STATISTICAL ANALYSIS PLAN

Final v1.0

Protocol BHR-700-301(Amendment 3, v4.0, 18 April 2018)

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

NCT Number: NCT03199963

Date: November 13, 2020

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LIST OF ABBREVIATIONS

AE	***Adverse Events***
CC	***Cranial-Caudal***
CI	***Confidence Interval***
FDA	***Food and Drug Administration***
ITT	***Intend-to-Treat***
ICH	***International Committee for Harmonization***
MD	***Mammographic Density***
MedDRA	***Medical Dictionary for Drug Regulatory Affairs***
MLO	***Mediolateral Oblique***
PBRS	***Peachtree BioResearch Solution***
PD	***Pharmacodynamic***
PK	***Pharmacokinetic***
PI	***Principal Investigator***
PP	***Per-Protocol***
SAE	***Serious Adverse Events***
SAP	***Statistical Analysis Plan***
SAS	***Statistical Analysis System***
SOC	***System Organ Class***
US	***United States***

1. INTRODUCTION

1.1 Objectives

The primary objective of this study is to determine the efficacy of 8 mg/day (4 mg/breast) of BHR-700 gel compared to placebo for reducing breast tissue density in women identified as having dense breast tissue upon analysis of screening mammography using the Food and Drug Administration (FDA) cleared Cumulus 2D software..

1.2 Design

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

Subjects who give informed consent will have screening evaluations, including hormone measures of FSH, Estradiol and Estrone to determine menopausal state. Those subjects meeting entry criteria, will be stratified, based on their hormone levels, into pre/peri and post menopause groups and randomized within those groups 2:1 to receive either 8 mg/day (4 mg/breast) BHR-700 gel or placebo for up to 52 weeks. At the Principal Investigator's (PI) discretion, subjects may be allowed to reduce the dose to 4 mg/day (2 mg/breast) in cases of intolerance.

Subjects will apply the gel to both breasts once per day. The first dose will be applied under the supervision of the PI/designee. Subsequent doses will be self-administered daily by the subject until she has completed 52 weeks of study drug administration. Study drug compliance will be checked at each study visit. Subjects will be asked to capture daily gel administration in a diary and drug canisters will be weighed on release to the subject and on return. The canister weight will be recorded in grams. If the study drug is discontinued or interrupted, the reason(s) will be recorded. During treatment period, subjects will be evaluated at Day 1 and every 13 weeks (±2 weeks) thereafter.

A planned sample size of 330 women, identified as having dense breast tissue upon screening mammography, will be randomized to receive either BHR-700 gel or placebo (at 2:1 ratio). Considering an attrition rate of approximately 15%, it is expected to have 272 evaluable women (4-OHT: 181 & Placebo: 91) who will have both baseline and 52 week measurements of percent mammographic density (MD) of the breast.

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

1.3 Change in Study Conduct

The study was early terminated. Following careful consideration and review of the development program for BHR700 (4-Hydroxytamoxifen Gel, 4-OHT), it was determined that breast density reduction may not be the optimal surrogate marker to support drug development for a target indication of the reduction of the risk of breast cancer.

Planned analyses will be conducted using data available in the clinical database. The sample size of the study may no longer be powered due to the lower number of subjects and shorter duration of treatment for a large proportion of subjects due to the early termination of the study. Therefore, the

interpretation of the analysis results will be cautious. Moreover, the emphasis of the statistical analysis will be on descriptive statistics, rather than hypothesis testing.

2. ELABORATION OF STUDY PROTOCOL

2.1 Study Populations

Three analysis populations will be defined and analyzed:

1. Intent-to-treat (ITT) population will contain all subjects who are randomized into the study. All efficacy parameters will be analyzed using the ITT population. In the case of a subject who was randomized but did not take the study drug, the analysis will be performed for this subject using the randomized treatment.
2. Per-protocol (PP) population will contain all ITT subjects who completed Week 52 assessments and do not have any major protocol deviation. The major protocol deviations will be identified by BH Ireland before the database is locked and unblinded.
3. Safety population will contain all subjects who receive at least one dose of study drug. All safety parameters will be analyzed using safety population.

