Statistical Analysis Plan for BHR-200 (0.36% transdermal estradiol gel)

Protocol No. BHR-200-201

A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of BHR-200 (0.36% transdermal estradiol gel) for the Maintenance of Testosterone Suppression in Men with Advanced Androgen-Sensitive Prostate Cancer

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Statistical Analysis Plan Revision History

Version	**Date**	**Author(s)**	**Summary of Changes/Comments**
Version 0.1	June 15, 2017	[redacted]	First version
Version 1.0	August 19, 2017	[redacted]	Final version

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1 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
°C	Celsius
°F	Fahrenheit
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BHR	BHR Pharma, LLC
BHR-200	Transdermal 17-β estradiol gel (all strengths currently in development)
BMI	Body Mass Index
BSAP	Alkaline Phosphatase, Bone Specific
BUN	Blood urea nitrogen
CRF	Case report form
dL	Deciliter
ECG	Electrocardiogram
EOS	End of Study (visit)
EPIC	Expanded Prostate Cancer Index Composite
ET	Early Termination (visit)
FDA	U.S. Food and Drug Administration
FSH	Follicle-Stimulating Hormone
g	Gram
GCP	Good Clinical Practice
GnRH	Gonadotropin-Releasing Hormone
HbA1c	Glycated haemoglobin
ICH	International Conference on Harmonisation
kg	Kilogram
LDH	Lactate dehydrogenase
LH	Luteinizing Hormone
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
ng	Nanogram
OTC	Over the counter
pg	Picogram

PK	Pharmacokinetic
pmol	Picomole
PSA	Prostate-Specific Antigen
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SHBG	Sex Hormone Binding Globulin
µg	Microgram
U.S.	United States
WHO	World Health Organization
	For the purpose of consistency, the following units will be used throughout this document: Estradiol: pg/mL (1 pmol/L= 0.2724 pg/mL) Testosterone: ng/dL (1 nmol/L = 28.82 ng/dL)

2 INTRODUCTION

This document presents the statistical analysis plan (SAP) for Study BHR200-201, a randomized, double-blind, placebo-controlled, dose-finding study of BHR-200 (0.36% transdermal estradiol gel) for the maintenance of testosterone suppression in men with advanced androgen-sensitive prostate cancer. A total of 34 study subjects were randomized at 7 centers in the US before study termination.

The planned analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR). The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials

Hedlund, P.***O. (2000). Side effects of endocrine treatment and their mechanisms: castration,***

antiandrogens, and estrogens. Prostate Suppl., 10, 32-37.

[ICH, 2005].

This study was discontinued prematurely by the sponsor because of slow enrollment.

3 STUDY OBJECTIVES

3.1 Primary objective

- To evaluate the safety and efficacy of three different doses of BHR-200 (0.36% transdermal estradiol gel) compared to placebo for the maintenance of testosterone (T) suppression in men with advanced androgen-sensitive prostate cancer.

3.2 Secondary objectives

- To select the dose(s) for a subsequent Phase 3 trial.

4 STUDY OVERVIEW

4.1 Study design

This was a multi-center, randomized, double-blind, placebo-controlled, dose-finding study in men with advanced androgen-sensitive prostate cancer. Patients participated in a 24-week double-blind treatment period and were allowed to continue treatment with their assigned study drug for up to 52 weeks as long as they remained chemically castrated. Patients who gave informed consent had screening evaluations, and if fulfilling the entry criteria, were randomized to one of 4 treatment groups: 1mL, 2mL or 3mL of 0.36% BHR-200 (transdermal estradiol gel) or placebo. Study drug was initiated on the day (+/- 5 days) they would be scheduled to receive the next GnRH agonist depot injection. Patients were offered low-dose radiation to aid in the prevention of gynecomastia. Patients applied the study drug once per day. The first dose was applied under the supervision of the

PI/designee. Subsequent doses were self-administered daily by the patient until one of the following occurred:

- he was no longer chemically castrated as demonstrated by testosterone levels greater than or equal to 50 ng/dL,
- a rise in PSA over baseline of ≥0.5 ng/mL was observed,
- he had completed 24 weeks of double blind treatment, and elected not to continue into the extension period, or
- he had completed 52 weeks of study drug administration.

At the conclusion of study participation, patients were advised to resume standard of care treatment under the supervision of their healthcare provider. While on treatment, patients were evaluated at Day 1, every 2 weeks, for the first 24 weeks, and every 4 weeks thereafter, with a final post-treatment follow-up visit 2 weeks (+/- 2 days) post last dose administration.

