)

In Appendix 16.2.4, Listing 4 (LMH01a) details subjects' general medical history, Listing 5 (LMH02a) presents special medical history (breast cancer), Listing 6 (LMH03a) presents menstrual history, Listing 7 (LCM01a) presents prior medications and treatments during the blinded phase, and Listing 28 (LCM01b) presents medications and treatments ongoing from the blinded phase on entry to the open-label phase. Concomitant medications and treatments in the blinded phase and open-label phase are presented in Listing 8 (LCM02a) and Listing (LCM02b), respectively.

Table 3 (TMH01a), Table 4 (TMH02a), Table 5 (TMH03a), and Table 6 (TCM01a) in Section 14.1 summarize the general medical history, breast cancer history, menstrual history, prior medications and treatments for the ITT population, respectively. Also summarized in Section 14.1 are the subjects' concomitant medications and treatments (Table 59 [TCM01b], Table 7 [TCM02a], and Table 60 [TCM02b]).

Protocol deviations are presented for the blinded phase and the open-label phase in Appendix 16.2.4 Listing 9 (LPD01a) and Listing 30 (LPD01b), respectively. There were 44 protocol deviations, 32 minor and 12 major.

11 EFFICACY, PHARMACOKINETIC, PHARMACODYNAMIC, AND OTHER RESULTS

No efficacy results were reported. .Hormone, Bone Biomarker, Coagulation and PK results are described in Section 12.4. 12.4.112.4.112.4.1

12 SAFETY EVALUATION

12.1 Extent of Exposure

During the blinded phase of the study, 222/223 subjects (99.6%) received study treatment; 149 subjects received at least 1 application of the BHR700-4OHT Gel and 73 subjects received at least 1 application of the placebo gel (Table 4).

The study randomization schedule for the blinded phase is presented in Appendix 16.1.7 Listing 3 (LRN01a).

Twenty four subjects completed 1 year of blinded treatment in the blinded phase.

Thirteen subjects elected to participate in the open-label phase and receive 1 year of treatment with the BHR700-4OHT Gel; 6 of these subjects had received placebo during the blinded phase, and 7 subjects had received BHR700-4OHT. None of the subjects completed the open-label phase, 1 subject withdrew due to an AE, and 12 subjects discontinued due to early study termination by the Sponsor (Table 57 [TDS01b]).

12.1.1 Treatment Compliance

Listings of study drug compliance are presented for the blinded phase and the open-label phase in Appendix 16.2.5 Listing 11 (LSD01a) and Listing 31 (LSD01b), respectively, and are summarized by visit in Section 14.3.1 Table (-) TSD01a.

Overall treatment compliance from Baseline to Week 52 is summarized in Table 6. Compliance was >85% for both treatment groups.

Three women reduced their treatment dose from 8 mg per day to 4 mg per day, allowed at the discretion of the Investigator.

Protocol deviations related to dosing during the blinded phase included missed doses (10 subjects), incorrect kit dispensed to subject (3 subjects), and dosing incorrectly (2 subjects) (Listing 9 [LPD01a]). In the open-label phase, 2 protocol deviations related to missed doses (2 subjects) and 1 related to incorrect dosing (Listing 30 [LPD01b]).

Table 6 Overall Compliance from Baseline to Week 52 (Blinded Phase) – ITT Population

	BHR700-4OHT Gel Group	Placebo Group	Total
Number of subjects who completed blinded phase and returned all cannisters	15	7	22
Mean % of drug administered as planned dose (SD)	85.1 (13.7)	88.4 (12.8)	86.1 (13.2)
Min - Max	42.2-97.6	61.1-98.5	42.2-98.5

SD=standard deviation
Source: Section 14.3.1 Table (-) TSD01a

12.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19 was used at the start of the trial on 21 Aug 2017, with subsequent versions 19.1, 20.0, 20.1, 21.0 implemented during the conduct of trial. Version 22.1 was implemented at the time of the end date of the study. These versions were used for the coding of adverse reactions and AEs during the reporting period. The line listings and the summary tabulations are arranged alphabetically by primary System Organ Class (SOC) and Preferred Term (PT) level.

An AE was considered treatment-emergent if the AE started on or after the day of taking the first study drug dose.

12.2.1 Brief Summary of Adverse Events

Adverse event listings for the blinded phase and open-label phase are presented for the safety population in Appendix 16.2.7 Listing 12 (LAE01a), and Listing 32 (LAE01b), respectively, and are summarized in Section 14.3.1 Table 12 (TAE01a) and Table 64 (TAE01b).

Adverse events in the blinded phase are summarized in Table 7.

The 149 subjects in the BHR700-4OHT Gel group experienced a total of 358 AEs, and the 73 subjects in the placebo group experienced a total of 178 AEs.

Overall the incidence of AEs and treatment-related AEs was similar in both treatment groups.

Five SAEs were reported by 5 subjects in the BHR700-4OHT Gel treatment group; these are described in detail in Section 12.3.2.

Table 7 Summary of Adverse Events (Blinded Phase) – Safety Population

	BHR700-4OHT Gel Group n (%)	Placebo Group n (%)	Total N (%)
Safety population	149	73	222
Total number of AEs	358	178	536
Subjects with at least one AE	71 (47.7%)	43 (58.9%)	114 (51.4%)
Subjects with at least one mild AE	56 (37.5%)	31 (42.4%)	87 (39.2%)
Subjects with at least one moderate AE	49 (32.9%)	29 (39.7%)	88 (39.6%)
Subjects with at least one severe AE	8 (5.4%)	4 (5.5%)	12 (5.4%)
Subjects with SAEs	5 (3.4%)	0	5 (2.3%)
Related AEs	43 (28.9%)	19 (26.0%)	62 (27.9%)

AE=adverse event; SAE=serious adverse event
Source: Section 14.3.1 Table 12 (TAE01a), Appendix 16.2.6.1 Listing 12 (LAE01a)

12.2.2 Display of Adverse Events

Listings of AEs by MedDRA SOC and PT are presented for the blinded phase and the open-label phase in Appendix 16.2.7 Listing 12 (LAE01a) and Listing 32 (LAE01b), respectively, and are summarized in Section 14.3.1 Table 13 (TAE02a) and Table 65 (TAE02b), respectively.

A summary of AEs by MedDRA body system is summarized in Table 8.

Table 8 Adverse Events by MedDRA Body System and Treatment Group (Blinded Phase) – Safety Population

Body System	BHR700-4OHT Gel Group (n=149)	Placebo Group (n=74)	Total (N=223)
Infections and infestations	39 (26.2%)	19 (26.0%)	58 (26.1%)
Musculoskeletal and connective tissue disorders	20 (13.4%)	4 (5.5%)	24 (10.8%)
Reproductive system and breast disorders	20 (13.4%)	11 (15.1%)	31 (14.0%)
Gastrointestinal disorders	18 (12.1%)	14 (19.2%)	32 (14.4%)
Respiratory, thoracic, and mediastinal disorders	18 (12.1%)	12 (16.4%)	30 (13.5%)
Skin and subcutaneous tissue disorders	18 (12.1%)	10 (13.7%)	28 (12.6%)
General disorders and administration site conditions	15 (10.1%)	4 (5.5%)	19 (8.6%)
Nervous system disorders	11 (7.4%)	5 (6.8%)	16 (7.2%)
Injury, poisoning, and procedural complications	8 (5.4%)	6 (8.2%)	14 (6.3%)
Investigations	7 (4.7%)	5 (6.8%)	12 (5.4%)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	7 (4.7%)	1 (1.4%)	8 (3.6%)
Vascular disorders	6 (4.0%)	3 (4.1%)	9 (4.1%)
Psychiatric disorders	5 (3.4%)	3 (4.1%)	8 (3.6%)
Renal and urinary disorders	5 (3.4%)	3 (4.1%)	8 (3.6%)
Eye disorders	4 (2.7%)	3 (4.1%)	7 (3.2%)
Blood and lymphatic system disorders	1 (0.7%)	0	1 (0.5%)
Ear and labyrinth disorders	1 (0.7%)	4 (5.5%)	5 (2.3%)
Endocrine disorders	1 (0.7%)	0	1 (0.5%)
Immune system disorders	1 (0.7%)	2 (2.7%)	3 (1.4%)
Metabolism and nutrition disorders	1 (0.7%)	2 (2.7%)	3 (1.4%)
Product issues	1 (0.7%)	0	1 (0.5%)
Hepatobiliary disorders	0	2 (2.7%)	2 (0.9%)

MedDRA=Medical Dictionary for Regulatory Activities
Note: % is based on the number of subjects in ITT population, MedDRA version 19.1
Source: Section 14.2.2.1 Table 13 (TAE02a)

Listings of severe AEs by MedDRA SOC and PT are presented for subjects in the blinded phase and the open-label phase in Appendix 16.2.7 Listing 14 (LAE03a) and Listing 34 (LAE03b), respectively; and are summarized in Section 14.3.1 Table 15 (TAE04a) and Table 67 (TAE04b) respectively.

In the blinded phase, the ratio of severe AEs reported mirrored the drug randomization of 2:1 for the BHR700-4OHT Gel group compared to placebo group. In the BHR700-4OHT Gel group, 2 subjects had severe AEs in the body system “Infections and infestations” (influenza and urinary tract infection – both reported as unrelated to the study drug by the Investigator) and 2 had severe AEs in the body system “Skin and subcutaneous disorders” (pruritus – both reported as possibly related to study drug by the Investigator).

Study drug related AEs are presented for subjects in the blinded phase and the open-label phase in Appendix 16.2.7 Listing 15 (LAE04a) and Listing 35 (LAE04b), respectively, and are summarized by MedDRA Body System and PT in Section 14.3.1 Table 16 (TAE05a) and Table 68 (TAE05b), respectively.

During the blinded phase, for the BHR700-4OHT Gel group, the highest incidences of study drug related AEs were in the "Skin and subcutaneous tissue disorders" body system (17 subjects [11.4%]) and the "Reproductive system and breast disorders" body system (16 subjects [10.7%]). For the placebo-treated subjects, the highest incidences of study drug related AEs were in the "Reproductive system and breast disorders" body system (7 subjects [9.6%]), and the "Skin and subcutaneous tissue" body system (5 subjects [6.8%]).

The number (%) of subjects with AEs by MedDRA PT and overall frequency are summarized for subjects in the blinded phase and the open-label phase in Section 14.3.1 Table 17 (TAE06a) and Table 69 (TAE06b), respectively. In the blinded phase, nasopharyngitis (8.1%) was the most commonly reported AE in the BHR700-4OHT Gel group, and upper respiratory tract infection and cough (11%) were most commonly reported in the placebo group.

12.2.3 Analysis of Adverse Events

All reported AEs for the trial were in line with the safety profile of the drug, and from the reported AEs, there is strong evidence that transdermal administration of BHR700-4OHT Gel overall may be better tolerated by subjects and importantly did not exhibit the undesirable effects typically seen with oral administration of tamoxifen. As seen in Table 8, the percentages of reported AEs were very similar (±5%) across BHR700-4OHT Gel and placebo with only 2 body systems being reported with a difference greater than 5%; these were: "Musculoskeletal and connective tissue disorders" (+7.9% AEs reported for subjects on BHR700-4OHT Gel compared to placebo), and "Gastrointestinal disorders" (+7.1% AEs reported for subjects on placebo compared to BHR700-4OHT Gel).

A higher number of musculoskeletal AEs were reported in the active treatment arm. Considering bone biomarkers and routine biochemistry results were largely unremarkable, these are of limited or uncertain clinical significance. Inflammatory markers were not measured during this study.

As BHR700-4OHT Gel and endoxifen have approximately 100 times the potency of tamoxifen and its other metabolites in reducing proliferation of breast cancer cells *in vitro*, we would expect to see an increase of reported AEs however from the conduct of this trial, we have seen very minimal reported AEs which indicates a very safe profile for BHR700-4OHT Gel.

During the study, 3 subjects had laboratory abnormalities that were assessed as clinically significant by the Investigator, and reported as AEs. These are described in Section 12.4.

No clinically significant changes in menstrual cycles occurred apart from the single case of post-menopausal bleeding discussed in Section 12.3.2.

Breast evaluation was unremarkable for most study participants.

12.2.4 Listing of Adverse Events by Subject

Adverse event listings for the blinded phase and the open-label phase are provided in Appendix 16.2.7 Listing 12 (LAE01a) and Listing 32 (LAE01b), respectively.

12.3 Deaths, Other SAEs, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other SAEs, and Other Significant Adverse Events

Serious adverse event listings are provided for the blinded phase and the open-label phase in Appendix 16.2.7 Listing 13 (LAE02a), and Listing 33 (LAE02b), respectively.

Serious adverse events are summarized for the blinded phase and the open-label phase in Section 14.3.1 Table 14 (TAE03a), and Table 66 (TAE03b), respectively.

Table 9 presents the number and percentage of subjects with serious AEs by MedDRA SOC and PT.

12.3.1.1 Deaths

There were no on-study deaths during this trial.