2.2 Study Endpoints

2.2.1 *Primary Endpoint*

Primary endpoint is the percentage reduction of mammographic left breast tissue density on a follow-up mammogram compared to the baseline mammogram after 52 weeks of treatment.

A comparison of percentage reduction in breast density between BHR-700 gel and placebo treatment groups at 52 weeks using the FDA-cleared Cumulus 2d software will be performed.

The primary endpoint will be analyzed for blind treatment phase only.

2.2.2 *Secondary Endpoints*

1 The percentage reduction in breast density at Week 52 using two breast density measurement methods (Cumulus versus Volpara).
2 The percentage of women who underwent a change in BI-RADS category when comparing pre-and post-treatment measurements.
3 The percentage of women with a ± 10% absolute decrease in quantitative mammographic density (Cumulus) between baseline and 52 weeks,
4 Change in serum concentration of: cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).
5 Change in serum concentration of sex hormone binding globulin (SHBG).
6 Change in serum concentration of Protein C-activity, Protein S-activity, Antithrombin 111 antigen, and Activated Protein C resistance (APCR).
7 Change in serum concentration of select bone biomarkers CTx and BSAP.
8 Incidence and severity of AEs and laboratory values.
9 The menstrual cycle of premenopausal women.
10 Pharmacokinetic (PK) plasma concentration of the E and Z isomers of 4-OHT after 13, 26, 52, 78, and 104 weeks of application of 4 mL BHR-700 gel to the breasts.

The secondary endpoints are for both blind and open-label treatment phases.

2.3 Sample Size

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

3. STATISTICAL METHODS

3.1 General

All data will be analyzed using the Statistical Analysis System (SAS®; Version 9.2 or higher).

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

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

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

3.2 Subject Disposition, Demographics, Baseline Characters and Study Drug Compliance

- Subject disposition will be summarized for all enrolled subjects.
- Demographics and baseline characters will be summarized on ITT population using descriptive statistics.
- General medical history, breast cancer history, menstrual history and concomitant medications data will be summarized on ITT population.
- Study drug compliance will be summarized by visit using descriptive statistics. The compliance (%) is defined as the percentage of drug administrated as planned dose, which will be calculated as below

$$\frac{\text{Weight (g)of dispensed canisters} - \text{Weight (g)of returned canisters}}{3.52\text{g} \times \text{number of days of treatment period}} \times 100\%$$

The expected weight of daily dose is based on BHR “Rule of Thumb” guidance below.

- 4 squirts is an 8 mg/day dose.
- Each squirt is supposed to be 1 mL.
- 1 mL of gel = 0.88 g (based on the density of the gel: 0.88g/mL).
- 4 squirts (mL)×0.88 g/mL = 3.52 g expected in a normal 8mg/day dose day.

Sections 4.1.1 and 4.2.1 list the planned summary tables and data listings for blinded phase.
Sections 5.1.1 and 5.2.2 list the planned summary tables and data listings for open-label phase.

Drug compliance will be calculated only for the subjects who returned all canisters dispensed. Drug compliance will be set as missing for the subjects who didn't return all canisters dispensed.

3.3 Analysis of Study Endpoints

3.3.1 *Safety Analysis*

The safety analysis will be conducted on safety population. The safety population includes all subjects who received at least one dose of study drug.

Adverse Events

- All adverse events (AE) will be summarized with MedDRA primary system organ class (SOC) and preferred term.
- Summary tables of severe AEs, SAEs and study drug related AEs will also be provided.
- Listings of all AE, serious adverse events (SAE), and severe AEs will be provided.

Laboratory Tests

- Laboratory data (haematology and blood chemistry) will be summarized for baseline, post baseline, and change from baseline.

Vital sign and Physical Exam

- Vital sign and physical exam abnormalities will be summarized. The data listings of individual abnormalities will be provided.

Urine Pregnancy Test

- Urine pregnancy test results will be listed by subjects.

Sections 4.1.2 and 4.2.2 list the summary tables and data listings planned for blinded phase.
Sections 5.1.2 and 5.2.2 list the summary tables and data listings planned for open-label phase.

3.3.2 *Efficacy Analysis*

Since the study was terminated early, no efficacy analysis planned for the study report, while safety data will be summarized and reported in the study report.