4.2 Study Drug Administration

The 0.36% BHR-200 gel formulation contains 3.6 mg/g estradiol in a clear, colorless, absorptive hydroalcoholic gel base formulated to provide continuous release of estradiol. BHR-200 was supplied in a non-aerosol canister with a 1mL metered-dose pump. A single pump actuation delivered 3 mg of estradiol in 0.87 g of gel. The gel was applied to clean, dry, intact skin of the upper arms and shoulders.

4.3 Sample Size and Power Analysis

The planned sample size was 120 male patients. Assuming the response rate (the proportion of patients maintaining castrate levels of T (T < 50 ng/dL) for the placebo group was 5%, the response rate for the low dose group of BHR-200 was 50%, the response rate for the mid dose group was 80%, and the response rate for the high dose group of BHR-200 was 95%, 30 patients per treatment group provided at least 90% power to detect the difference in proportion of patients maintaining castrate levels of T (T < 50 ng/dL) between any dose of BHR-200-treated patients and the placebo-treated patients using a two-sided Fisher-Exact test with a 5% significance level.

However, this study was discontinued prematurely by the sponsor. A final total of 34 study subjects will be included in the analyses.

4.4 Randomization and Blinding

All site personnel were blinded to treatment assignment. The Investigator (or designee) was responsible for drug accountability and dispensing of the study drug. In the case of an AE or serious adverse event (SAE) for which the Investigator must know a specific treatment allocation to ensure the patient's safety, unblinding of treatment assignment was permitted. Instructions for "breaking the blind" were provided to the Investigator. It should be stressed that unblinding the treatment allocation was only allowed for safety concerns in an emergency situation. If time allowed, the Investigator was encouraged to discuss the matter with the study Medical Monitor prior to "breaking the blind" whenever possible. If possible, the relationship of the AE to the study drug was to be assessed before the treatment code was broken. In all cases, the Medical Monitor was to be notified within 24 hours after the code had been broken. If the treatment assignment was unblinded, study drug was permitted to be discontinued at the Investigator's discretion. Please note that patient 110-001 withdrew from the study and was unblinded on 5/13/16.

5 ANALYSIS ENDPOINTS

5.1 Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the response rate (the proportion of patients maintaining castrate levels of T (T < 50 ng/dL)). The primary analysis on the primary efficacy endpoint is to compare the response rate from each of the 3 BHR-200 dose levels against the response rate for the placebo-treated patients at Week 12.

Secondary Efficacy Endpoints:

(1) The response rate at Week 24. The same statistical analysis method that applied to Week 12 analysis will be used for Week 24.
(2) The Kaplan-Meier curve for time to T > 50 ng/dL through Week 12 for each treatment group.
(3) The Kaplan-Meier curve for time to T > 50 ng/dL through Week 24 for each treatment group.

Exploratory Endpoints:

All other efficacy parameters (e.g., FSH, LH, SHBG, and PSA) will be summarized by treatment group at each study visit using descriptive statistics. Serum levels of estradiol and estrone will be summarized by treatment group at each study visit using descriptive statistics. The Expanded Prostate Cancer Index Composite (EPIC)-Hormonal Assessment and the EPIC-Sexual Assessment will be summarized by treatment group at each study visit using descriptive statistics.

5.2 Safety Endpoints

The following safety data was collected and evaluated at pre-specified time points:

- Vital signs: blood pressure, heart rate, respiration rate, and body temperature.
- ECG.
- Biomarkers: bone biomarkers and prostate-specific antigen (PSA).
- Central laboratory assessments for blood chemistry, hematology, and urinalysis, as well as coagulation factors, and hormone assessments.
- Post-treatment events (adverse events [AEs] and serious AEs [SAEs]).

  Please note that 2 SAEs have been reported from the 34 enrolled patients:

  (1) Patient 102-001 reported an unrelated SAE of Worsening of Patient Small Bowel Obstruction on 1/15/16 and resolved on 1/16/16. The patient completed the study on 01/27/2016.

  (2) Patient 106-004 reported an unrelated SAE of Robotic Assisted Right Lymphocelectomy on 5/11/17 and resolved on 5/12/17. The patient withdrew consent on 05/16/2017.

5.3 Pharmacokinetic Endpoints

The following pharmacokinetic data was collected and evaluated at each visit: serum estradiol and estrone.