12.3.1.2 Other Serious Adverse Events

Of the 5 reported serious events during the clinical study, 3 were deemed possibly related to study drug (2 SAEs in the blind phase, and 1 SAE in the open-label phase). These events are described in detail in Section 12.3.2 and an analysis is performed for each in Section 12.3.3.

12.3.1.3 Other Significant Adverse Events

Considering this and the very small number of reported SAEs received over the duration of the study, the IP shows a very positive safety profile and showed no new signals for BHR700-4OHT Gel.

Table 9 Number and Percentage of Subjects with Serious AEs by MedDRA SOC and PT – Safety Population

System Organ Class	MedDRA Preferred Term	BHR700-4OHT Gel Group n (%)	Placebo Group n (%)	Total N (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		3 (2.0%)	0	3 (1.4%)
	Invasive ductal breast carcinoma	2 (1.3%)	0	2 (0.9%)
	Intraductal proliferative breast lesion	1 (0.7%)	0	1 (0.5%)
	Endometrial adenocarcinoma	1 (0.7%)	0	1 (0.7%)
Respiratory, thoracic and mediastinal disorders		1 (0.7%)	0	1 (0.5%)
	Pulmonary embolism	1 (0.7%)	0	1 (0.5%)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class
% is based on the number of subjects in ITT population
MedDRA version 19.1
Source: Section 14.3.1 Table 14 (TAE03a) and Section 14.3.1 Table 66 TAE03b

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

12.3.2.1 Narratives of Serious Adverse Events

Subject Number	Case Number	Treatment	Death	Serious Adverse Event	Details	SAE Criteria
101-003	2019-07833(3)	BHR700-4OHT	–	X	Intraductal proliferative breast lesion	Important medical event
101-018	2019-07834(2)	BHR700-4OHT	–	X	Invasive ductal breast carcinoma	Important medical event
104-006	2019-07634(4)	BHR700-4OHT	–	X	Endometrial adenocarcinoma	Important medical event
104-059	2019-09046(2)	BHR700-4OHT	–	X	Invasive ductal breast cancer	Important medical event
104-065	2018-06506(2)	BHR700-4OHT	–	X	Pulmonary embolism	Hospitalization

Protocol	BHR-700-301
Subject No.	101-003
Subject Demographics:	52-year-old female
Treatment Group:	BHR700-4OHT Gel
Date of First Study Drug Application:	23 Mar 2018
Date of Event:	19 Apr 2018
Serious Criteria	**Important Medical Event**
Serious Adverse Event (Preferred Term)	Intraductal Proliferative Breast Lesion

This clinical trial case was reported by an Investigator in USA to Besins Healthcare and concerns a 52-year-old female patient who experienced an SAE of ductal carcinoma in situ with seriousness criteria important medical event during the treatment with double-blinded study drug.

Study ID: BHR 700-301; Site ID: 101; Patient ID: 101-003

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.

The patient's medical history included breast biopsy in 2016 with results of benign. The patient has a family history of breast cancer: specified type unknown in mother, in May 2014 and ductal carcinoma in situ in sister, at age 46. The patient's concurrent conditions and concomitant medications were not reported.

The patient was screened on 05 Mar 2018, which included consenting process, physical exam/breast exam, 2D mammogram and screen blood work; the patient met all study eligibility criteria. On 23 Mar 2018, the patient was randomized into the study and the same day, began treatment with investigational product, at a daily dose of 8 mg via topical route (lot number and expiration date: not reported) for breast density.

It was reported that on 30 Mar 2018, the patient was called and reported no changes, everything was going well. Also, the patient administered the investigational product while on vacation and had no issues with travel. The patient was informed that she had a breast MRI ordered by her primary physician at another facility. The patient confirmed that she receives breast MRI annually and had no breast symptoms or complaints prior to her recent breast MRI. The results of her breast MRI recommended that she should undergo a right breast biopsy. On 05 Apr 2018, the patient underwent a right breast core biopsy with results of lobular carcinoma in situ. On that same day, the subject's study participation was terminated and use of the investigational drug was discontinued.

On 20 Apr 2018, the patient underwent right breast lumpectomy (right breast excision of lesions) with results of ductal carcinoma in situ, intermediate grade, lobular carcinoma in situ and microcalcifications in association with benign ducts. The patient underwent a surgical consult on 08 May 2018, which included biopsy reports with a final diagnosis of ductal carcinoma in situ. On 15 May 2018, the patient underwent a diagnostic mammogram which revealed a post-lumpectomy scar in the right breast secondary to excision of a known malignancy. There are no suspicious calcifications identified in the lumpectomy bed or in the adjacent tissues.

The event was considered serious with seriousness criteria important medical event and moderate in CTC-grade intensity.

No further treatment except lumpectomy was received for this serious adverse event.

At the time of reporting, the patient's outcome was recovered.

Action taken with blinded study drug was permanently discontinued.

A causal relationship between study drug and the event of ductal carcinoma in situ was assessed as no reasonable possibility by the Investigator.

The company assessed the causal relationship between blinded study drug and event of Ductal carcinoma in situ as no reasonable possibility.

As the study was terminated on 21 Dec 2018, unblinding for the blinded phase of study was performed.

Date received by Besins Healthcare: 07 Mar 2019

Additional information was received on 26 Mar 2019 and significant information was received:

The kit number for the investigational product was 10077.

It was reported that the patient did not return for end of study procedures as she was going through her cancer surgery. A family member returned the investigational product to clinic. It was confirmed that the patient underwent a breast, right, core biopsy (collected on 5 Apr 2018) which revealed lobular carcinoma in situ and a breast, right, lumpectomy (collected on 19 Apr 2018) which revealed ductal carcinoma in situ, intermediate grade.

The causal relationship between study drug and the event of ductal carcinoma in situ was considered not reasonably possible, taking into consideration the short duration of study drug exposure (23 Mar 2018 through 04 Apr 2018), and the family history of ductal carcinoma in situ in sister and breast cancer (unknown type) in mother.

It was reported that currently the patient had no further medical incidents and was being followed at other facility. The next appointment of the patient at another facility would be on 02 Aug 2019.

Date received by Besins Healthcare: 26 Mar 2019

Additional information was received on 17 Apr 2019 and significant information was received:

It was confirmed that the patient underwent a right breast lumpectomy procedure on 19 Apr 2018 and the lumpectomy pathology results were received on 20 Apr 2018.

Date received by Besins Healthcare: 17 Apr 2019

Additional information was received on 20 Jan 2021 and significant information was received: The stop date for the event was updated to 20 Apr 2018.

Date received by Besins Healthcare: 20 Jan 2021.

Protocol	BHR-700-301
Subject No.	101-018
Subject Demographics:	63-year-old female
Treatment Group:	BHR700-4OHT Gel
Date of First Study Drug Application:	28 Jun 2018
Date of Event:	30 Jan 2019
Serious Criteria	**Important Medical Event**
Serious Adverse Event (Preferred Term)	Invasive ductal breast carcinoma

This clinical trial case was reported by an Investigator in USA to Besins Healthcare and concerns a 63-year-old female patient who experienced serious adverse event of Invasive ductal carcinoma after the use of double-blinded study drug.

Study ID: BHR 700-301; Site ID: 101; Patient ID: 101-018

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

The patient's medical history included hypertension in 20 Jun 2018, hypothyroidism in 11 Apr 2016, back pain on unknown date in 2003, insomnia on unknown date in 2003 and overweight. The patient had a medical history of left breast excisional biopsy at age 16- benign. The patient had a family history of maternal uncle prostate cancer, maternal uncle leukemia, maternal grandfather lung cancer, maternal aunt lung cancer and cousin male lung cancer. The patient also had a family history of breast cancer half-sister at age 47, breast cancer specified type unknown- bilateral.

The patient's concomitant medications included Microzide (hydrochlorothiazide), Synthroid (levothyroxine sodium), Flexeril (cyclobenzaprine hydrochloride), Elavil (amitriptyline hydrochloride) at the time of onset of the adverse event.

On 28 Jun 2018, the patient started treatment with blinded study drug at a dose of 8 mg per day via topical route (Batch number and expiry date: unknown) for the treatment of breast density. The patient received the last dose on 23 Dec 2018.

On 23 Jan 2019, the left breast examination was performed which was abnormal and revealed 2x2 cm firm mass at 6 o'clock. The inspection, palpation and pain on palpation was found to be normal. The right breast inspection revealed an abnormal scar at 12 o'clock. Palpation and pain on palpation were normal. On the same day, the patient's blood pressure was 126/78 mm Hg, heart rate 86 beats/min and temperature 98.2. It was reported that physical examination of the patient was normal; however, the patient complained of eyes burning. Mammogram was obtained on 30 Jan 2019 and the findings were highly suggestive of malignancy according to BI-RADS Assessment Category 5. The findings were mass in left breast and abnormal lymph nodes found in the left axilla. Calcifications in the left breast were suspicious. The findings revealed that the breast was heterogeneously dense, which may obscure small masses. There was a high density, irregular mass measuring 20 millimeters with spiculated margins seen in the posterior third of the left breast lower outer quadrant at 5 o'clock located 8 cm from the nipple. There were multiple groups of amorphous and round calcifications with regional distribution seen in the middle third of the left breast at 3 o'clock located 10 cm from the nipple. In the right breast, there were no masses, suspicious micro calcifications or architectural distortion were evident. On the same day, ultrasound findings revealed irregular anti-parallel mass with

indistinct margins measuring 18 mm. Several small cysts and possible satellite adjacent to this mass were seen. Ultrasound demonstrated multiple simple cysts seen in the middle of the left breast. Multiple abnormal lymph nodes were also seen in the left axilla. The patient was informed of the exam results. Ultrasound-guided core biopsy and surgical consultation were recommended. On the same day, left breast biopsy of the suspicious mass was performed. The pathology results were reported on 31 Jan 2019 which revealed invasive ductal carcinoma.

The event was considered as serious with seriousness criteria important medical event with moderate intensity of CTC-grade.

It was reported that cancer treatment was followed as the corrective treatment for the event.

The outcome for the event was not recovered/resolved.

Action taken with blinded study drug was not applicable.

A causal relationship between study drug and the event of invasive ductal carcinoma was assessed as no reasonable possibility by the Investigator.

The company considered that the causal relationship between blinded study drug and invasive ductal carcinoma was no reasonable possibility, taking into consideration the patient's advancing age and family history of breast cancer, prostate cancer, leukemia and lung cancer.

As the study was terminated on 21 Dec 2018, unblinding for the blinded phase of study was performed.

Date received by Besins Healthcare: 06 Mar 2019.

Additional information was received from mail on 26 Mar 2019 and have significant information

The patient had a triple-negative breast cancer. It was confirmed that the result of left breast excisional biopsy at age 16 was negative, benign.

The lot number for investigational product was 18B0177/78 and kit ID number was 10507.

It was confirmed that on 30 Jan 2019, patient had an ultrasound core, biopsy which revealed invasive ductal carcinoma. On 26 Feb 2019, the left breast biopsy of patient was performed which revealed fibrocystic changes with lobular atrophy, mammary fibrosis, focal usual ductal hyperplasia, sclerosing adenosis and apocrine cystic change. Same day, lymph node left axillary biopsy was performed which revealed poorly differentiated infiltrating ductal carcinoma.

On 13 Mar 2019, the patient began treatment with chemotherapy which was ongoing at the time of report. It was reported that the patient's most recent visit for chemotherapy was on 20 Mar 2019.

It was reported that as the patient had triple-negative breast cancer, therefore, cancer was unlikely to respond to hormonal therapy medicines.

Date received by Besins Healthcare: 26 Mar 2019

Additional information was received from the Investigator on 09 Apr 2019.

It was reported that the patient had a hormone receptor-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative) and would not be related to this tamoxifen gel study which involves potential estrogen receptor-related mediation of breast tissue.

Taking into consideration the above fact along with the patient's advancing age and family history of breast cancer, prostate cancer, leukemia and lung cancer, the company causality was also assessed as no reasonable possibility between the study drug and event of Invasive ductal carcinoma.

Date received by Besins Healthcare: 09 Apr 2019

Protocol	BHR-700-301
Subject No.	104-006
Subject Demographics:	61-year-old female
Treatment Group:	BHR700-4OHT Gel
Date of First Study Drug Application:	01 Nov 2017
Date of Event:	11 Feb 2019
Serious Criteria	**Important Medical Event**
Serious Adverse Event (Preferred Term)	Endometrial adenocarcinoma

This clinical trial case was reported by an Investigator in USA to Besins Healthcare and concerns a 61-year-old female patient (weight: 66.2 kg, height: 166.3 cm) who experienced a serious adverse event of endometrial adenocarcinoma with seriousness criteria important medical event after the treatment with double-blinded study drug and subsequent treatment with open-label 4-hydoxy tamoxifen gel.

Study ID: BHR 700-301; Site ID: 104; Patient ID: 104-006

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.

The patients' concurrent conditions included moderate lower back ache since 14 Jan 2019, arthritis bilateral hands since 2015, diabetes and hypertension and mild heart disease since 2007, mild hypothyroidism and mild hypercholesterol since 1997. The patient medical history also included post-menopausal bleeding which started on an unknown date in Feb 2014 and ended on an unknown date in Mar 2014. The patient underwent an endometrial biopsy on 12 Mar 2014 with results of benign. The patient's last menstrual period date was 01 Mar 2012.