However, with careful review of the mammographic data after database lock, mammographic efficacy data may be analyzed as ad-hoc analyses as necessary.

3.3.3 *Subgroup analyses and Multiplicity adjustment*

- Multiplicity adjustment will not be applied for multiple testing in this study.

3.4 Handling of Missing Data

3.4.1 *Imputation of Missing Date for Safety Analyses*

For safety analyses, the incomplete date and time for the safety events will be imputed using the following rules.

- Missing start time of an AE reported on the first dose day will be imputed as dose time + 1 minute, and the AE will be considered as Treatment emergent AE (TEAE).
- Missing start time of an AE other than the first dose day will be imputed as 00:01 (hh:mm).
- Missing end time of an AE other than the first dose day will be imputed as 23:59 (hh:mm).
- Missing start date of any AE will be imputed as the 1st of the month.
- Missing end date of any AE will be imputed as the last day of the month.

If the severity of an AE is missing, then the AE will be considered as “Severe”. If the relationship to the study agent of an AE is missing, then the AE will be considered as “Related” to study agent.

3.4.2 Imputation of Missing Data for Efficacy Analyses

The study was terminated early so no statistical methods will be implemented for imputing missing data. The statistical analysis will focus on descriptive statistics of observed data.

3.5 Protocol Deviations

Listing for all protocol deviations will be provided.

Listing for major deviations that result in excluding from the PP population will also be provided for blinded phase.

See sections 4.2.1 and 5.2.1 for the data listings planned for blinded phase and open-label phase.

3.6 Pharmacodynamic and Pharmacokinetic (PD/PK) Data

- Bone biomarkers (CTx and BSAP) level and change from baseline will be summarized by visit and treatment group. Individual data listing will also be provided.
- Plasma concentration of study agent (4-OHT E&Z isomers) will be summarized by visit and treatment group. Individual data listing will also be provided.
- Hormones (FSH, Estradiol and Estrone) will be summarized by visit and treatment group. Individual data listing will also be provided.
- Coagulation parameters (Protein C Activity, Protein C antigen, Protein S antigen total, Protein S antigen free, Antithrombin III antigen, Activated protein C resistance) will be summarized by visit and treatment group. Individual data listing will be provided as well.

3.7 Key Data Items

Study Analysis Population Definition:

- Intended-To-Treat (ITT) population: All subjects who are randomized into the study.
- Per-Protocol (PP) population: All ITT subjects without any major protocol violations.
- Safety Population: All ITT subjects who receive at least one dose of study drug.

Important Derived Variables:

- Age = (Screening Date – Date of Birth +1)/365.25.
- Prior Medications and Treatments: the medications and treatments started before the subject was enrolled to the study without any change after enrollment.
- Concomitant Medication and Treatments: the medications and treatments started after the subject was enrolled to the study. Any medications and treatments started before enrollment but changed after enrollment will be considered as concomitant medications and treatments.
- Baseline: All clinical measurements (safety and efficacy data) collected at Day 1 or before the first dose will be analyzed as baseline. One baseline is for both blinded phase and open-label phase.
- Post Baseline: All clinical measurements (safety and efficacy data) collected after the first dose will be analyzed as post baseline. For blinded phase, the scheduled post-baseline visits are at Week 13, 26, 39 and 52. For open-label phase, the scheduled post-baseline visits are at Week 65, 78, 91 and 104.
- Study Drug Compliance by Visit

$$\frac{\text{Weight (g) of dispensed canisters} - \text{Weight (g) of returned canisters}}{3.52\text{g} \times \text{number of days between visits}} \times 100\%,$$

  - The number of days between visits = the date of current visit – the date of last visit +1
  - Drug compliance will be calculated only for the subjects who returned all canisters dispensed.
- Overall study drug compliance of the study phase will be the average of visit compliance
- Treatment emergent Adverse Events (TEAE): Any AEs started on or after the day of the first study drug dosed.