6 ANALYSIS POPULATIONS

6.1 Intent-to-treat (ITT) population

The Intent-to-treat (ITT) population will contain all patients who are randomized into the study. All efficacy parameters will be analyzed using the ITT population. In the case of a patient who was randomized but did not take the study drug, the analysis will be done for this patient using the randomized treatment.

6.2 Safety population

The Safety population will contain all patients who receive at least one dose of study drug.

All safety parameters will be analyzed using the Safety population.

7 DATA AND ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS program name, including the path that generates the output;
3. Any other output-specific details that require further elaboration.

In general, tables will be formatted with a column for each treatment group. The tables for baseline data will be formatted with an additional column displaying the findings for all subjects combined. In general, Row entries in tables are made only if data exists for at least one subject (*i.e.*, a row with all zeros will not appear). The exception to this rule applies to tables that list the termination status of subjects (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data are flagged in the individual subject data listings. Imputed data are not incorporated into any raw or primary datasets. These data are retained in derived (or analysis) datasets.

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD) and range (i.e. minimum and maximum values) for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percentage of responses will be presented in the form XX (XX.X).

- All p-values will be rounded to 4 decimal places. All p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999'.
- All summary tables will include the analysis population sample size (i.e., number of subjects).
- Study Day 1 is defined as the date at which the subject receives the first application of the study drug. All study days are determined relative to Day 1. Relative days will be calculated as:

  Relative Day = Assessment Date – First Application Date+1.

- Baseline values will be defined as those values recorded closest to, but prior to, the study drug on Day1 unless otherwise specified in the protocol.
- Change from baseline will be calculated as follows:

  Change = Post-baseline value – baseline value.

- Date variables will be formatted as YYYY-MM-DD for presentation.
- Tables, figures, and listings will be presented in landscape orientation.
- SAS® Version 9.4 or higher will be the statistical software package used for all data analyses.
- All data from this study will be presented in a listing. All listings will be sorted by subject number and visit date, as applicable.
- Table and listing numbering will follow ICH guidelines for post-text table and listing numbering.

7.1 Visit windows

For the statistical analyses, data will be analyzed by their target date and time.

7.2 Missing Data

Missing values will not be imputed by estimated values, but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

7.3 Post-baseline repeated or unscheduled data

Repeated or unscheduled data post study drug administration will not be used for data analysis, except for summary tables of the numbers of subjects with notable values of vital signs, physical examination data, and ECG data. All repeated or unscheduled data will be reported in data listings.

8 SUBJECT ACCOUNTING AND STUDY DISPOSITION

A complete accounting of subject participation in the study will be summarized in a table. The purpose of this table is to provide an accounting of subjects from their entrance into the study (after signing informed consent) through their final visit and to account for subject evaluation in major analyses of safety, including reasons for early study termination. The table will display the number of subjects that were enrolled in the study and the number and percentage of subjects who:

- withdrew prior to dosing,

- are included in the safety population
- completed or did not complete the study.
- For those subjects who did not complete the study, the reason for their non-completion, noting the number and percentage of subjects for each reason.

9 BASELINE SUBJECT DATA

9.1 Demographic and Other Baseline Characteristics

Demographic information and other baseline characteristics will be presented using descriptive statistics for the Safety population. Demographic variables will include age, gender, race and ethnicity. Age will be calculated as the age in years from the birth date to the informed consent date and will be rounded down to the nearest integral value. Other baseline characteristics will include height, weight, and body mass index (BMI).

9.2 Medical History

Medical history will be summarized using counts and percentages for the Safety population, and will be mapped to preferred terms and System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The terms will be presented in alphabetical order. Subjects reporting more than one condition in a category will be counted only once for that category.

The subject's ADT history will be summarized.

10 PRIOR AND CONCOMITANT MEDICATIONS/NON-DRUG THERAPIES AND PROCEDURES

Prior medications are medications that are taken and stopped prior to the first application of the study drug. Concomitant medications are those medications that are ongoing at or started after the first application of the study drug. Prior and concomitant medications will be coded using the Anatomical-Therapeutic-Chemical (ATC) classification text from the WHO Drug Dictionary. Medications will be presented by ATC Class and Preferred Term. Prior and concomitant medications will be summarized for the Safety population. Subjects will only be counted one time in each unique ATC Class and Preferred Term category.