Concomitant medications included atorvastatin, metformin hydrochloride, carvedilol, lisinopril, ozempic (semaglutide), levothyroxine, Invokana (canagliflozin), vitamin D3 (cholecalciferol), Tylenol (paracetamol), Advil at the time of onset of the adverse event.

On 01 Nov 2017, the patient got enrolled in the study and began treatment with blinded study drug. The same day, patient started treatment with blinded study drug topical at a dose of 8 mg daily (lot number and expiration date; not reported) for breast density. The patient received last dose of blinded phase on 31 Oct 2018.

On 06 Nov 2018 the patient began therapy in the open-label phase of the study with 4-Hydroxytamoxifen Gel, topical at a dose of 8 mg daily (lot number and expiration date: not reported) for breast density. On 21 Dec 2018, the patient received last dose of drug in open-label phase.

It was reported that the Sponsor terminated the trial on 21 Dec 2018.

The patient reported experiencing intermittent bright red uterine bleeding since 14 Jan 2019.

According to the report, end of study procedures were performed on 05 Feb 2019 which was an early termination visit for the patient. Due to the patient's report of post-menopausal bleeding, an endometrial biopsy was performed which revealed a fair amount of tissue (bright red) that was concerning the Investigator. Based on the same, the final diagnosis was made for endometrial adenocarcinoma, endometrioid type, Figo Grade 2 of 3 (endometrial cancer) (SAE No: 1). It was also reported that an ultrasound was not performed at that time.

The event was considered serious, important medical event and severe in CTC-grade intensity.

Treatment was reported as referral to a GYN oncologist. Further details of corrective treatment were not reported.

At the time of reporting, the patient's outcome was not recovered.

Action taken with blinded study drug and 4-Hydroxytamoxifen Gel (open-label) was not applicable as the study drug was stopped (21 Dec 2018) prior to the onset of serious adverse event.

A causal relationship between study drug and 4-Hydroxytamoxifen Gel and the event of endometrial adenocarcinoma was assessed as reasonably possible by the Investigator.

The company assessed the causal relationship between study drug and 4-Hydroxytamoxifen Gel and event of endometrial adenocarcinoma as reasonable possibility.

Analysis of similar event:

A review of the cumulative listing of similar event terms with cutoff date 22 Feb 2019 revealed no other reported cases with the same PT Endometrial adenocarcinoma.

The blind code was broken for regulatory purposes as the case qualifies for suspected unexpected adverse drug reaction (SUSAR).

Case comment: This clinical trial case concerns a 61-year-old female patient who experienced serious adverse event of endometrial adenocarcinoma after the use of blinded therapy drug and 4-Hydroxytamoxifen Gel (in open-label phase) for treatment of breast density increased. Event is considered as unexpected. Investigator causality was provided as reasonable possibility and the company causality for endometrial adenocarcinoma was assessed as reasonable possibility considering temporal relationship between event onset and 4-Hydroxytamoxifen Gel therapy onset date. The patient had a medical history of post-menopausal bleeding which may have an underlying endometrial cause. Moreover, the patient's age, hypertension and diabetes are known risk factor for endometrial carcinoma. Lack of information pertaining to family history, parity status and intake of any estrogen replacement therapy precludes the comprehensive assessment of the case.

Date received by Besins Healthcare: 12 Feb 2019

Upon internal review on 25 Feb 2019 for the information initially received on 12 Feb 2019, the following information was corrected:

The Investigator reassessed the seriousness criterion for the event of "endometrial adenocarcinoma, endometrioid type Figo grade 2 of 3" from life threatening to Important medical event. Based on the same, the corresponding updates have been made in the seriousness criteria section as well as in the narrative.

Additional information was received on 28 Feb 2019 and significant information was received:

It was stated that the patient was never scheduled for an ultrasound. Also reported that the patient came in for the end of study visit due to Sponsor terminating the trial. On 05 Feb 2019 the patient came in at 7:30 am and presented with adverse event of intermittent vaginal spotting. The only procedures done for the end of study visit that day were study related labs, physical and breast exam, collection of study investigational product, adverse events and concomitant

medications. The biopsy was done by the Investigator as it was expected to be more definitive than the ultrasound. The biopsy was done without the protocol required ultrasound and the results were back on 11 Feb 2019 with the diagnosis of endometrial carcinoma. It was confirmed that the biopsy was performed on 05 Feb 2019 and the diagnosis was made available on 11 Feb 2019. The patient was scheduled for consultation with gynecologist oncology on 13 Feb 2019. It was reported that the patient had an ultrasound with the gynecology oncologist on 15 Feb 2019 and was scheduled for surgery on 11 Mar 2019.

Company comment: Follow-up information was received on 28 Feb 2019: No change in previous case assessment.

Date received by Besins Healthcare: 28 Feb 2019

Additional information was received on 28 Mar 2019 and significant information was received.

The batch number and kit number of the investigational product was received:

For blinded phase:

Week 1 Kit number was 10040 and lot number was 17B0166/67

Week 13 Kit number was 10141 and lot number was 17B0166/67

Week 26 Kit number was 10216 and lot number was 17B0166/67

Week 39 Kit number was 10339 and lot number was 17B0166/67

For open-label phase:

Day 1 Kit number was 90009 and lot number was 18B0203.

It was reported that the drug kits did not have expiration dates on them.

It was confirmed that the biopsy was collected by the primary Investigator on 05 Feb 2019 and the results of biopsy were returned on 11 Feb 2019. 11 Feb 2019, was the first day on which Investigator became aware of the event of "endometrial adenocarcinoma, endometrioid type, Figo Grade 2 of 3". So, the date of start of the event endometrial adenocarcinoma, endometrioid type, Figo Grade 2 of 3 (SAE No: 1) was updated to 11 Feb 2019 (the date of awareness).

On 13 Feb 2019, the patient saw the Gynecologist Oncologist. On 15 Feb 2019, patient had a transvaginal ultrasound and the surgery was planned tentatively for 11 Mar 2019.

The patient had a robotic assisted laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node mapping with left obturator and right external lymphadenectomy, sacral colpopexy and anterior vaginal suspension surgery. It was reported that the patient did not require any adjuvant therapy but would require surveillance exams every 04 months for the first 2 years.

Date received by Besins Healthcare: 28 Mar 2019

No change in previous medical assessment.

Additional information was received on 09 Apr 2019 and significant information was received:

The patient had a past medical history of pregnancy (gravida: 6, para living: 3), abortion (para term: 3) and dilatation and curettage (thrice) due to miscarriages, dense breasts, vitiligo and female cystocele pneumonia. The patient past surgical history included gall bladder surgery

(cholecystectomy) on 28 Jan 2011, breast biopsy sample on 28 Jan 1999 (result unknown) and tonsillectomy on 28 Jan 1985.

The patient's concurrent conditions included alcohol use (current beer, occasionally: 1 a week), non-smoker, never had substance abuse and food allergy. The patient was allergic to Bactrim (lead to rash and throat tightness), erythromycin (lead to violent vomiting), penicillin (lead to rash), adhesive bandage (caused a blister and skin peeling) and Lorcet. The patient's first menstrual cycle was at age of 13 and her last cycle was in 2015. The patient's last pap smear was in 2017 with normal results and last mammogram was in 2018 with normal results.

The patient family history included: hypertension, heart disease, high cholesterol and prostate cancer in father; breast cancer, diabetes mellitus, hypertension and stroke in mother; hypertension in sister.

Additional concomitant medication of Lantus 100 units/ml subcutaneous spray was added. Details were updated for the concomitant medication of ozempic, levothyroxine and Invokana.

It was reported that, the patient began to have post-menopausal spotting approximately 3 weeks ago.

On 13 Feb 2019, the patient had a chest x-ray which revealed no effusions, no cardiomegaly, no mediastinal or hilar mass, no life support lines and no pneumothorax. Osseous Structure had no acute fracture or destructive lesion, mild multilevel degenerative disk disease in the visualized thoracic spine.

The event verbatim was updated from endometrial adenocarcinoma, endometrioid type, Figo Grade 2 of 3 to Stage IA Grade 1 endometrioid adenocarcinoma as this was the final diagnosis as per the pathology report from the Oncologist.

On 11 Mar 2019, patient had a surgery for the event and patient recovered from the event. The patient had a robotic assisted laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node mapping with left obturator and right external lymphadenectomy, sacral colpopexy and anterior vaginal suspension surgery. It was reported that the patient had a normal sized uterus, tubes and ovaries. Patient had a small endometrial carcinoma with minimal invasion, probable grade 1. Patient had second degree vaginal prolapse with enterocele and also had a cystocele and stress incontinence. A sacral colpopexy was performed, shortening the uterosacral ligaments and incorporating in the vaginal cuff closure. Also, on 11 Mar 2019, the samples from body site: uterus, cervix, bilateral tubes and ovaries were collected for MLH1 promoter methylation analysis. On 12 Mar 2019, the patient had a lab test of hemoglobin with result of 11.8 g/dl and hematocrit with result of 34.8%. The microscopic examination showed the diagnosis of diaphragm washings cytology (thin prep and cell block): mesothelial cells and histiocytes are present. Negative for malignant cells. Left obturator sentinel lymph node, lymphadenectomy: 2 lymph nodes, no evidence of metastatic carcinoma. Multiple hematoxylin and eosin levels and AE1 immunostains are examined. Right external sentinel lymph node, Lymphadenectomy: One lymph node, No evidence of metastatic carcinoma. Multiple hematoxylin and eosin levels and AE1 immunostains are examined. Uterus, cervix, bilateral tubes and ovaries, hysterectomy and bilateral salpingo-oophorectomy: endometrial adenocarcinoma endometrioid type, Figo grade 1, with 1 mm out of 16 mm myometrial invasion. No lymphovascular invasion identified. Cervix, bilateral fallopian tubes and ovaries are negative.

On 13 Mar 2019, the immunohistochemistry revealed positive estrogen and progesterone receptors. On 26 Mar 2019, the result of MLH1 promoter methylation detected (51%).

It was confirmed that the patient had never taken any hormone replacement therapy.

Date received by Besins Healthcare: 09 Apr 2019

Case comment: Follow-up information was received on 09 Apr 2019: The patient had a past medical history of pregnancy (gravida: 6, para living: 3), abortion (para term: 3) and dilatation and curettage (thrice) due to miscarriages, dense breasts, vitiligo and female cystocele pneumonia, which did not affect the previous assessment of the case. no change in previous assessment.

Additional information was received on 22 May 2019 and significant information was received:

It was reported that the patient was doing very well and was back at work. The patient was not back for follow ups with the gynecology oncologist or the clinical site. It was also reported that there were no follow ups due with the gynecology oncologist in Aug/Sep as far.

Date received by Besins Healthcare: 22 May 2019

Protocol	BHR-700-301
Subject No.	104-059
Subject Demographics:	61-year-old female
Treatment Group:	BHR700-4OHT Gel
Date of First Study Drug Application:	03 Aug 2018
Date of Event:	04 Sep 2019
Serious Criteria	**Important Medical Event**
Serious Adverse Event (Preferred Term)	Invasive ductal breast carcinoma

This clinical trial case was reported by an Investigator in USA to Besins Healthcare and concerns a 61-year-old female patient who experienced a serious event of invasive ductal carcinoma, left breast with seriousness criteria important medical event after the treatment with study drug (4-Hydroxy Tamoxifen Gel or placebo).

Study ID: BHR 700-301; Site ID: 104; Patient ID: 104-059

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.

The patient's medical history included right breast cyst (in 1979), right breast cyst aspiration-benign (in 1979), endometriosis (1978-1995), dysplasia of vaginal cuff (in 2013), total abdominal hysterectomy with bilateral salpingo-oophorectomy (in 1995), colonoscopy-benign (in 2005), appendix stones (in 2017), laparoscopy (in 1978, 1979 and 1980), bone tumor-benign, left leg (1970), removal of bone tumor-benign, left leg (in 1972 at the age of 14) and colposcopy of vaginal cuff (in 2013). Patient's concurrent conditions included atrophic vaginitis (ongoing since 2015), lower back pain (ongoing since 2017), osteoporosis (ongoing since 2013), abdominal bloating (ongoing since 2008), abdominal cramps (ongoing since 2008), arthritis of spine (ongoing since 2017), heartburn (ongoing since 2008), sinus headaches (ongoing since 2003), sinus allergies (since 2002-ongoing status not reported), headaches (ongoing since 1970). It was reported that patient's mother was deceased with heart disease, and history of diabetes II, hypertension, hyperlipidemia, patient's father was deceased with heart disease and history of diabetes II, hypertension, her sister had history of diabetes II, her maternal great aunt had history of colon cancer and maternal aunt had history of ovarian cancer.

The patient's concomitant medications included Probiotics (probiotics NOS), Advil (ibuprofen), Tums (calcium carbonate), Gass X (simethicone), Advil cold and sinus (chlorphenamine maleate; ibuprofen; pseudoephedrine hydrochloride), Miralax (polyethylene glycol 3350), HQRA (hydroquinone; mometasone; tretinoin) and intensive recovery cream (01 application topical, twice daily since 23 Jul 2018) all for unknown indications.

On 10 Jul 2018, at the time of screening, the patient's mammogram was normal with a 'C' density. On 03 Aug 2018, the patient started treatment with the study drug at a daily dose 8 mg (batch no:17B0166/67 on Drug Day 1 and Drug Week 13, expiry: not provided) topically for the indication of breast density. On 21 Dec 2018, the study drug was discontinued due to Sponsor terminating the trial. On 27 Dec 2018, the patient was early termed from the study. It was reported that no mammogram was done at early termination visit due to protocol.

On 26 Jul 2019, the patient had annual mammogram-tomosynthesis which showed breast composition as BI-RADS B-scattered fibroglandular densities (25-50% glandular) and also depicted asymmetric density, left breast at 3:00 posterior third, for which additional evaluation with dedicated ultrasound of this area suggested and BI-RAD Category-0, incomplete, needs additional imaging evaluation. The supplement left breast ultrasound was done and the results were suspicious, taller than wider lesion with left breast at 5:00, 6 cm from the nipple, show a taller that wide, hypoechoic nodule within an echogenic periphery, measuring 4x4x6 mm in size for which definitive characterization with ultrasound-guided core biopsy was suggested and BI-RADS Category IV-suspicious for malignancy. On 05 Aug 2019, an ultrasound-guided biopsy of the left breast was attempted. The lesion could not be easily identified, only an area of vague shadowing was seen. Ultrasound-guided biopsy was therefore cancelled. It was recommended to attempt a stereotactic biopsy or contrasted magnetic resonance imaging. The patient opted for the magnetic resonance imaging with guided biopsy at that time. On 12 Aug 2019, the magnetic resonance imaging of breast with and without contrast with subtraction and reconstruction images was done which revealed BI-RADS Category 1- Negative, Right Breast, BI-RADS Category IV-suspicious for malignancy, Left Breast. There were 2 enhancing nodules, one of which appeared to perhaps correspond to a lesion seen both mammographically and monographically. The other appears to not have a definite mammographic correlate. The lesions were in close proximity to one another, such that it may be difficult to perform both MRI biopsies at the same time. One may be too posterior to biopsy, this being in the more posterior 6:00 position, it was believed that this corresponded with the abnormality at the 5:00 position on sonogram. Attempt at magnetic resonance imaging guided core needle biopsy of both lesions is recommended. Malignancy cannot be excluded. If MRI biopsy cannot be performed, wire localization and excisional biopsy surgically would be recommended following magnetic resonance imaging guided wire localization. MRI-guided breast biopsy was recommended for left breast. On 28 Aug 2019, the magnetic resonance imaging guided vacuum assisted left breast biopsy and tissue marker placement and post-digital left mammogram was done. Successful magnetic resonance imaging guided biopsy of the 2 breast lesions, one at 6:00 and one at 5:00 were done and results were reported on 04 Sep 2019. On 04 Sep 2019, results for the pathology for left breast, 6:00, 8.1 cm from nipple, MRI-guided biopsy showed invasive ductal carcinoma Nottingham histological grade: 6/9 (Grade II/III). architecture: 2/3, nuclear grade: 2/3, mitotic count: 2/3, maximum contiguous tumor dimensions is 0.4 cm. Tumor involves multiple cores, lymphovascular invasion: not identified, ductal carcinoma in situ: not identified, unremarkable skeletal muscle identified. Prognostic markers are pending and left breast, 5:00, 7.4 cm from nipple, magnetic resonance imaging guided biopsy-scant breast tissue, micro calcifications present in benign epithelium, negative for malignancy. The same day, patient was diagnosed with invasive ductal carcinoma, left breast (severity: severe) which was considered serious with seriousness criteria important medical event. It was reported that the patient has been referred to breast oncology surgeon for treatment and the first consultation appointment was scheduled on 11 Sep 2019.

It was reported that the patient had no prior use of study drug prior to trial.

The patient was referred to breast clinic for further treatment plan.

At the time of reporting, the outcome of the event was not recovered/not resolved.

Action taken with study drug was not applicable as study drug had been discontinued earlier due to early termination of the trial by the Sponsor.

The causal relationship as assessed by the reporter between study drug and event was reasonable possibility.

The company considered that the causal relationship between study drug and event was reasonable possibility.

Analysis of similar events comment:

A review of the cumulative listing of similar event terms with cutoff date 13 Sep 2019 revealed one similar case with PT: invasive ductal breast carcinoma reported in a patient in same study for the indication of breast density. In that previous case, it was reported that the patient had a hormone receptor-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative) and would not be related to this tamoxifen gel study which involves potential estrogen receptor-related mediation of breast tissue. Thus, the relationship to study drug was assessed as not reasonably possible by both the Investigator and medical monitor in the previous case.

Date received by Besins Healthcare: 05 Sep 2019.

Case comment: This clinical trial case was received from USA and concerns a 61-year-old female patient who experienced a serious adverse event of invasive ductal carcinoma after the treatment with study drug for reducing breast tissue density. Event is unexpected. Company causality for invasive ductal carcinoma is assessed as reasonable possible in line with the Investigator assessment. However significant family history of malignancy (ovarian and colon cancer) is a potential confounder.

Additional information was received from the Investigator from Besins Healthcare on 18 Sep 2019 and significant information was received.

On 28 Aug 2019, the pathology report of left breast, 6:00", 8.1 cm from nipple for diagnosis, grading and description of the tumor revealed estrogen receptor-positive with 99% strong intensity (reference range: ≥1% positive - <1% negative), progesterone receptor-positive with 95% moderate intensity (reference range: ≥1% positive - <1% negative), HER-2 was negative with (1+) intensity (reference range: 0 negative, 1+ negative, 2+ equivocal, 3+ positive) and MIB-1 (Ki-67) was Low with 9% (reference range: <10% low proliferation, ≥10% or ≤20% intermediate proliferation, >20% high proliferation). Also, the immunostains performed with appropriate controls showed P63 and calponin were positive for myoepithelial cells.

The reporter's causality was reconfirmed as reasonable possibility. As per the Principal Investigator the study drug was given to the patient as a topical gel that she applied directly to her breast every day.

The company considered that the causal relationship between study drug and event was no reasonable possibility.

Case comment: This clinical trial case was received from USA and concerns a 61-year-old female patient who experienced a serious adverse event of invasive ductal carcinoma after the treatment with study drug for reducing breast tissue density. Event is unexpected. Company causality for invasive ductal carcinoma is assessed as no reasonable possibility considering the subject's advanced age, personal history of dysplasia of the vaginal cuff, family history of ovarian and colon carcinoma, limited time exposed to study drug (20 weeks), change in breast density and study drug's mechanism of action.

Date received by Besins Healthcare: 18 Sep 2019

Additional information was received from the Investigator from Besins Healthcare on 26 Sep 2019 and significant information was received. Patients' obstetric history included menarche at the age of 10 and surgical menopause at the age of 36. The patient had never been pregnant (Gravida 0, Para 0) due to endometriosis and had multiple laparoscopic surgeries for endometriosis. The patient's other medical history included heart palpitations, rash due to iodine allergy, tonsillectomy (Apr 1961 at the age of 3), wisdom teeth extraction (May 1975 at the age of 17), exploratory surgery for infertility (Aug 1980 at the age of 22), D & C (May 1986 at the age of 28), total abdominal hysterectomy (Jan 1995), right knee surgery of torn meniscus (Jun 2009 at the age of 51), removal of nasal polyps (Mar 2011), uterine biopsy (Jun 2013). She had used hormone replacement for 02 years and never used oral contraceptive. The patients' father had history of prostate cancer, patient's mother had hypercholesterolemia and her paternal great aunt had colon cancer. She had a prior history of tobacco use at approximately 1/2 pack per day for 23 years which she left in 2005. She drinks 1-2 glasses of wine every day and did not make use of recreational drugs. She did 30 minutes of cardio exercise 5 days per week. On 10 Sep 2019 at 07:27 hours, interpretation of outside films noted it was not clear if there was residual mass and/or clip migration. Therefore, if a breast conservation would be planned, a scout imaging on the day of localization would be recommended. Due to posterior central location, a wire would be preferred. There was no mammographic evidence of malignancy in the right breast. BI-RADS category 6: known biopsy proven malignancy. It was reported that, internal review of patient's films suggested a repeat left mammogram for surgical planning due to possible medical migration of clips and inability to discern a residual mass on the immediate post-procedure film.

On 11 Sep 2019, the patient went to GYN oncology Breast MD for consultation. At the time of consultation, at 08:13 hours, the patient vital signs were: pulse 86, respiratory rate 16, blood pressure 140/80, temperature 97.7^{o}F and weight measured 80.7 kg. The staging data included stage form: BRE Breast staging form AJCCV8, Cancer diagnosis: malignant neoplasm of female breast, Clinical TNM: cT1 cN0 cM0, Clinical stage: IA, Histological Grade Group (G): G2. Also, the findings of pathology report were discussed with the patient which included pathophysiology of invasive ductal carcinoma, significance of ER/PR and HER-2/neu testing and treatment options. It was reported that diagnosis of invasive ductal carcinoma still stands at this point. The patient would return to scheduled surgery with staging of the axilla via axillary ultrasound, finer needle aspiration and sentinel lymph node biopsy. Also, breast conservation versus mastectomy was discussed with the patient. The patient would like to consider lumpectomy with sentinel lymph node biopsy at this time. The patient would likely require radiation post breast surgery, depending on final pathology. At PAT appointment, the patient would have left mammogram completed prior to the surgery for preoperative planning to determine the location of the barbell clip relative to the biopsy site and if there would be a residual mass.

Case comment based on follow-up information received on 26 Sep 2019: There is no change in company causality and it remains as no reasonable possibility. Additional confounding factors as per the follow-up information includes patient's nulliparity, early surgical menopause at 36 years of age leading to use hormone replacement therapy for 2 years. It is suspected that based on the study drug mechanism of action a change in breast density from 'C' to 'B' occurred which led to increase likelihood of detection of a suspicious lesion by mammogram in this case.

Date received by Besins Healthcare: 26 Sep 2019

Protocol	BHR-700-301
Subject No.	104-065
Subject Demographics:	50-year-old female
Treatment Group:	BHR700-4OHT Gel
Date of First Study Drug Application:	17 Aug 2018
Date of Event:	29 Aug 2018
Serious Criteria:	**Hospitalization**
Serious Adverse Event (Preferred Term)	Pulmonary embolism

This clinical trial case was reported by an Investigator in USA to Besins Healthcare and concerns a 50-year-old female patient who experienced a serious adverse event of 'acute and recurrent right lobe pulmonary embolus' (Pulmonary embolism), which required hospitalization, during the use of double-blinded study drug.

The patient was enrolled in study protocol number: BHR 700-301, IND number: 590801, EudraCT No: 2017-002906-10 and study name: BHR Breast Density Trial- BHR 700-301 with Study drug 4-Hydroxy-Tamoxifen gel. The study is a double-blind one with 2:1 randomization to active.

The patient's medical history included pulmonary embolus post surgery in 2013, depression, breast density increase, respiratory failure, diabetes I (since 1986). In 2012, she had severe auto accident, thoracic spinal fusion/pins and screws inserted in thoracic back, cardiac catheterization, and nerve damage of thoracic spine, back pain, sinus allergies and back muscle spasms. She had anxiety (since 2017). She was a former smoker. She has a family history of cancer (mother). As per hospital records patient was a non-smoker who has never smoked but patient admitted for being a former smoker having quit in 2010. Also, respiratory failure was stated in the hospital records which was not known. COPD was found in an own hospital record. Her body mass index was 27.81102 (classified as overweight). She was allergic to Cipro.

The patient's concomitant medication at the time of the adverse events included Ultram (tramadol hydrochloride), topiramate and tizanidine tablet, which were commenced at a dose of 50 mg daily, 200 mg daily and 2 mg daily. Hydrocodone-acetaminophen was commenced at dose of 7.35 mg daily per oral, as required for the treatment of back pain since 2012. Singulair (montelukast sodium) was commenced at dose of 10 mg per oral daily as required for the treatment of sinus allergies since 2012. Effexor (venlafaxine hydrochloride) was commenced at dose of 75 mg once daily for the treatment of anxiety since 2017. On an unknown date, lorazepam 0.5 mg tablet was commenced at an unknown dose for an unknown indication.

On 17 Aug 2018, treatment with double-blinded study drug was commenced topically at a dose of 8 mg daily for the treatment of breast density.

On 27 Aug 2018, 2 weeks prior to this report, the patient had exertional dyspnea and chest x-ray was done with no findings. On 29 Aug 2018, a CT with contrast of chest and pulmonary angiogram was done and revealed that there was a filling defect in a distal right lower lobe 7th or 8th order pulmonary artery extending into adjacent peripheral branches for a minimal degree. XR chest, frontal (one view) revealed that her lungs, pleura and heart were unremarkable. Her aorta has no calcified plaque and there was extensive hardware along the bilateral ribs and along the upper thoracic spine. Electrocardiogram revealed boarder line sinus rhythm. She was hospitalized from 29 Aug 2018 to 31 Aug 2018 with a pulmonary embolus. Upon arrival in the emergency room she underwent comprehensive laboratory studies with pertinent lab values as

follows: White blood cell count was 7.9, red blood cell count was 4.13, hemoglobin was 11.8, hematocrit was 36.3, platelet count was 320, blood glucose was 117, blood urea was 12, creatinine was 0.8, potassium was 3.6, albumin was 4.1, alkaline phosphatase was 114, aspartate aminotransferase was 17, alanine aminotransferase was 22, bilirubin total was 0.3, glomerular filtration rate was 76, creatinine clearance was 81.3, troponin was 0.02, N-terminal prohormone brain natriuretic peptide was 104. On 29 Aug 2018, right pleural based lung nodule was examined but the result was not reported. On 30 Aug 2018, ultrasound venous, bilateral lower extremities revealed that there was no superficial venous thrombosis and her troponin was <0.02. The patient stated that her MD's felt pulmonary embolus was related to poor surgery in 2013 due to auto accident. She also said she had a pulmonary embolus at that time. Her physical examination was performed and her vitals & measurements are as follows: Her body temperature was 36.6°C (oral), heart rate was: 70 (monitored), Respiratory rate was 18, blood pressure was 103/65 and $Sp0_2$ (peripheral capillary oxygen saturation, an estimate of the amount of oxygen in the blood) was 100%. She has no acute distress, her skin was warm, dry, intact without rash and skin color was normal. Her eyes extraocular movements are grossly intact with clear conjunctiva. Her pupils are equal, round and reactive to light (PERRL). Her head was normocephalic and atraumatic and she has moist mucus membranes. Her neck has no obvious swelling, no nodes, normal range of motion and no jugular vein distention. The pulmonary tests revealed that she has no respiratory distress, breath sounds were normal diminished breath sounds bibasilar and chest wall was non-tender. The cardiovascular tests revealed a regular rhythm, regular rate, no murmur, distal extremities are warm, well perfused and no edema. The gastrointestinal tests revealed a non-distended, non-tender, soft, and normal bowel sound. On 29 Aug 2018, prothrombin time was 12.7 seconds, partial thromboplastin time was 24.7 seconds, heparin PTT was >200.0 Critical .On 30 Aug 2018, her White blood cell count was 8.2 x10"3/rncL, red blood cell (RBD) was 4.02 $x10^6$/mcL, hemoglobin (Hgb) was 11.3 g/dL Low, hematocrit (Hct) was 35.5 % Low, mean corpuscular volume (MCV) was 88.3 fL, mean cell hemoglobin (MCH) was 28.1 pg, mean corpuscular hemoglobin concentration (MCHC) was 31.8%, red cell distribution width (RDW) was 15 2, high platelets was 269 $x10^3$/mcL, mean platelet volume (MPV) was 10.2 fL, Neutro Auto was 48.6 %, Lymph Auto was 37.6 %, Mono Auto was 6.1 %, Eos, Auto was 7 %, Basophil Auto was 0.5 %, Neutro Absolute was 4 $x10^3$/mcL, Lymph Absolute was 3.1 $x10^3$/mcL and Mono Absolute was 0.5 $x10^3$/mcL. Eos Absolute was 0.6 x10A3/mcL high, baso absolute was 0 $x10^3$/mcL, RDW-SD: 49 fL, Immature Gran Absolute was 0 $x10^3$/mcL, Immature Gran Auto was 0.2 %, NRBC Absolute was 0 x10"3/mcL, NRBC Auto was 0 %, glucose level was 160 mg/dL high, BUN was 13 mg/dL, creatinine level was 0.82 mg/dL, BUN/Creat Ratio was 15.9 ratio, sodium level was 145 mmol/L, potassium level was 3.7 mmol/L, chloride level was 112 mmoA_high, CO_2 was 25 mmol/L, anion gap was 12 ratio, calcium level was 81 mg/dL low, protein total was 6.2 g/dL low, albumin level was 3.3 g/dL low, globulin was 2.9 g/dL, A/G Ratio was 1.1 ratio, Alk Phos was 79 unit/L, AST was 18 unit/L, ALT was 20 unit/L, bilirubin total was 0.4 mg/dL, magnesium level was 2.1 mg/dL, hemoglobin A1c was 8% high and eAvg glucose was 183 mg/dL. Her inpatient medications included heparin bolus - cardiac, 2000 units, 0.4 mL, IV Push, as needed (prn), PRN, heparin bolus-cardiac, 4000 units, 0.8 ml, IV Push, as needed (prn), PRN, heparin IV additive 25,000 units + premix dextrose 5% in water (titrate) 500 ml, hydrocodone-acetaminophen 7.5 mg-325 mg oral tablet, 1 tab, oral, q4h (floating), PRN, Klor-Con *(potassium), 20 mEq, 1 tab, oral, once, lorazepam, 0.5 mg, 1 tab, oral, daily, PRN, montelukast, 10 mg, 1 tab, oral, at bedtime, her own medication in ADM, 1 EA, N/A, q72h (floating), refrigerated medication in ADM, 1 EA. N/A, as needed (prn), PRN, sodium chloride

0.9% flush, 10 mL, IV Push, As needed (prn), PRN, tizanidine, 4 mg, 1 tab, Oral, at bedtime, PRN, tramadol, 50 mg, 1 tab, Oral, q6h (floating), PRN, tramadol, 100 mg, 2 tab, oral, q6h (floating), PRN and venlafaxine. 75 mg, 1 cap, oral, daily. She was discharged home– Asymptomatic on 31 Aug 2018 with no issues, there were no follow-up chest X-rays or CT scans to state that the PE was resolved. She was prescribed Elliquis 5 mg (apixaban) and she was back at work. No further diagnostic tests were done. Her discharge medications included Eliquis, 5 mg, 1 tab, oral, bid, Eliquis 5 mg oral tablet, 5 mg, 1 tab, oral, bid, hydrocodone-acetaminophen 7.5 mg-325 mg oral tablet, 1 tab, oral, q4h (floating). PRN, lorazepam 0.5 mg oral tablet, 0.5 mg, 1 tab, oral, daily, PRN, montelukast 10 mg oral tablet, 10 mg, 1 tab, oral, every evening, Novolog 100 units/mL subcutaneous solution, 60 units, daily.

Investigating: Pharmacy record from 4/20/18 tizanidine 4 mg oral tablet, 4 mg, 1 tab, oral, at bedtime, PRN, tramadol 50 mg oral tablet, 50 mg, 1 tab, oral, q6h (floating), PRN, venlafaxine 75 mg oral capsule, extended release, 75 mg, 1 capsule, oral, daily.

At the time of this report, the outcome of the adverse event was unknown.

On 14 Sep 2018, treatment with blinded study drug was discontinued.

The Investigator assessed the causal relationship between the adverse events and blinded study drug as possible.

The company considered the causal relationship between Pulmonary embolism and blinded study drug as possible. Past medical history of pulmonary embolism might have been triggered by blinded study drug and Plausible temporality is also present. So, by considering these along with Investigator’s assessment causality assessed as possible.

Date received by Besins Healthcare: 14 Sep 2018

Version 1 was created on 18 Sep 2018, to unblind the study drug information. The study drug was reported to be 4-Hydroxy-Tamoxifen gel.

Version 2 was created to update the information received on 10 Oct 2018 from the clinical trial site:

It was stated that in 2012, COPD was found in patient’s previous hospital record. On 23 Jan 2016, she had cardiac catheterization. As per hospital records, she was a former smoker and she quit smoking in 2010.

The expiry date of the study drug 4-Hydroxy-Tamoxifen gel was updated to 01 Oct 2019.

She stated that her physician (MD) felt that pulmonary embolus was related to her prior surgery in 2013 which was due to an auto accident.

The Investigator and company’s causality of the previously reported adverse event remains unchanged.

Date received by Besins Healthcare: 10 Oct 2018.

12.3.2.2 Narratives of Adverse Events Leading to Discontinuation

Subject Number	Treatment	Discontinuation for Adverse Events
101-003*	BHR700-4OHT	X
101-009	BHR700-4OHT	X
101-016	BHR700-4OHT	X
101-017	BHR700-4OHT	X
104-014	BHR700-4OHT	X
104-019	BHR700-4OHT	X
104-033	BHR700-4OHT	X
104-054	BHR700-4OHT	X
104-065*	BHR700-4OHT	X
116-001	BHR700-4OHT	X

*These subjects experienced SAEs which lead to discontinuation of subject from the study. Narratives for these patients are included in Section 12.3.2.1

Subject identifier:	101-009
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Hair thinning, Fatigue
Subject age:	55 years
Menopausal group	Post-menopausal

Narrative:

Subject 101-009, a 55-year-old, White, Not Hispanic or Latino, post-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 09 May 2018.

Reported medical history included menopausal symptoms, and muscular right neck pain.

The subject experienced mild hair thinning and mild fatigue starting on 03 July 2018. As a result of these events, the study drug was discontinued on 12 Jul 2018.

Concomitant medication(s) on the start date of the event included unspecified herbal and traditional medicine. The subject did not receive any treatment for the events.

The event was ongoing at the subject's End of Study Visit. Both the events were considered possibly related to study drug.

The final dose of study drug was administered on 05 Jul 2018. The subject discontinued the study on 12 Jul 2018 due to adverse event.

Subject identifier:	101-016
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Cystic acne lower chin/cheek, Application site reaction, Erythema
Subject age:	41 years
Menopausal group	Pre/peri-menopausal

Narrative:

Subject 101-016, a 41year-old, White, Not Hispanic or Latino, pre/peri-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 13 Jun 2018.

Reported medical history included anxiety and seasonal allergies.

The subject experienced mild erythema with skin slightly pink after application for first few days on 13 Jun 2018 which resolved on 16 Jun 2018. She again experienced mild application site reaction with skin slightly pink after application minor irritation, increased breast sensitivity and mild acne cystic on 20 Jul 2018. As a result of the events, the study drug was discontinued on 19 Jul 2018.

Concomitant medication(s) on the start date of the event included sertraline and cetirizine hydrochloride. The subject did not receive any treatment for the event.

The events were resolved on 21 Jul 2018. The events were considered possibly related to study drug.

The final dose of study drug was administered on 19 Jul 2018. The subject discontinued the study on 19 Jul 2018 due to adverse event.

Subject identifier:	101-017
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Product odour abnormal
Subject age:	74 years
Menopausal group	Post-menopausal

Narrative:

Subject 101-017, a 74-year-old, White, Not Hispanic or Latino post-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 08 Jun 2018.

Reported medical history included hysterectomy and uterine leiomyoma.

The subject experienced product odour abnormal on 08 Jul 2018. As a result of the event, the study drug was discontinued on 09 Jul 2018.

There were no concomitant medications on the start date of the event. The subject did not receive any treatment for the event.

The event was resolved on 10 Jul 2018. The event was considered possibly related to study drug.

The final dose of study drug was administered on 08 Jul 2018. The subject discontinued the study on 09 Jul 2018 due to adverse event.

Subject identifier:	104-014
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Itching under each breast, Rash under each breast, Flu
Subject age:	64 years
Menopausal group	Post-menopausal

Narrative:

Subject 104-014, a 64-year-old White, Not Hispanic or Latino, post-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 03 Jan 2018.

Reported medical history included left breast abscess, abscess drainage, chronic obstructive pulmonary disease, colonoscopy, penicillin allergy, wellbutrin allergy, overactive bladder, menopause, sinus headache, tonsillectomy, uterine dilation and curettage, and wisdom teeth removal.

The subject experienced severe flu on 23 Apr 2018. She was treated with ceftriaxone sodium sesquaterhydrate, levofloxacin, methylprednisolone acetate, oseltamivir, and salbutamol. The event was resolved on 07 May 2018. The event was considered unrelated to study drug.

The subject experienced mild red rash under each breast on 26 May 2018 and moderate itching under each breast on 27 May 2018. Both events improved to mild on 30 May 2018. The subject experienced mild red rash on upper left breast on 04 Jun 2018. As a result of the events, the study drug was discontinued on 24 Jul 2018.

Concomitant medication(s) on the start date of the event included fluticasone propionate; salmeterol xinafoate; calcium; oxybutynin hydrochloride; echinacea purpurea; ginkgo biloba; multivitamins; potassium; paracetamol; salbutamol; vitamin D nos; and cetirizine hydrochloride. The subject was treated with hydrocortisone acetate for the events.

All events were resolved on 10 Jul 2018. The events were considered probably related to study drug.

The final dose of study drug was administered on 03 Jun 2018. The subject discontinued the study on 24 Jul 2018 due to adverse event.

Subject identifier:	104-019
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Bilateral lower leg cramps, Bilateral lower leg itching
Subject age:	63 years
Menopausal group	Post-menopausal

Narrative:

Subject 104-019, a 63-year-old, White, Not Hispanic or Latino, post-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 31 Jan 2018.

Reported medical history included allergic sinusitis, anxiety, left ring finger joint pain, low back pain, benign right breast aspiration, Caesarean sections, excision of squamous cell cancer in right breast, right and left carpal tunnel release, colonoscopy, dyspareunia, fractured nose, fibrocystic breasts, headaches, hypercholesterolemia, swelling in left ring finger joint, meningitis, menopausal symptoms, esophagogastroduodenoscopy, osteopenia, intermittent skin irritation of bilateral groin, rectum boil removal, squamous cell carcinoma of right breast, stress, trigger finger, ruptured right ear drum, and right ear drum rebuilt, and bilateral legs vascular insufficiency.

The subject experienced severe bilateral lower leg cramps and bilateral lower leg itching on 01 Feb 2018. As a result of the events, the study drug was discontinued.

Concomitant medication(s) on the start date of the event included acetylsalicylic acid; calcium; colecalciferol; fluoxetine hydrochloride; unspecified herbal and traditional medicine; nystatin; omega-3 fatty acids; omeprazole; ascorbic acid; bioflavonoids; magnesium hydroxide; sodium bicarbonate; probiotics nos; simvastatin; curcuma longa rhizome; paracetamol; and vitamin B12 nos. The subject was treated with diphenhydramine hydrochloride for the events.

Both events were resolved on 02 Feb 2018. The events were considered possibly related to study drug.

The final dose of study drug was administered on 01 Feb 2018. The subject discontinued the study on 07 Feb 2018 due to adverse event.

Subject identifier:	104-033
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Intermittent bilateral breast itching
Subject age:	43 years
Menopausal group	Pre/peri-menopausal

Narrative:

Subject 104-033, a 43-year-old, White, Not Hispanic or Latino, pre/peri-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 20 Mar 2018.

Reported medical history included allergic sinusitis, basal cell carcinoma of scalp and right upper arm, biopsy endometrium, squamous cell carcinoma and excision of squamous cell cancer of right shoulder, intermittent constipation, painful intercourse, novasure uterine ablation, bilateral fibriocystic breast disease, headaches, hysteroscopy, menorrhagia, Ascus PAP smear, stress, urinary incontinence, and vestibulectomy.

The subject experienced moderate intermittent bilateral breast itching on 29 Mar 2018. As a result of the event, the study drug was discontinued.

There were no concomitant medications on the start date of the event. The subject did not receive any treatment for the events.

The event was resolved on 22 Apr 2018. The event was considered probably related to study drug.

The final dose of study drug was administered on 19 Apr 2018. The subject discontinued the study on 02 May 2018 due to adverse event.

Subject identifier:	104-054
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Impingement pain left shoulder
Subject age:	53 years
Menopausal group	Post-menopausal

Narrative:

Subject 104-054, a 53-year-old, White, Not Hispanic or Latino, post-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 17 Jul 2018.

Reported medical history included allergic sinusitis, anemia, bilateral knees arthritis, arthroscopy right shoulder for impingement syndrome, asthma, back pain, cholecystectomy, cholelithiasis, chronic fatigue syndrome, colonoscopy, constipation, depression, heart burn, right tennis elbow repair, emphysema, bilateral tubal ligation, fibromyalgia, hemorrhoids, erichiosis, hypercholesterolemia, hypertension, total abdominal hysterectomy, polyps in bowel, Lymes disease, Burdorferi Lymes disease, menopausal symptoms, migraine, deviated septum, scalp pain, impingement syndrome of right shoulder, back arthritis, neck arthritis, left thumb tendon repair, uterine dilation and curettage, bilateral varicose vein, and wisdom teeth removal.

The subject experienced moderate impingement pain of left shoulder on 01 Aug 2018. As a result of the event the study drug was discontinued.

Concomitant medication(s) on the start date of the event included loratadine; docusate sodium; venlafaxine hydrochloride; fluticasone propionate; ibuprofen; sennoside a+b; lidocaine; lisinopril; budesonide; formoterol fumarate; paracetamol; salbutamol sulfate; and esomeprazole sodium. The subject did not receive any treatment for the events.

The event was ongoing at the subject’s End of Study Visit. The event was considered unrelated to study drug.

The final dose of study drug was administered on 06 Aug 2018. The subject discontinued the study on 11 Sep 2018 due to adverse event.

Subject identifier:	116-001
Treatment:	BHR700-4OHT
Criteria for the narrative:	AE leading to discontinuation of study drug
Preferred terms:	Bilateral discoloration of breast
Subject age:	51 years
Menopausal group	Pre/peri-menopausal

Narrative:

Subject 116-001, a 51-year-old, White, Not Hispanic or Latino, pre/peri-menopausal female was randomized to receive BHR700-4OHT. The first dose was administered on 13 Feb 2018.

Reported medical history included breast mass, breast tenderness, eczema, and seasonal allergy.

The subject experienced mild bilateral discoloration of breast on 23 May 2018. As a result of the event, the study drug was discontinued.

There were no concomitant medications on the start date of the event. The subject did not receive any treatment for the event.

The event was resolved on 29 May 2018. The event was considered possibly related to study drug.

The final dose of study drug was administered on 22 May 2018. The subject discontinued the study on 02 Aug 2018 due to adverse event.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

A total of 5 SAEs were reported during the study in the BHR700-4OHT Gel group vs 0 SAEs in the placebo group, none of which has had a fatal outcome. Four of the 5 SAEs were from the SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)”: 2 invasive ductal breast carcinoma, 1 intraductal proliferative breast lesion and 1 endometrial carcinoma. The other remaining SAE was from the SOC “Respiratory, thoracic and mediastinal disorders”: pulmonary embolism.

Out of the 5 reported SAEs, 2 SAEs (Case 2019-07833 Ductal Carcinoma In Situ and Case 2019-07834 Invasive Ductal Carcinoma) were assessed by the Investigator and by the Sponsor of the study as having no reasonable possibility of causality to BHR700-4OHT Gel and therefore have no impact on the safety profile of the investigational product.

The full narratives for these cases are listed in Section 12.3.2 analyses of the reported cases and causalities are listed below:

Subject 101-003 (Case 2019-07833) Ductal Carcinoma in Situ

Both the Investigator and the Sponsor assessed the causal relationship between the study drug and the event of ductal carcinoma in situ as considered ‘not reasonably possible’, taking into consideration the short duration of study drug exposure (23 Mar 2018 through 04 Apr 2018), patient’s medical history of benign breast biopsy in 2016, and a family history of unknown type breast cancer in her mother and ductal carcinoma in situ in her sister.

During the conduct of the trial, the subject’s primary physician had scheduled her for her annual breast MRI and she had no complaints or concerns at the time. Based on the MRI, the subject

underwent a core biopsy followed by a lumpectomy, with findings consistent with a diagnosis of carcinoma in situ of the right breast.

Subject 101-018 (Case 2019-07834) Invasive Ductal Carcinoma

Subject 101-018 was a 63-year-old female who experienced a SAE of 'invasive ductal breast carcinoma' on 30 Jan 2019 after the use of double-blinded study drug. Her first study drug application was on 28 Jun 2018. The subject's pertinent medical history included benign left breast excisional biopsy at age 16, family history of bilateral breast cancer of unknown type in her half-sister at age 47 as well as prostate cancer, leukemia, and lung cancer. After a mass was detected upon examination of the left breast, the subject underwent mammography with findings consistent with BI-RADS Assessment Category 5, indicating a strong probability of cancer. An ultrasound-guided core biopsy was performed that day, and pathology report revealed invasive ductal carcinoma. It was later reported that the subject had triple-negative breast cancer and underwent chemotherapy treatments.

The Investigator found there was 'no reasonable possibility' of a causal relationship between the study drug and the event 'invasive ductal carcinoma' since the cancer was hormone receptor-negative and this tamoxifen gel involves potential estrogen receptor-related mediation of breast tissue. The company also considered the causal relationship 'no reasonable possibility', taking into consideration the subject's advancing age and family history of malignancy in multiple family members including breast cancer, prostate cancer, leukemia, and lung cancer, it was believed that there was no reason to indicate a causal link between the study drug and event of invasive ductal carcinoma.

It was also reported that the subject had a hormone receptor-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative), indicating that it would not be related to this BHR700-4OHT Gel study which involves potential estrogen receptor-related mediation of breast tissue. That information, along with the subject's advancing age and family history of breast cancer, prostate cancer, leukemia, and lung cancer shows other more likely causes of this event.

The remaining 3 of the 5 reported SAEs (Cases 2018-06506, 2019-07634 and 2019-09046) were initially classified as SUSARs however Case 2019-09046 was downgraded on follow-up. These are discussed in detail below:

Subject 104-006 (Case 2019-07634) Endometrial Adenocarcinoma

Subject 104-006 was a 61-year-old female who experienced a SAE of 'endometrial adenocarcinoma' on 11 Feb 2019 after treatment with double-blinded study drug and subsequent treatment with open-label BHR700-4OHT Gel. Her first study drug application was on 01 Nov 2017. The subject's pertinent medical history included post-menopausal bleeding in Feb and Mar 2014 for which she underwent an endometrial biopsy, yielding benign results diabetes, and has a family history of cancer (father prostate cancer and mother breast cancer). In Jan 2019, the subject experienced bright red uterine bleeding for which an endometrial biopsy was performed. The pathology report revealed a diagnosis of endometrial adenocarcinoma, and the subject underwent a laparoscopic hysterectomy and recovered.

At the time of reporting, there was a lack of information pertaining to family history, parity status, and intake of any estrogen replacement therapy that precluded the comprehensive assessment of causality which was considered as possibly related initially. During the retrospective analysis after the study had ended, there was more of a case for the company to

consider the causal relationship between study drug and event to be ‘no reasonable possibility’ due to the subject's age, hypertension, diabetes and history of post-menopausal bleeding which are all risk factors for endometrial carcinoma and may have had an underlying endometrial cause.

Subject 104-059 (Case 2019-09046) Invasive Ductal Breast Carcinoma

Subject 104-059 was a 61-year-old female who experienced a serious adverse event of ‘invasive ductal breast carcinoma’ on 04 Sep 2019. Her first study drug application was on 03 Aug 2018. The subject’s pertinent medical history included right breast cyst and aspiration (benign), endometriosis, dysplasia of vaginal cuff, total abdominal hysterectomy with bilateral salpingo-oophorectomy nulliparity, early menarche (10 years), HRT, long term tobacco use, and atrophic vaginitis. Her family history included malignancy (ovarian and colon cancer). About 7 months after the study was early terminated, the subject underwent mammogram-tomosynthesis followed by left breast ultrasound. An ultrasound-guided core biopsy was attempted but failed; the subject instead had an MRI with and without contrast. The MRI revealed 2 lesions which were biopsied using MRI-guided core biopsy. Pathology results indicated invasive ductal carcinoma of the left breast.

Both the Investigator and the company initially deemed the event of invasive ductal breast carcinoma to have a ‘reasonable possibility’ of having a causal relationship with the study drug, however at the time of reporting, there was a lack of information pertaining to family history and other previously unknown subject risk factors such as the subject's advanced age, personal history of dysplasia of the vaginal cuff, family history of ovarian and colon carcinoma, limited time exposed to study drug (20 weeks), change in breast density, and study drug's mechanism of action.

The company later assessed the event as ‘no reasonable possibility’ of being study drug related primarily based on the subject’s change in breast density after treatment (from C to B) and the study drug’s mechanism of action. The subject also had multiple risk factors including early menarche, HRT, tobacco use, and family history of ovarian cancer.

It was also reported that the subject's mother was deceased from heart disease, having had a history of type II diabetes, hypertension, and hyperlipidemia. The subject’s father was deceased from heart disease, having a history of type II diabetes and hypertension. Her sister had history of type II diabetes, her maternal great aunt had history of colon cancer, and her maternal aunt had history of ovarian cancer.

Further to this, the SAE occurred in Subject 104-059, whose plasma [Z] isomer of 4OHT was below quantifiable level in Dec 2018 and there is no record of a mammogram at 6 months treatment. It is also suspected that based on the study drug mechanism of action, a change in breast density from 'C' to 'B' occurred which led to increased likelihood of detection of a suspicious lesion by mammogram in this case. These are other reason why the assessment of relatedness to study drug is challenged and therefore “no reasonable possibility” of being study drug related is a more reasonable assessment.

This event was unexpected and, although company causality for invasive ductal carcinoma was initially assessed as ‘reasonable possibility’ in line with the Investigator assessment, significant family history of malignancy (ovarian and colon cancer) was considered a potential confounder as well as the numerous other previously mentioned possible underlying causes.

Subject 104-065 (Case 2018-06506) Pulmonary Embolism

Subject 104-065 was a 50-year-old female who experienced a SAE of 'pulmonary embolism' on 29 Aug 2018. Her first study drug application was on 17 Aug 2018. The subject's pertinent medical history included a prior pulmonary embolus in 2013, respiratory failure, and COPD. Although she initially denied being a smoker, she later admitted to being a former smoker, having quit in 2010. Family history was noncontributory. Ten days after first study drug application, the subject experienced exertional dyspnea. Chest x-ray on this day yielded no findings, however CT with contrast and pulmonary angiogram performed 2 days later revealed a pulmonary artery filling defect. The subject was admitted for a pulmonary embolism. Both Investigator and company deemed this pulmonary embolism event initially to be 'possibly related' to study drug based on the temporal relationship between the event and first study drug application however once the subject revelated they had a history of pulmonary embolism and was a prior smoker, there were other more likely causes for the event. Further to this, no laboratory results are available for plasma 4OHT levels or coagulation screen to support the causal relationship.

Family history included cancer in the subject's mother. Hospital records indicated that the subject was a non-smoker who had never smoked, but the subject admitted being a former smoker, having quit in 2010. Hospital records also indicated respiratory failure and COPD. Her body mass index was 27.8 (classified as overweight) and she was also allergic to ciprofloxacin.

With all this considered now during the clinical assessment, it seems more likely that this event was cause by the subject's medical history of previous pulmonary embolism and being a prior smoker, as well as further history of respiratory failure and COPD.

Final conclusion

A total of 5 SAEs were reported during the study in the BHR700-4OHT Gel group vs 0 SAEs in the placebo group. None of the SAEs had a fatal outcome. Four of the 5 SAEs were from the SOC "Neoplasms benign, malignant and unspecified" (incl cysts and polyps): 2 invasive ductal breast carcinoma, 1 intraductal proliferative breast lesion, and 1 endometrial carcinoma.

Mammographically dense breast tissue, which is the underlying indication in this study, is itself a risk factor for breast cancer. This could be the underlying factor for SAEs predominantly being reported from the "Malignancy" SOC: 3 of the 4 malignant events occurred in the breast while the fourth, endometrial carcinoma, also has a reported link to breast malignancy. Also, all 4 of these subjects had additional multiple risk factors, including family history of malignancies. Other risk factors included diabetes, advanced age, HRT, and smoking. With all this in consideration, it is not possible to reasonably say that any of the reported SAEs were caused by the product BHR700-4OHT Gel.

The number of SAEs overall reported for the clinical trial is extremely low compared to industry standards for a clinical trial and despite the seeming imbalance between the BHR700-4OHT Gel and placebo arm, a statistically valid conclusion cannot be drawn with regards to any potential difference in the risk of any of the reported SAEs between the 2 arms.

With all this in consideration, it is this company's conclusion that the benefit-risk profile of the IP of BHR700-4OHT Gel remains positive and has not changed during the conduct of the trial. The clinical trial was not terminated early due to safety concerns and no significant actions were

taken during the conduct of the trial for safety reasons by Besins Healthcare, as the Sponsor of the clinical trial.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Clinical laboratory assessments for this study included hematology, blood chemistry, and coagulation.

Clinical laboratory evaluation results are presented in Appendix 16.2.8. Results of hematology laboratory tests for the ITT population are presented by subject for the blinded phase and the open-label phase in Listing 16 (LAB01a) and Listing 36 (LAB01b), respectively; blood chemistry results are presented in Listing 17 (LAB02a) and Listing 37 (LAB02b), respectively; and coagulation results are presented in Listing 25 (LCR01a) and Listing 44 (LCR01b), respectively.

Urine pregnancy test results are presented for the blinded phase and the open-label phase in Listing 37 (LAB03a) and Listing 38 (LAB03b), respectively.

Laboratory values are summarized in Section 14.3.4. Hematology results are summarized for the blinded phase and the open-label phase in Table 20 (TLB01a), and Table 72 (TLB01b). Clinical chemistry results are summarized in Table 21 (TLB02a) and Table 73 (TLB02b), respectively; and coagulation results and change from baseline are summarized in Table 55 (TCR01a) and Table 85 (TCR01b), respectively.

Routine hematology and biochemistry results were unremarkable, as were lipids (Listing [-] LBA_add).

Urine pregnancy test results for the blinded phase and the open-label phase are summarized in Table 22 (TLB03a) and Table 74 (TLB03b), respectively. No pregnancies were reported during the study.

Also completed were hormone testing results, which are presented for the blinded phase and the open-label phase in Appendix 16.2.8 Listing 22 (LHR01a) and Listing 42 (LHR01b), respectively. Hormone results and change from baseline are summarized for the blinded phase and the open-label phase in Section 14.3.4 Table 53 (THR01a) and Table 83 (THR01b), respectively.

Bone biomarker results are presented by subject for the blinded phase and the open-label phase in Appendix 16.2.8 Listing (-) LBB02a and Listing (-) LBB02b, respectively, and are summarized in Table (-) (TBB01a) and Table (-) (TBB01b), respectively. Bone biomarkers data did not suggest any clinically significance safety changes in the BHR700-4OHT Gel treatment arm.

Pharmacokinetic concentrations of BHR700-4OHT are represented for subjects in the BHR700-4OHT Gel group in Appendix 16.2.5 Listing (-) (LPK01). The number and percentage of subjects with measurable PK concentration by visit is presented in Table 23 (TPK01).

At each visit, the majority of subjects had PK concentrations of E-4-OHT below the lower limit of quantitation. The pharmacologically active [Z] isomer of 4OHT had consistently low plasma

levels in all study subjects at relevant data collection timepoints during the trial. The data at 13 and 26 weeks show plasma levels that are 3 times lower than levels found with 20 mg of oral tamoxifen. The levels at 52 weeks were less reliable due to early termination of the study. Levels of Z-4-OHT only reached measurable concentrations for >50% of subjects at Week 13 and Week 26. The levels at 52 weeks were less reliable due to early termination of the study.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Coagulation results and change from baseline are summarized in Section 14.3.4 Table 55 (TCR01a) and Table 85 (TCR01b), respectively.

Hormone results and change from baseline are summarized for the blinded phase and the open-label phase in Section 14.3.4 Table 53 (THR01a) and Table 83 (THR01b), respectively.

Coagulation profile parameters were within the reference ranges for the majority of subjects with no overall clinically significant effects. SHBG levels, which are relevant for the estrogenic potential of BHR700-4OHT Gel, were not raised and results did not show any clinically relevant changes.

12.4.2.2 Individual Subject Changes

There were 3 subjects with laboratory abnormalities during the blinded phase these were assessed as clinically significant by the Investigator, and reported as AEs. These are assessed below:

- Subject 101-005 (Placebo)
    - Elevated liver function tests were reported at Week 26 (Listing 17 [LAB02a]). The Investigator assessed these elevations as possibly related to study drug, and the subject's participation in the trial was discontinued.
        - Alanine aminotransferase (ALT: normal range 0-45 U/L) was 26, 68, and 51 U/L at Baseline, Week 26- and Week 52 - 4-months following study drug discontinuation, respectively.
        - Aspartate aminotransferase (AST: normal range 0-41 U/L) was 24, 58, and 41 U/L, at Baseline, Week 26- and Week 52 - 4-months following study drug discontinuation, respectively.
    - Bilirubin levels remained within reference range.
- Subject 102-006 (Placebo)
    - Low Protein S result (37 IU/dL) at Week 26 (Listing 25 [LCR01a]) was assessed as possibly related to study drug by the Investigator. The baseline Protein S level (79 IU/dL) was within the reference range (63–141 IU/dL). Study drug was held, and 2 months later (Week 32), the subject's Protein S level (69 IU/dL) was within the reference range (63–141 IU/dL). Study drug was restarted, and at Week 52, the Protein S level (73 IU/dL) remained within the reference range.
- Subject 104-020 (BHR700-4OHT)

- Elevated hemoglobin A1c (HbgA1c) was reported as an AE. The AE was assessed as mild in severity and possibly related to study drug by the Investigator. A positive rheumatoid factor, reported as an AE in this same subject, was assessed as unrelated to study drug. There was no change in study drug related to either of these laboratory abnormalities.

12.4.2.3 Individual Clinically Significant Abnormalities

Laboratory abnormalities not reported as AEs that were, however, assessed as clinically significant by the medical monitor, included one case of elevated glucose and 4 cases of elevated triglyceride levels.

- One subject (105-034 [BHR700-4OHT]) with a medical history of Type 2 diabetes, had clinically significant elevations in glucose (26.6 mmol/L [normal range: 3.9-7.8]) and triglycerides (3.5 mmol/L [normal range: 0.31.7]) at Week 26; both results had returned to near baseline levels at Week 52 (Listing 17 [LAB02a]).
- Two subjects (104-008 [placebo], 108-002 [placebo]) with elevated triglyceride levels (2.4 mmol/L and 2.10 mmol/L, respectively [normal range: 0.3-1.7]) at Baseline had clinically significant increases in elevated triglyceride levels (5.2 mmol/L and 5.3 mmol/L, respectively) at Week 52 (Listing 17 [LAB02a]).
- One subject (104-047 [BHR700-4OHT]) with elevated triglycerides at Baseline (2.3 mmol/L [normal range 0.3-1.7]), had clinically significant increases in elevated triglyceride level at Week 26 (4.4 mmol/L), with some improvement observed at Week 52 (3.3 mmol/L) (Listing 17 [LAB02a]).

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Listings of vital signs are represented by subject in Appendix 16.2.8; results are presented by subject for the blinded phase and the open-label phase in Listing 19 (LVS01a) and Listing 39 (LVS01b), respectively. Vital signs and change from baseline are summarized in Section 14.3.4 Table 18 (TVS01a) and Table 70 (TVS01b), respectively.

Abnormalities of physical examination are presented by subject for the blinded phase and the open-label phase in Appendix 16.2.8 Listing 20 (LPE01a) and Listing 40 (LPE01b), respectively. Physical examination by visit is summarized for the blinded phase and the open-label phase in Section 14.3.4 Table 19 [TPE01a] and Table 71 (TPE01b), respectively. No issues of clinical significance were noted for vital signs and physical examination.

12.6 Safety Conclusions

Of the AEs reported, approximately 75% of those in the BHR700-4OHT Gel group and 80% in the placebo group were deemed unrelated to study treatment. Only 5% of the AEs in the BHR700-4OHT Gel group and 2.8% in the placebo group were thought to be ‘probably related’ to study treatment.

A total of 5 SAEs were reported during the study in the BHR700-4OHT Gel group vs 0 SAEs in the placebo group. None of the SAEs had a fatal outcome. Four of the 5 SAEs were from the SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)”: 2 invasive ductal breast carcinoma, 1 intraductal proliferative breast lesion and 1 endometrial carcinoma.

Mammographically dense breast tissue, which is the underlying indication in this study, itself is a risk factor for breast cancer. This could be the reason for SAEs predominantly being reported from the malignancy SOC: 3 of the 4 malignant events occurred in the breast while the fourth, endometrial carcinoma, also has a reported link to breast malignancy. Also, all 4 of these patients had additional multiple risk factors, including family history of malignancies. Other risk factors included diabetes, advanced age, HRT, and smoking. With all this in consideration, it is not possible to reasonably conclude that any of the reported SAEs were caused by the product BHR700-4OHT Gel

Further to this, the overall number of SAEs reported for the clinical trial is extremely low compared to industry standards for a clinical trial and despite the seeming imbalance between the BHR700-4OHT Gel and placebo arm, a statistically valid conclusion cannot be drawn with regards to any potential difference in the risk of any of the reported SAEs between the 2 arms. There is also strong evidence regarding the positive of the tolerability of the BHR700-4OHT Gel over an oral alternative due to also the low reported AEs and SAEs especially in regard to the route of administration.

With all this in consideration, it is this company's conclusion that the benefit-risk profile of the investigational product BHR700-4OHT Gel remains incredibly positive and has not changed during the conduct of the trial. The clinical trial was not terminated early due to any safety concerns and no significant actions were taken during the conduct of the trial for safety reasons by Besins Healthcare as the Sponsor of the clinical trial.

13 DISCUSSION AND OVERALL CONCLUSIONS

A total of 223 subjects were enrolled and randomized; 149 subjects received BHR700-4OHT Gel and 74 received placebo gel. This study was terminated early due to reasons not related to safety.

The study was terminated early due to a change in clinical development strategy for BHR700-4OHT Gel to pursue focus on a “cancer prevention” indication rather than on “breast density reduction” alone. As such, it was determined that the healthy population, not stratified by being at high risk of breast cancer enrolled in the BHR-700-301 study was not optimal for pursuit of a “cancer prevention” indication for 4-OHT Gel. The Sponsor understands that a high-risk population represents the most clinically meaningful cohort for further development strategy. Mammographic breast density reduction in women at high risk of developing breast cancer may be an important strategy to modify breast cancer risk. The optimal population should include women at high risk of development breast cancer, according to risk assessment models that incorporate mammographic breast density as well as other non-modifiable risk factors (such as Tyrer Cuzick).

The study drug was well tolerated with breast and reproductive system AEs occurring at the same rate as placebo. Importantly, vasomotor type symptoms known to occur with high frequency with systemic selective estrogen receptor modulators (SERM) therapy, did not occur at a frequency higher than placebo.

Most laboratory results outside of the reference range were not clinically significant and there was no suggestion that BHR700-4OHT Gel is prothrombotic as seen with systemic SERM therapy. The important SAE of endometrial adenocarcinoma is confounded by the subject’s past history of endometrial bleeding, and the subject who developed a pulmonary embolism has a

past medical history of PE and no supporting laboratory coagulation profile to support the causal relationship.

The information necessary for appropriate use of the product to minimize the frequency and severity of adverse reactions is included in the relevant sections of the IB, however this study has demonstrated very minimal related AEs for BHR700-4OHT Gel.

It is the Sponsor's conclusion that the benefit-risk profile of BHR700-4OHT Gel remains positive and has not changed during the conduct of the trial. The clinical trial was not terminated early due to safety concerns and no significant actions were taken for safety reasons during the conduct of the trial.

14 TABLES

14.1 Demographic Data Summary Tables

Table 1	TDS01a	Subject Disposition (Blinded Phase) – All Subjects
Table 57	TDS01b	Subject Disposition (Open-Label Phase) – All Subjects
Table 2	TDM01a	Summary of Demographics (Blinded Phase) – ITT Population
Table 58	TDM01b	Summary of Demographics (Open-Label Phase) – ITT Population
Table 3	TMH01a	Summary of General Medical History – ITT Population
Table 4	TMH02a	Summary of Breast Cancer Medical History – ITT Population
Table 5	TMH03a	Summary of Menstrual History – ITT Population
Table 6	TCM01a	Summary of Prior Medications and Treatments (Blinded Phase) – ITT Population
Table 59	TCM01b	Summary of Medication and Treatments Ongoing from the Blinded Phase (Open-Label Phase) – ITT Population
Table 7	TCM02a	Summary of Concomitant Medications and Treatments (Blinded Phase) – ITT Population
Table 60	TCM02b	Summary of Concomitant Medications and Treatments (Open-Label Phase) – ITT Population

14.2 Efficacy Data Summary Tables (Not Applicable)

14.3 Safety Data Summary Tables

14.3.1 Displays of Treatment Compliance and Adverse Events

Table (-)	TSD01a	Summary of Study Drug Compliance by Visit (Blinded Phase) – ITT Population
Table 12	TAE01a	Summary of Adverse Events (Blinded Phase) – Safety Population
Table 64	TAE01b	Summary of Adverse Events (Open-Label Phase) – Safety Population
Table 13	TAE02a	Number (%) of Subjects with Adverse Events by MedDRA Body System and Preferred Term (Blinded Phase) – Safety Population
Table 65	TAE02b	Number (%) of Subjects with Adverse Events by MedDRA Body System and Preferred Term (Open-Label Phase) – Safety Population
Table 14	TAE03a	Number (%) of Subjects with Serious Adverse Event by MedDRA Body System and Preferred Term (Blinded Phase) – Safety Population
Table 66	TAE03b	Number (%) of Subjects with Serious Adverse Event by MedDRA Body System and Preferred Term (Open-Label Phase) – Safety Population
Table 15	TAE04a	Number (%) of Subjects with Severe Adverse Events by MedDRA Body System and Preferred Term (Blinded Phase) – Safety Population
Table 67	TAE04b	Number (%) of Subjects with Severe Adverse Events by MedDRA Body System and Preferred Term (Open-Label Phase) – Safety Population
Table 16	TAE05a	Number (%) of Subjects with Study Drug Related Adverse Events by MedDRA Body System and Preferred Term (Blinded Phase) – Safety Population

Table 68	TAE05b	Number (%) of Subjects with Study Drug Related Adverse Events by MedDRA Body System and Preferred Term (Open-Label Phase) – Safety Population
Table 17	TAE06a	Number (%) of Subjects with Adverse Events by MedDRA Preferred Term and Overall Frequency (Blinded Phase) – Safety Population
Table 69	TAE06b	Number (%) of Subjects with Adverse Events by MedDRA Preferred Term and Overall Frequency (Open-Label Phase) – Safety Population

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

See Section 12.3.2 for SAE narratives.

14.3.4 Laboratory Values, Vital Signs, Physical Examination and Other Observations Relating to Safety

Table 20	TLB01a	Summary of Laboratory (Hematology) Tests Results (Blinded Phase) – Safety Population
Table 72	TLB01b	Summary of Laboratory (Hematology) Tests Results (Open-Label Phase) – Safety Population
Table 21	TLB02a	Summary of Laboratory (Blood Chemistry) Tests Results (Blinded Phase) – Safety Population
Table 73	TLB02b	Summary of Laboratory (Blood Chemistry) Tests Results (Open-Label Phase) – Safety Population
Table 22	TLB03a	Summary of Urine Pregnancy Test Results (Blinded Phase) – Safety Population
Table 74	TLB03b	Summary of Urine Pregnancy Test Results (Open-Label Phase) – Safety Population
Table 55	TCR01a	Summary of Coagulation Parameter Results and Change from Baseline (Blinded Phase) – ITT Population
Table 85	TCR01b	Summary of Coagulation Parameter Results and Change from Baseline (Open-Label Phase) – ITT Population
Table 53	THR01a	Summary of Hormones Results and Change from Baseline (Blinded Phase) – ITT Population
Table 83	THR01b	Summary of Hormones Results and Change from Baseline (Open-Label Phase) – ITT Population
Table (-)	TBB01a	Summary of Bone Biomarker Test Results (Blinded Phase) – Safety Population
Table (-)	TBB01b	Summary of Bone Biomarker Test Results (Open-Label Phase) – Safety Population
Table 23	TPK01	Number and Percentage of Subjects with Measurable PK Concentration by Visit - ITT Population
Table 18	TVS01a	Summary of Vital Signs and Change from Baseline by Visit (Blinded Phase) – Safety Population
Table 70	TVS01b	Summary of Vital Signs and Change from Baseline by Visit (Open-Label Phase) – Safety Population

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16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

BHR700301 Protocol_Ver4.0_Amend3_Final_18Apr2018 - clean.pdf

Summary of Changes_BHR700301 Protocol_Ver4.0_ Amend3_Final_18Apr2018-clean.pdf

BHR700301 Protocol_Ver3.0_ Amend2_Final_01Aug2017 - clean (2).pdf

Summary of Changes_BHR700301 Protocol_Ver3(F)_01Aug2017 – clean.pdf

BHR-700-301 Protocol_Version 2.0_ Amendment 1_Final_07Jun2017 - clean.pdf

16.1.2 Sample Case Report Form

BHR-700-301_Blank Case Report Form_1.0_2017-07-06

16.1.3 List of Independent Ethics Committees and Institutional Review Boards and Representative Written Information for Subjects

Not applicable for the abbreviated CSR.

16.1.4 List and Description of Investigators and Other Important Study Participants

Not applicable for the abbreviated CSR.

16.1.5 Signatures of Principal/Coordinating Investigator and/or Sponsor's Responsible Medical Officer

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: Elizabeth O'Brien **Date:** 30 AUG 2021
Print name: Dr Elizabeth O'Brien Bergin, MB., BAO., BCh., DCH., DME., Dip Pharm Med., MRCGP
Affiliation: Besins Healthcare Ireland Ltd.
Address: 16 Pembroke Street Upper, Dublin 2, Ireland

Signed: **Date:** 8/27/2021
Print name: Professor Jennifer Harvey, MD
Affiliation: University of Rochester Medical Center
Address: 25 East Boulevard, Rochester, NY 14610, USA

Signed: **Date:** 27Aug2021
Print name: Dr Dion Chen, PhD*
Senior Biostatistician
Affiliation: Peachtree Bioresearch Solutions
Address: 4985 Lower Roswell Road, Building 100, Marietta, GA, 30068, USA

*Note: Dr Chen's role in the CSR is limited to the provision of the tables and listings only.

16.1.6 List of Investigational Product(s) Batch Numbers

Not applicable for the abbreviated CSR

16.1.7 Randomization Scheme and Codes

Listing 3	LRN01a	Randomization (Blinded Phase) – ITT Population

16.1.8 Audit Certificates

Not applicable for the abbreviated CSR

16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan: BHR-700-301_SAP_Final_v1.0_13NOV2020.pdf

16.1.10 Documentation of Interlaboratory Standardization Methods and Quality Assurance Procedures

Not applicable for the abbreviated CSR

16.1.11 Publications Based on the Study

Not applicable for the abbreviated CSR

16.1.12 Important Publications Referenced in the Report

Not applicable for the abbreviated CSR

16.2 Subject Data Listings

16.2.1 Discontinued Subjects

Listing 1	LDS01a	Discontinued Subjects (Blinded Phase) – ITT Population
Listing 26	LDS01b	Discontinued Subjects (Open-Label Phase) – ITT Population

16.2.2 Protocol Deviations

Listing 9	LPD01a	Protocol Deviations (Blinded Phase) – ITT Population
Listing 30	LPD01b	Protocol Deviations (Open-Label Phase) – ITT Population

16.2.3 Subjects Excluded from the Efficacy Analysis

Not applicable

16.2.4 Demographic Data

Listing 2	LDM01a	Demographic Characteristics (Blinded Phase) – ITT Population
Listing 27	LDM01b	Demographic Characteristics (Open-Label Phase) – ITT Population
Listing 4	LMH01a	General Medical History – ITT Population
Listing 5	LMH02a	Special Medical History (Breast Cancer) – ITT Population
Listing 6	LMH03a	Menstrual History – ITT Population
Listing 7	LCM01a	Prior Medications and Treatments* (Blinded Phase) – ITT Population

Listing 28	LCM01b	Medication and Treatments Ongoing from the Blinded Phase (Open-Label Phase) – ITT Population
Listing 8	LCM02a	Concomitant Medications and Treatment (Blinded Phase) – ITT Population
Listing 29	LCM02b	Concomitant Medications and Treatment (Open-Label Phase) – ITT Population

16.2.5 Compliance and/or Drug Concentration Data

Listing 11	LSD01a	Study Drug Compliance (Blinded Phase) – ITT Population
Listing 31	LSD01b	Study Drug Compliance (Open-Label Phase) – ITT Population
Listing(-)	LPK01	PK Concentration by Subject and Visit - ITT Population

16.2.6 Individual Efficacy Response Data

Not applicable

16.2.7 Adverse Event Listings

Listing 12	LAE01a	Adverse Events (Blinded Phase) – Safety Population
Listing 32	LAE01b	Adverse Events (Open-Label Phase) – Safety Population
Listing 13	LAE02a	Serious Adverse Events (Blinded Phase) – Safety Population
Listing 33	LAE02b	Serious Adverse Events (Open-Label Phase) – Safety Population
Listing 14	LAE03a	Severe Adverse Events (Blinded Phase) – Safety Population
Listing 34	LAE03b	Severe Adverse Events (Open-Label Phase) – Safety Population
Listing 15	LAE04a	Study Drug Related Adverse Events (Blinded Phase) – Safety Population
Listing 35	LAE04b	Study Drug Related Adverse Events (Open-Label Phase) – Safety Population

16.2.8 Listing of Individual Laboratory Measurements and Other Safety Observations (by Subject)

Listing 16	LAB01a	Results of Laboratory Tests - Hematology (Blinded Phase) – ITT Population
Listing 36	LAB01b	Results of Laboratory (Hematology) Tests (Open-Label Phase) – ITT Population
Listing 17	LAB02a	Results of Laboratory (Blood Chemistry) Tests (Blinded Phase) – ITT Population
Listing 37	LAB02b	Results of Laboratory (Blood Chemistry) Tests (Open-Label Phase) – ITT Population
Listing (-)	LBA_add	Listing of Serum Concentration of CHOL, HDL, LDL and TRIG – ITT Population
Listing 18	LAB03a	Results of Urine Pregnancy Test (Blinded Phase) – ITT Population
Listing 38	LAB03b	Results of Urine Pregnant Test (Open-Label Phase) – ITT Population
Listing 22	LHR01a	Hormones Results (Blinded Phase) – ITT Population
Listing 42	LHR01b	Hormones Results (Open-Label Phase) – ITT Population
Listing 25	LCR01a	Coagulation Results (Blinded Phase) – ITT Population

Listing 44	LCR01b	Coagulation Results (Open-Label Phase) – ITT Population
Listing (-)	LBB02a	Bone Biomarkers (Double-Blind Phase) - ITT Population
Listing (-)	LBB02b	Bone Biomarkers (Open-Label Phase) - ITT Population
Listing 19	LVS01a	Vital Signs (Blinded Phase) – ITT Population
Listing 39	LVS01b	Vital Signs (Open-Label Phase) – ITT Population
Listing 20	LPE01a	Abnormalities of Physical Exam (Blinded Phase) – ITT Population
Listing 40	LPE01b	Abnormalities of Physical Exam (Open-Label Phase) – ITT Population

16.3 Case Report Forms

16.3.1 CRFs of Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events

Subject Number	Treatment	Serious Adverse Event	Withdrawal for Adverse Events
101-003	BHR700-4OHT	X	X
101-005	Placebo		X
101-009	BHR700-4OHT		X
101-016	BHR700-4OHT		X
101-017	BHR700-4OHT		X
101-018	BHR700-4OHT	X	
104-006	BHR700-4OHT	X	
104-014	BHR700-4OHT		X
104-019	BHR700-4OHT		X
104-033	BHR700-4OHT		X
104-043	Placebo		X
104-054	BHR700-4OHT		X
104-059	BHR700-4OHT	X	
104-065	BHR700-4OHT	X	X
104-082	Placebo		X
105-002	Placebo		X
105-021	Placebo		X
116-001	BHR700-4OHT		X

16.3.2 Other CRFs Submitted

Not applicable

16.4 Individual Subject Data Listings

All subject data are included in Appendix 16.2.