Normal Ranges for Vital Signs

Vital Signs (unit)	Lower Limit	Upper Limit
Systolic BP (mmHg)	<90	>120
Diastolic BP (mmHg)	<60	>80
Pulse Rate (bpm)	<60	>100
Respiration Rate (bmp)	<12	>18
Body Temperature (F)	<98	>99.1

LABORATORY ASSESSMENTS

BLOOD CHEMISTRY	**HEMATOLOGY WITH % DIFFERENTIAL**	**BONE BIOMARKERS**
ALAT (SGPT) ALBUMIN ALKALINE PHOSPHATASE ASAT (SGOT) UREA NITROGEN CALCIUM CARBON DIOXIDE (CO2) CHLORIDE	HEMATOCRIT HEMOGLOBIN WHITE CELL COUNT BASOPHILS EOSINOPHILS LYMPHOCYTES MONOCYTES	BONE CTx BONE BSAP **HORMONES** FOLLICLE STIMULATING HORMONE (FSH) LUTEINIZING HORMONE (LH) SEX HORMONE BINDING GLOBULIN (SHBG)

CHOLESTEROL, TOTAL HDL LDL-CHOL CALCULATION CREATININE BILIRUBIN, DIRECT GLUCOSE LACTIC DEHYDROGENASE POTASSIUM SODIUM BILIRUBIN, TOTAL PROTEIN, TOTAL SERUM TRIGLYCERIDES	NEUTROPHIL, SEGS TOTAL NEUTROPHILS RED CELL COUNT PLATELET COUNT	ESTRADIOL ESTRONE **COAGULATION FACTORS** PROTEIN C ACTIVITY PROTEIN S ACTIVITY ANTITHROMBIN III ANTIGEN ACTIVATED PROTEIN C RESISTANCE (APCR)
Formulas of Metric Conversion: • 1 inch = 2.54 cm • 1 lb = 0.4536 kg • $^{o}C = (^{o}F - 32)x5/9$		

3.8 Change to Planned Protocol Analysis

Since the study was early terminated, many subjects did not have visit of End of Blinded Phase at week 52. The current nominal Visit of “Week 52” will include both “Week 52” and “End of Study” (EOS). No imputation will be done for the missing data.

Since the study was terminated early, a brief clinical study report will be planned for this study and will focus on the safety and PK/PD results, where PK/PD results of blind phase will be reported only. The baseline characters, safety data and PK/PD data will be reported in the study report.

However, mammographic efficacy data may be analyzed appropriately as ad-hoc analyses after carefully reviewed data. The results of ad-hoc analyses will be reported separately.

4. OUTPUT PLANNED FOR THE STUDY REPORT (BLINDED PHASE)

4.1 Tables to be Included in Study Report

In the following sections, the different results are presented in the order in which it is planned to make them appear in the study report.

The table templates are available in the Appendix of the SAP. The content shown in the templates are an example only. It is not based on real study data or details concerning design.

4.1.1 *Summary of subject information*

1. Table [TDS01a] Subject Disposition (Blinded Phase) – All Subjects
2. Table [TDM01a] Summary of Demographics (Blinded Phase) – ITT Population
3. Table [TMH01a] Summary of General Medical History – ITT Population
4. Table [TMH02a] Summary of Breast Cancer Medical History – ITT Population
5. Table [TMH03a] Summary of Menstrual History – ITT Population

6. Table [TCM01a] Summary of Prior Medications and Treatments (Blinded Phase) – ITT Population
7. Table [TCM02a] Summary of Concomitant Medications and Treatments (Blinded Phase) – ITT Population
8. Table [TSD01a] Summary of Study Drug Compliance by Visit (Blinded Phase) – ITT Population

4.1.2 *Summary of safety endpoints*

9. Table [TAE01a] Summary of Adverse Events (Blinded Phase) – Safety Population
10. Table [TAE02a] Number (%) of Subjects with Adverse Events by Body System and Preferred Term (Blinded Phase) – Safety Population
11. Table [TAE03a] Number (%) of Subjects with Serious Adverse Events by Body System and Preferred Term (Blinded Phase) – Safety Population
12. Table [TAE04a] Number (%) of Subjects with Severe Adverse Events by Body System and Preferred Term (Blinded Phase) – Safety Population
13. Table [TAE05a] Number (%) of Subjects with Study Agent Related Adverse Events by Body System and Preferred Term (Blinded Phase) – Safety Population
14. Table [TAE06a] Number (%) of Subjects with Adverse Events by Preferred Term and Overall Frequency (Blinded Phase) – Safety Population
15. Table [TVS01a] Summary of Vital Signs and Change from Baseline (Blinded Phase) – Safety Population
16. Table [TPE01a] Summary of Physical Examination (Blinded Phase) – Safety Population
17. Table [TLB01a] Summary of Laboratory (Hematology) Test Results – Safety Population
18. Table [TLB02a] Summary of Laboratory (Blood Chemistry) Test Results – Safety Population
19. Table [TLB03a] Summary of Urine Pregnancy Test Results (Blinded Phase) – Safety Population