If the medication start date is completely missing then the medication will be considered concomitant unless it can be determined that the medication end date occurred prior to the start of the study. If the medication start date is partially missing and the partial date is not sufficient to determine if the medication was taken after the start of the study, then the medication will be considered concomitant for the study unless it can be ruled out by the partial date and/or medication end date.

The non-drug therapies and procedures will be mapped to preferred terms and SOC using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

11 EFFICACY

Since the study was stopped prematurely, no planned inferential efficacy analyses will be performed for all of the efficacy parameters. However, the all efficacy endpoints including primary, secondary and exploratory parameters (e.g., FSH, LH, SHBG, and PSA) will be summarized by treatment group at each study visit using descriptive statistics. Serum levels of estradiol and estrone will also be summarized by treatment group at each study visit using descriptive statistics. The Expanded Prostate Cancer Index Composite (EPIC)-Hormonal Assessment and the EPIC-Sexual Assessment will be summarized by treatment group at each study visit using descriptive statistics.

12 SAFETY

Safety will be measured by the incidence of AEs, changes in vital signs and clinical safety laboratory results, and electrocardiogram results. All safety analysis will be conducted in the Safety population.

For safety data, the last non-missing pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline. In all summary tables the data will be presented by study dose group.

12.1 Exposure to Study Drug

The number of applications of study drug administered and the total weight of gel applied to each subject will be summarized descriptively by dose group for the Safety population.

12.2 Vital Signs

Vital sign parameters include systolic and diastolic blood pressure, body weight, height, BMI, respiration rate, temperature, and heart rate. Vital sign values and changes from baseline in these parameters will be presented using descriptive summaries by visit.

A shift from baseline analysis of abnormalities (normal, abnormal/clinically significant, and abnormal/ not clinically significant) will also be presented by counts and percentages at each post-administration visit and in an overall view regardless of post-administration assessment time point. In addition, at each time point, the sums of subjects with normal, abnormal CS, and abnormal NCS values at that time point will be summarized. Also, at each time point the sums of subjects with normal, abnormal CS, and abnormal NCS values at baseline and values at that time point will be summarized.

12.3 12-Lead Electrocardiogram (ECG)

A 12-lead ECG was to be performed at Screening and at Week 12, 24, 36, 48, 52, 54/EOS.

ECG parameters include PR interval (msec), QRS interval (msec), RR interval (msec), QT interval (msec), and QTc interval (msec). ECG values and changes from baseline will be presented using descriptive summaries by visit.

A shift from baseline analysis of abnormalities (normal, abnormal/clinically significant, and abnormal/ not clinically significant) will also be presented by counts and percentages at each post-administration visit and in an overall view regardless of post-administration assessment time point. In addition, at each time point, the sums of subjects with normal, abnormal CS, and abnormal NCS values at that time point will be summarized. Also, at each time point the sums of subjects with

normal, abnormal CS, and abnormal NCS values at baseline and values at that time point will be summarized.

12.4 Physical Examination

Physical examination results will be summarized at each visit as normal, abnormal/clinically significant or abnormal/not clinically significant, and compared in a shift analysis to the baseline result for each physical examination category and in an overall view regardless of post-administration assessment time point. In addition, at each time point, the sums of subjects with normal, abnormal CS, and abnormal NCS values at that time point will be summarized. Also, at each time point the sums of subjects with normal, abnormal CS, and abnormal NCS values at baseline and values at that time point will be summarized.

12.5 Adverse Events

Adverse events (AEs) will be mapped to preferred terms and SOC using the MedDRA coding dictionary.

Summaries of AEs will be also presented based on treatment-emergent AEs (TEAEs), defined as AEs that begin (or if preexisting medical conditions that worsen) after receiving the first application of the study drug. If the adverse event start date is partially or completely missing then the adverse event will be considered treatment-emergent.

The number and percentage of subjects experiencing AEs will be summarized by SOC and preferred term. Subjects will be counted only once at the SOC level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. SOCs, and preferred terms within SOC, will be displayed alphabetically. Similarly, AEs leading to discontinuation from the study will be presented by SOC and preferred term as well. The treatment-related AEs, defined as AEs with relationship of 'Possibly' or 'Probably' related to the study treatment, will be summarized by SOC and preferred term.

Summaries by SOC and preferred term and maximum intensity or relationship to study treatment will also be provided for AEs. A summary by SOC and preferred term and maximum intensity will be provided for treatment-related AEs as well. Subjects with multiple occurrences of the same SOC or preferred term will be summarized at the maximum intensity or the strongest relationship to study treatment reported for that adverse event. If a subject has an AE with unknown intensity, then the subject will be counted in the intensity category of "Severe". If a subject has an AE with unknown relationship to study treatment, then the subject will be counted in the relationship category of "Related" even if the subject has another occurrence of the same event with a relationship to study treatment.

Additionally, the number and percentage of subjects experiencing AEs will be summarized by preferred term in an order of decreasing frequency.

The number and percentage of subjects experiencing serious AEs will be summarized by SOC and preferred term.

An overall summary table of the adverse events will be produced. This table displays the number and percentage of subjects who:

- have any treatment emergent adverse events
- have any treatment emergent adverse events at least possibly related to the study drug

- have any treatment emergent adverse events presented by maximum intensity
- have any treatment emergent serious adverse events
- have any treatment emergent serious adverse events at least possibly related to the administration of the study drug
- have any treatment emergent adverse events leading to discontinuation from the study
- have any treatment emergent adverse events leading to death
- have any treatment emergent adverse events leading to death that are at least possibly related to administration of the study drug.

12.6 Clinical Laboratory Parameters

Shift analysis (High/Normal/Low), compared to the baseline result, at each visit and an overall view regardless of post-administration assessment time point, and descriptive statistics for the central laboratory values and changes from baseline at each visit will be presented by treatment group, for laboratory parameters collected in the study that include:

Hematology: Hematocrit, Hemoglobin, WBC with differential, RBC, Platelets

Blood Chemistry: Alanine transaminase (ALT), Albumin, Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), Blood urea nitrogen (BUN), Calcium, Carbon dioxide, Chloride, total Cholesterol, HDL Cholesterol, LDL Cholesterol, Creatinine, Direct bilirubin, Glucose, Lactate dehydrogenase (LDH), Potassium, Sodium, total Bilirubin, total Protein, Triglycerides

Coagulation Factors: Protein C-activity and antigen, Protein S-activity, Protein S-antigen, Antithrombin III antigen, and Activated protein C resistance (APCR)

Endocrine: Glycated hemoglobin (HbA1C)

Hormones: Follicle stimulating hormone (FSH), Luteinizing hormone (LH), and Sex hormone-binding globulin (SHBG)

Urinalysis: Appearance, Color, Glucose, Ketones, Microscopic, Nitrites, Occult blood, pH, Protein, Specific Gravity

Biomarkers:

- Bone: C-telopeptide crosslink of type 1 collagen (CTx) – a marker of bone resorption; Alkaline Phosphatase, Bone Specific (BSAP) – a marker of bone formation
- Prostate: Prostate specific antigen (PSA)

Pharmacokinetic: Estradiol, Estrone (no shift analysis will be performed for Estradiol and Estrone data).

13 QUALITY OF LIFE QUESTIONNAIRE

The Expanded Prostate Cancer Index Composite (EPIC) was developed by researchers at the University of Michigan and UCLA to measure health related quality of life among men with prostate

cancer (Wei et.al. 2000). Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed linearly to a 0-100 scale, with higher scores representing better health related quality of life (HRQOL). The EPIC-Hormonal Assessment and the EPIC-Sexual Assessment will be summarized by treatment group at each study visit using descriptive statistics.

13.1 EPIC – Hormonal Component

The EPIC – Hormonal Assessment is a 6-question survey designed to measure the Quality of Life (QoL) issues specific to hormonal function in patients with prostate cancer.

13.2 EPIC – Sexual Component

The EPIC – Sexual Assessment is a 9-question survey designed to measure the Quality of Life (QoL) issues specific to sexual function and sexual satisfaction in patients with prostate cancer.

14 OPTIONAL LOW-DOSE RADIATION

Patients were offered optional low-dose radiation for the prevention of gynecomastia (Hedlund 2000, Widmark et. al. 2003). Timing of the administration of the low-dose radiation was at the discretion of the Investigator. Data collected on the CRF will be presented in a data listing.

15 REFERENCES

Hedlund, P.O. (2000). Side effects of endocrine treatment and their mechanisms: castration, antiandrogens, and estrogens. Prostate Suppl., 10, 32-37.

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Wei, J. T., Dunn, R. L., Litwin, M. S., Sandler, H. M., & Sanda, M. G. (2000). Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology, 56(6), 899-905.

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