4.1.3 *Summary of PK/PD endpoints*

20. Table [THR01a] Summary of Hormones Results (Blinded Phase) – ITT Population
21. Table [TBB01a] Summary of Bone Biomarker Results (Blinded Phase) – ITT Population
22. Table [TCP01a] Summary of Coagulation Parameters Results (Blinded Phase) – ITT Population
23. Table [TPK01a] Summary of Plasma Concentration Results (Blinded Phase) – ITT Population
24. Table [TEM01a] Summary of Endometrial Change (Blinded Phase) – ITT Population (Only if data available)

4.2 Listings to be Included in the Clinical Study Report

4.2.1 *Listings of subject information*

1. Listing [LDS01a] Discontinued Subjects (Blinded Phase) – ITT Population
2. Listing [LDM01a] Demographic Characteristics (Blinded Phase) – ITT Population
3. Listing [LRN01a] Randomization (Blinded Phase) – ITT Population
4. Listing [LMH01a] General Medical History – ITT Population
5. Listing [LMH02a] Special Medical History (Breast Cancer) – ITT Population
6. Listing [LMH02a] Menstrual History – ITT Population
7. Listing [LCM01a] Prior Medications and Treatments (Blinded Phase) – ITT Population
8. Listing [LCM02a] Concomitant Medications and Treatments (Blinded Phase) – ITT Population
9. Listing [LPD01a] Protocol Deviations (Blinded Phase) – ITT Population

10. Listing [LPD02a] Protocol Deviations Lead to Exclusion from PP Population (Blinded Phase) – ITT Population
11. Listing [LSD01a] Study Drug Compliance (Blinded Phase) – ITT Population

4.2.2 *Listings of safety data*

12. Listing [LAE01a] Adverse Events (Blinded Phase) – Safety Population
13. Listing [LAE02a] Serious Adverse Events (Blinded Phase) – Safety Population
14. Listing [LAE03a] Severe Adverse Events (Blinded Phase) – Safety Population
15. Listing [LAE04a] Study Drug Related Adverse Events (Blinded Phase) – Safety Population
16. Listing [LAB01a] Results of Laboratory Tests - Hematology (Blinded Phase) – ITT Population
17. Listing [LAB02a] Results of Laboratory Tests – Blood Chemistry (Blinded Phase) – ITT Population
18. Listing [LAB03a] Results of Urine Pregnant Tests (Blinded Phase) – ITT Population
19. Listing [LVS01a] Vital Signs (Blinded Phase) – ITT Population
20. Listing [LPE01a] Abnormalities of Physical Exam (Blinded Phase) – ITT Population

4.2.3 *Listings of efficacy and PK/PD data*

21. Listing [LEF01a] Breast Density (Blinded Phase) – ITT Population
22. Listing [LBR01a] Breast Tissue Composition BI-RADS Grade (Blinded Phase) – ITT Population
23. Listing [LHR01a] Hormones Results (Blinded Phase) – ITT Population
24. Listing [LBB01a] Bone Biomarkers (Blinded Phase) – ITT Population
25. Listing [LCR01a] Coagulation Parameters (Blinded Phase) – ITT Population
26. Listing [LPK01a] Plasma PK Concentrations (Blinded Phase) – ITT Population
27. Listing [LEM01a] Endometrial Results (Blinded Phase) – ITT Population (only if data available)

5. OUTPUT PLANNED FOR THE STUDY REPORT (OPEN-LABELPHASE)

5.1 Tables to be Included in Study Report

In the following sections, the different results are presented in the order in which it is planned to make them appear in the study report.

The table templates are available in the Appendix of the SAP. The content shown in the templates does only mean as an example. It is not based on real study data or details concerning design.

5.1.1 *Summary of subject information*

25. Table [TDS01b] Subject Disposition (Open-Label Phase) – All Subjects
26. Table [TDM01b] Summary of Demographics (Open-Label Phase) – ITT Population
27. Table [TCM01b] Summary of Medications and Treatments Ongoing from the Blinded Phase (Open-Label Phase) – ITT Population
28. Table [TCM02b] Summary of Concomitant Medications and Treatments (Open-Label Phase) – ITT Population

5.1.2 *Summary of safety endpoints*

29. Table [TAE01b] Summary of Adverse Events (Open-Label Phase) – Safety Population

30. Table [TAE02b] Number (%) of Subjects with Adverse Events by Body System and Preferred Term (Open-Label Phase) – Safety Population
31. Table [TAE03b] Number (%) of Subjects with Serious Adverse Events by Body System and Preferred Term (Open-Label Phase) – Safety Population
32. Table [TAE04b] Number (%) of Subjects with Severe Adverse Events by Body System and Preferred Term (Open-Label Phase) – Safety Population
33. Table [TAE05b] Number (%) of Subjects with Study Agent Related Adverse Events by Body System and Preferred Term (Open-Label Phase) – Safety Population
34. Table [TAE06b] Number (%) of Subjects with Adverse Events by Preferred Term and Overall Frequency (Open-Label Phase) – Safety Population
35. Table [TVS01b] Summary of Vital Signs and Change from Baseline (Open-Label Phase) – Safety Population
36. Table [TPE01b] Summary of Physical Examination (Open-Label Phase) – Safety Population
37. Table [TLB01b] Summary of Laboratory (Hematology) Test Results (Open-Label Phase) – Safety Population
38. Table [TLB02b] Summary of Laboratory (Blood Chemistry) Test Results (Open-Label Phase) – Safety Population
39. Table [TLB03b] Summary of Urine Pregnancy Test Results (Open-Label Phase) – Safety Population

5.2 Listings to be Included in the Clinical Study Report

5.2.1 *Listings of subject information*

28. Listing [LDS01b] Discontinued Subjects (Open-Label Phase) – ITT Population
29. Listing [LDM01b] Demographic Characteristics (Open-Label Phase) – ITT Population
30. Listing [LCM01b] Medication and Treatments Ongoing from the Blinded Phase (Open-Label Phase) – ITT Population
31. Listing [LCM02b] Concomitant Medications and Treatments (Open-Label Phase) – ITT Population
32. Listing [LPD01b] Protocol Deviations (Open-Label Phase) – ITT Population
33. Listing [LSD01b] Study Drug Compliance (Open-Label Phase) – ITT Population

5.2.2 *Listings of safety data*

34. Listing [LAE01b] Adverse Events (Open-Label Phase) – Safety Population
35. Listing [LAE02b] Serious Adverse Events (Open-Label Phase) – Safety Population
36. Listing [LAE03b] Severe Adverse Events (Open-Label Phase) – Safety Population
37. Listing [LAE04b] Study Drug Related Adverse Events (Open-Label Phase) – Safety Population
38. Listing [LAB01b] Results of Laboratory Tests – Hematology (Open-Label Phase) – ITT Population
39. Listing [LAB02b] Results of Laboratory Tests – Blood Chemistry (Open-Label Phase) – ITT Population
40. Listing [LAB03b] Results of Urine Pregnant Tests (Open-Label Phase) – ITT Population
41. Listing [LVS01b] Vital Signs (Open-Label Phase) – ITT Population
42. Listing [LPE01b] Abnormalities of Physical Exam (Open-Label Phase) – ITT Population

6. REFERENCES

Protocol: 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, Amendment 3, v4.0, April 16, 2018, BHR Pharma, LLC.

7. ATTACHMENT: THE SHELLS OF TABLES, FIGURES AND LISTINGS PLANNED FOR CLINICAL STUDY REPORT

Approval for Statistical Analysis Plan

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**

Reference: **BHR-700-301/SAP**
Version: **1.0**
Date effective:

Author: [redacted]

Author's signature: Date:

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Reviewer/Approver: [redacted]
Position: [redacted]

Signature for sponsor: Date:
