Clinical Study Protocol

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

Investigational Drug:	BHR-200 (0.36% transdermal estradiol gel)
Protocol Number:	BHR-200-201
Phase:	2
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Sponsor

BHR PHARMA, LLC

[redacted]

Contract Research Organization(s)

Biostatistics & Data Management

[redacted]

Monitoring

[redacted]

Central Laboratory

[redacted]

Central Pharmacy

[redacted]

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SPONSOR APPROVAL

A randomized, blinded, placebo-controlled, dose-finding study to evaluate the safety and efficacy of three different doses of BHR-200 (0.36% transdermal estradiol gel) compared to placebo for maintaining testosterone suppression in men with advanced androgen-sensitive prostate cancer.

Version: Amendment 4
Date: 13 June 2016

BHR PHARMA, LLC

[redacted]

[redacted]

PRINCIPAL INVESTIGATOR AGREEMENT

A randomized, double-blind, placebo-controlled, dose-finding study to evaluate the safety and efficacy of three different doses of BHR-200 (0.36% transdermal estradiol gel) compared to placebo for maintaining testosterone suppression in men with advanced androgen-sensitive prostate cancer.

Version: Amendment 4
Date: 13 June 2016

As an Investigator conducting this study, I agree:

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

PRINCIPAL INVESTIGATOR

Name

Signature Date

Study Synopsis

Study Title	A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of BHR-200 (0.36% transdermal estradiol gel) for Maintaining Testosterone Suppression in Men with Advanced Androgen-Sensitive Prostate Cancer
Development Phase	Phase 2
Investigational Product (IP)	0.36% BHR-200 (0.36% transdermal estradiol gel)
Active Pharmaceutical Ingredient (API)	Estradiol (17β-estradiol)
Study Centers	Multicenter, conducted at approximately 10-15 US sites
Study Duration	Up to 56 weeks per patient: 2 weeks screening, up to 24 weeks double-blind study drug followed by up to 28 weeks of double-blind extension study drug, 2 weeks End of Study
Study Objectives	
Primary	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.
Secondary	To select the dose(s) for a subsequent Phase 3 trial.
Study Endpoints	
Primary	Maintenance of T suppression, defined as the absence of any T level measurement greater than or equal to 50 ng/dL during Weeks 4 to 12 of double blind treatment.
Secondary	Maintenance of T suppression, defined as the absence of any T level greater than or equal to 50 ng/dL during Weeks 4-24 of double blind treatment. Incidence and severity of adverse events with special attention given to thromboembolic events. Serum concentrations of: follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG), and prostate-specific antigen (PSA).
Study Design	
Methodology	This is a multi-center, randomized, double-blind, placebo-controlled, dose-finding study in men with advanced androgen-sensitive prostate cancer. Patients who give informed consent will have screening evaluations, and if fulfilling the entry criteria, will be randomized to one of 4 treatment groups: 1 mL, 2mL or 3mL of 0.36% BHR-200 (transdermal estradiol gel) or placebo. Study drug will be initiated on the day (+/- 5 days) they would be scheduled to receive the next GnRH agonist depot injection. Patients will be offered low-dose radiation to aid in the prevention of gynecomastia. Patients will apply the study drug 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 patient until one of the following occurs:

	• he is 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 is observed, • he has completed 24 weeks of double blind treatment, and elected not to continue into the extension period, or • he has completed 52 weeks of study drug administration. At the conclusion of study participation, patients will be advised to resume standard of care treatment under the supervision of their healthcare provider. While on treatment, patients will be evaluated at Day 1 and 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.
Number of Patients	Planned sample size is 120 male patients with advanced androgen-sensitive prostate cancer, randomized equally to one of four treatment groups (N=30 per group).
Inclusion Criteria	1. Males, Ages 18 and older 2. Body Mass Index (BMI) between 18 and 35 kg/m^2 (inclusive) 3. Not currently hospitalized 4. Clinical indication of adenocarcinoma of the prostate evidenced by a biopsy report on record 5. At present receiving ADT treatment with a. a GnRH agonist b. for at least 2 months but not longer than 36 months without interruption **Note:** If the patient received GnRH agonist treatment prior to the treatment described under 5a and b, there must be evidence of a period without GnRH agonist treatment for a minimum of 2 months prior to starting the present treatment as is seen, for example with intermittent treatment regimens. 6. Able to initiate Screening procedures 2 weeks prior to the next scheduled injection with a GnRH agonist 7. Willing to discontinue current ADT regimen for the duration of the study 8. T level less than 50 ng/dL at Screening 9. WHO/ECOG performance status of 0 or 1 10. Life expectancy of at least 1 year 11. Adequate renal function demonstrated by not having elevated blood urea nitrogen (BUN) or Creatinine Screening lab values 12. Willing and able to communicate with the Investigator and study staff, and willing and able to complete all phases and all procedures required of the study 13. Provide voluntarily consent to participate in this study and provide written informed consent prior to start of any study-specific procedures
Exclusion Criteria	1. History or presence of allergic or adverse response to estradiol 2. Presence of symptomatic metastatic disease, risk of spinal cord compression or presence of clinically significant urinary obstruction as determined by the Principal Investigator 3. History within the past 2 years of deep vein thrombosis (DVT), pulmonary embolism (PE_2), a known thrombophilic disorder (eg.protein C, protein S, or antithrombin deficiency), or cerebrovascular accident (CVA) 4. History within the past 2 years of myocardial infarction or a coronary

	vascular procedure (e.g. percutaneous coronary intervention, coronary artery bypass graft) 5. History of congestive heart failure 6. Use of any investigational drug, biologic, or device within 28 days prior to the first dose of study gel 7. Use of any of the following known inducers or inhibitors of cytochrome P450 3A4 (CYP3A4): phenobarbital, carbamazepine, rifampin, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, St. John's Wort preparations (Hypericum perforatum), and grapefruit juice 8. Hematological parameters (Hematocrit or Hemoglobin) outside 20% of the upper or lower limits of normal at Screening 9. Active skin rash, sunburn, or other skin disorder on the upper arm(s) that requires treatment or may affect skin absorption of study gel 10. Resting uncontrolled hypertension (HTN) (160/100 mmHg) at Screening 11. Co-existent malignancy or a history of malignancy during the past 5 years, with the exception of basal and/or squamous cell carcinoma of the skin 12. Any other significant concurrent illness or disease or condition that in the opinion of the Investigator might interfere with the patient's ability to receive the treatment outlined in the protocol or might put him at additional risk
Test Product, Dose, and Mode of Administration	The 0.36% BHR-200 gel formulation contains [redacted]
Duration of Treatment	Up to 24 weeks for primary and secondary efficacy assessments with an option to continue randomized treatment up to 52 weeks as long as chemical castration is maintained (t level < 50 ng/dL) and no rise in PSA is observed of more than 0.5 ng/mL over baseline level.
Criteria for Evaluation	
Efficacy Measures	Serum total T will be measured on Day 1 before administration of study drug and thereafter will be measured every 2 weeks through Study Week 24, and every 4 weeks through Study Week 52. FSH, LH, and SHBG will be measured on Day 1 before administration of study drug, and thereafter FSH, LH, and SHBG will be measured every 12 weeks for the duration of the study. PSA will be measured on Day 1 before administration of study drug, and thereafter, PSA will be measured every 4 weeks for the duration of the study.
Safety Measures	Safety assessments will include evaluation of all adverse events (AEs), with special attention given to cardiovascular and thromboembolic events. Protein C-activity and antigen, Protein S-activity, Protein S-antigen, Antithrombin III antigen, and Activated protein C resistance (APCR) will be measured at Screening, on Day 1 before administration of study drug, and thereafter will be measured every 12 weeks for the duration of the study. Routine laboratory parameters (i.e., blood chemistry hematology, and

	urinalysis) will be measured at Screening, on Day 1 before administration of study drug, and thereafter will be measured every 12 weeks for the duration of the study with a final collection at the End of Study Visit, if abnormal at the prior visit or if not performed within the last 4 weeks. AEs will be collected at each Study Visit beginning with the first dose of Study Drug (Study Day 1).
Pharmacokinetic	Serum estradiol and estrone will be measured on Day 1 before administration of study drug, and thereafter every 2 weeks through Study Week 24 and every 4 weeks through Study Week 52.
Sample Size Determination	The sample size for this dose-finding study is a total of 120 patients. The sample size is based on the following assumptions: • the response rate (the proportion of patients maintaining castrate levels of T (T < 50 ng/dL) for the placebo group is 5%, • the response rate of the low dose group of BHR-200 is 50%, • the response rate of the mid dose group is 80%, and • the response rate of the high dose group of BHR-200 is 95%. Thirty patients per treatment group will provide 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.
Statistical Methods	The primary efficacy endpoint is the response rate which is defined as the proportion of patients maintaining castrate levels of T (T < 50 ng/dL). The responder rate will be compared for each of the 3 BHR-200 dose levels against the responder rate for the placebo-treated patients at Week 12. The Cochran–Mantel–Haenszel (CMH) statistics will be used to compare 2 responder rates of 2 treatment groups adjusted for appropriate baseline characteristics. The following comparisons will be made between active dose levels and placebo, and the study will be considered successful if the first comparison reaches a significance level of $p<0.05$. Subsequent comparisons will be considered significant only if they reach a significance level of $p<0.05$ in addition to the comparison prior to it. • High dose vs. placebo • Mid dose vs. placebo • Low dose vs. placebo • Low dose vs. high dose • Mid dose vs. high dose • Low dose vs. mid dose Secondary efficacy endpoints will include: (1) The proportion of the responder 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 $\geq$ 50 ng/dL at Week 12 for each treatment group. (3) The Kaplan-Meier curve for time to T $\geq$ 50 ng/dL at Week 24 for each treatment group. 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. Safety variables will be summarized for each dose level and overall. Safety variables include adverse events (AEs), laboratory tests, vital signs, and physical examination findings. Treatment-emergent adverse events are defined as those AEs occurring after the first dose of study drug.

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List of Abbreviations and Terms

°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
CTCAE	Common Terminology Criteria for Adverse Events
CMH	Cochran–Mantel–Haenszel statistics
CRF	Case report form
CYP3A4	Cytochrome P450 3A4
CVA	Cerebrovascular accident
DES	Diethylstilbestrol
dL	Deciliter
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study (visit)
ET	Early Termination (visit)
FDA	U.S. Food and Drug Administration
FSH	Follicle-Stimulating Hormone
g	Grams
GCP	Good Clinical Practice
GnRH	Gonadotropin-Releasing Hormone
HbA1c	Glycated haemoglobin
HTN	Hypertension
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
kg	Kilogram
LDH	Lactate dehydrogenase
LH	Luteinizing Hormone

mg	Milligrams
mL	Milliliter
mmHg	Millimeter mercury
NCI	National Cancer Institute
ng	Nanogram
OTC	Over the counter
PATCH	Prostate Adenocarcinoma: TransCutaneous Hormones study
PE_1	Physical Exam
PE_2	Pulmonary Embolism
pg	Picogram
PK	Pharmacokinetic
pmol	Picomole
PSA	Prostate-Specific Antigen
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SHBG	Sex Hormone Binding Globulin
T	Testosterone
µg	Microgram
U.S.	United States
WHO	World Health Organization

For sake 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)

1.0 Introduction and Rationale

BHR PHARMA, LLC has developed an investigational transdermal gel formulation of estradiol for maintaining testosterone suppression in prostate cancer patients having achieved castrate testosterone levels (< 50 ng/dL) on treatment with gonadotropin releasing hormone (GnRH) agonists or antagonists.

Estrogens were used for many years as the original nonsurgical hormone suppression therapy for prostate cancer; they have been used in various formulations and dosages to treat the disease at all stages (Cox and Crawford 1995). Estrogen quickly and effectively inhibits GnRH and luteinizing hormone (LH) release via negative feedback loops at the hypothalamus and pituitary gland and, in turn, inhibits testosterone release, resulting in testosterone suppression. It is also possible that estrogen replacement in patients undergoing GnRH therapy (which also suppresses estrogen) will prevent short term adverse events (AEs) like hot flushes, fatigue and decreased libido, and long term events like osteoporosis and decreased muscle mass, commonly seen with GnRH therapy.

Even though estrogen was initially the first choice for testosterone suppression in prostate cancer patients, the GnRH agonists, such as leuprolide (leuprorelin), triptorelin, and goserelin, currently dominate the market (Kawakami et al. 2006). This is due to the association of oral synthetic estrogens with an increased risk of cardiovascular toxicity, particularly thromboembolism, and the therapeutic equivalency of the GnRH agonists in testosterone suppression.

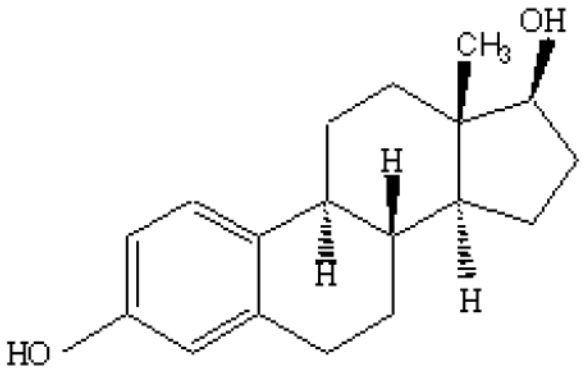
This association stemmed from a number of studies conducted with oral synthetic estrogens, notably diethylstilbestrol (DES) in the 1960s (Mellinger et al. 1967) and 1970s (Byar et al. 1973), which were confirmed in the 1990s (Robinson et al. 1995), showing that, even though DES therapy caused a modest decrease in mortality due to prostate cancer, it was associated with excessive risk of cardiovascular mortality, especially in those with a prior history of cardiovascular disease.

Given the recent concerns raised with the safety and tolerability of GnRH agonists (Higano 2003, Ockrim and Abel 2008, Efstathiou et al. 2009), interest in estrogen therapy is resurging. Research in men with prostate cancer shows promising evidence that when estrogen is delivered as 17β-estradiol rather than a synthetic estrogen and by a parenteral or transdermal route rather than oral the increase in thromboembolic risk is avoided and the safety and tolerability profile is improved relative both to oral estrogens and GnRH agonists (Bland et al. 2005, Ockrim et al. 2005, Purnell et al. 2006).

BHR-200 gel contains 17β-estradiol in [redacted] formulated to provide continuous release of 17β-estradiol into the blood. The active component of the transdermal gel is 17β-estradiol, identical to the naturally-occurring estrogen in the body. The remaining components of the gel are pharmacologically inactive. The chemical structure of 17β-estradiol is shown in Figure 1.

Figure 1

Chemical Structure of Estradiol



Common name:	estradiol 17β-estradiol
CAS Reg. No.:	50-28-2
Chemical Name:	estra-1,3,5(10)-triene-3,17ß-diol; estra-1,3,4(10)-triene-3,17-diol, (17 β)
Molecular Formula:	$C_{18}H_{24}O_2$
Molecular Weight:	272.39

Limited information exists on the use of estradiol in a population of healthy male volunteers, as most, if not all, early stage clinical work has been conducted with female participants. Estradiol has been given to women for long periods of time as hormone replacement therapy at a wide range of doses. In addition, pilot studies have documented the safe use of estradiol in men with prostate cancer as androgen deprivation therapy using transdermal administration in which plasma levels of estradiol were reached between 153 to 527 pg/mL for a duration up to 1 year (Bland et al. 2005). Similarly, in the PATCH study, 169 men have been given estradiol by simultaneous administration of 3-4, 100 µg/day transdermal patches for a mean follow-up period of 19 months in comparison with GnRH agonists, with a median plasma level of 239 pg/mL (Langley et al. 2013, Langley et al. personal communication 15Oct2013). Finally, estradiol supplementation has been used in transsexuals for lifelong treatment at dose levels significantly higher (Moore et al. 2003) than proposed for this study. Prolonged exposure in men and transsexuals at high dose levels has been associated with

gynecomastia, but no safety concerns have been associated with its use (Bland et al. 2005, Moore et al. 2003, Ockrim et al. 2003).

There are considerable potential benefits with using transdermal estradiol administration as maintenance treatment in ADT. These could include efficacy related benefits of avoidance or delay of the necessity for re-treatment with GnRH agonists or antagonists and lower or later occurrence of castration resistance. Possible safety benefits may include the reduction in GnRH- associated AEs of symptoms like hot flushes, sweating and fatigue, cardiovascular parameters like fasting glucose, fasting cholesterol and diastolic blood pressure, and bone loss. In addition, a recent study (Finkelstein et al. 2013) showed that in men made hypogonadal with the ADT goserelin and treated with testosterone gel in the presence or absence of anastrazole, a compound which prevents the conversion of testosterone to estradiol, the subjects incapable of converting testosterone experienced negative changes in fat measures and negative effects on libido and erectile dysfunction. Therefore, it is possible, that estradiol-based suppression would result in favorable changes in or maintenance of body composition and sexual function.

Although estrogens (administered both acutely and chronically) and GnRH analogs (after continuous chronic administration) suppress testosterone production and testicular function, there are clear differences and advantages for estrogens used for ADT in relation to side effect profile and patient well-being. Estrogens inhibit gonadotropin secretion acting both at the hypothalamic and pituitary level, and by acting on hypothalamic thermoregulatory and vasomotor centers they also eliminate the incidence and magnitude of hot flashes that ensues with the loss of gonadal steroids, both in postmenopausal women and in men undergoing ADT with GnRH analogs. GnRH analogs deplete endogenous sex steroids (e.g., testosterone and estradiol) eliminating both the undesirable (prostate cancer cell stimulation by testosterone) and the beneficial (e.g. bone protective estradiol) effects of the sex steroids. Exogenous estrogens, in addition to suppressing testosterone drive of the tumor, provide a built-in bone sparing activity by decreasing the number and activity of osteoclasts (Loose and Stancel, 2005) and reducing the incidence and frequency of osteoporosis and bone fractures. Largely due to these side effects, research since the mid-1980s has looked at the use of intermittent ADT as a way to reduce the side effects of continuous androgen suppression with GnRH analogs (Buchan and Goldberg, 2010). Administration of estradiol at high levels is associated with gynecomastia, a side effect whose impact can be reduced by providing preventive breast radiation. The doses proposed in the present study will result in serum estradiol levels well below those observed in the PATCH study, which may result in a reduction of this bothersome AE. With the use of BHR-200, BHR PHARMA, LLC proposes to provide clinicians with a means to provide continuous androgen suppression to patients who require it, while potentially alleviating the negative side effects associated with ADT.

Thus far, three Phase 1 clinical studies have been conducted to assess the safety and pharmacokinetic (PK) profile of multiple dose administration of transdermal estradiol gel in healthy male volunteers (Studies BHR-200-101, BHR-200-102), and in 9 patients with prostate cancer receiving ADT (BHR-200-103). Based on the PK results of Study BHR-200-101, BHR reformulated its transdermal estradiol gel to include lower concentrations of the penetration enhancers propylene glycol, oleic acid, and ethyl oleate. This reformulated product was the formulation of topical estradiol evaluated in study BHR-200-102 and study BHR-200-102. It is this formulation that will be used in the current protocol, BHR-200-201. Results from phase 1 studies BHR-200-101 and BHR-200-102 indicate that both formulations of transdermal estradiol gel at doses of 0.25g and 1.00g of 0.07% were well tolerated by healthy male volunteers. Study BHR-200-103 was a PK study in which a 0.36% formulation was given once daily or twice daily for 7 days. Mean steady state plasma levels were reached of 53 and 104 pg/mL, respectively. The gel was well tolerated. In all subjects testosterone levels remained below 50 ng/dL and in most patients the levels decreased during the treatment periods. While this is a small group of patients, these data are encouraging and consistent with findings in the PATCH study (Langley et al. 2013).

In this Phase 2 study, serum estradiol levels are expected to be between 60 and 180 pg/mL, with once daily dosing of BHR-200 gel at one of three dose levels: 3 mg estradiol per 1 mL gel, 6 mg estradiol per 2 mL gel or 9 mg estradiol per 3 mL gel.

In view of the absence of any data indicating safety issues, even at high dose levels, the planned route, dose, and duration of estradiol administration in this Phase 2 study are thought to pose minimal risk to men with advanced androgen-sensitive advanced prostate cancer (Bland et al. 2005, Moore et al. 2003, Ockrim et al. 2003). In addition, a patient whose testosterone levels increase above or equal to 50 ng/dL or whose PSA rises >0.5 ng/mL over baseline will be discontinued from the study and will be advised to resume standard of care treatment under the supervision of their healthcare provider.

2.0 Study Objective

The objective of this study is to evaluate the safety and efficacy of three different doses of BHR-200 compared to placebo for the maintenance of testosterone suppression in men with advanced androgen-sensitive prostate cancer in order to select the dose(s) for a subsequent Phase 3 study. From this Phase 2 study, one or more dosing regimens will be selected for the maintenance of testosterone suppression below 50 ng/dL.

3.0 Study Design

Patients will participate in a 24 week double-blind treatment period and will be allowed to continue treatment with their assigned study drug for up to 52 weeks as long as they remain chemically castrated. Entry criteria include prostate cancer patients who are currently receiving treatment with a GnRH agonist depot injection for at least 2 months but not longer than 36 months without interruption, and have testosterone levels < 50 ng/dL at Screening. At the scheduled time point for the next GnRH agonist depot injection, patients will be randomized to receive either placebo or low, mid or high dose BHR-200. The study will enroll 120 patients with 30 patients randomized into each of the 4 treatment groups as shown in Table 1.

Table 1 Treatment group allocation for study BHR-200-201

Treatment Group	Number of Patients		Dose	Number of Pump Actuations*
Placebo	30	10	0 mg estradiol	1 actuation
		10	0 mg estradiol	2 actuations
		10	0 mg estradiol	3 actuations
BHR-200 Low Dose	30		3 mg estradiol	1 actuation
BHR-200 Mid Dose	30		6 mg estradiol	2 actuations
BHR-200 High Dose	30		9 mg estradiol	3 actuations

*1 actuation of the pump dispenses [redacted]

Patients will be 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 will be at the discretion of the Investigator.

Levels of total Testosterone, estradiol, and estrone will be assessed every 2 weeks for all patients through Week 24 and then every 4 weeks through the End of Study Visit at Week 54 (see Schedule of Assessments in Appendix 1). Patients will remain in the study and administer daily doses of the assigned study drug until they are no longer chemically castrated as indicated by a measurement of T ≥50 ng/dL after 4 weeks of double-blind treatment, a rise over baseline PSA of > 0.5 ng/mL is observed, or if 52 weeks of study drug administration have been completed. Patients discontinued from the study will be advised to resume standard of care treatment in consultation with their healthcare provider.

Safety assessments will include AEs as well as the measurement of typical blood chemistry, hematology and urinalysis parameters, as well as coagulation factors, hormone assessments, bone biomarkers, and PSA (Section 6.1).

4.0 Patient Selection and Withdrawal

A total of 120 male patients who have advanced androgen-sensitive advanced prostate cancer will be enrolled in this study. Patients providing written informed consent and who meet the following inclusion/exclusion criteria will be eligible.

4.1 Inclusion Criteria

1. Males, Ages 18 and older
2. Body Mass Index (BMI) between 18 and 35 kg/m^2 (inclusive)
3. Not currently hospitalized
4. Clinical indication of adenocarcinoma of the prostate evidenced by a biopsy report on record
5. At present receiving ADT treatment with
   a. a GnRH agonist
   b. for at least 2 months but not longer than 36 months without interruption

Note: If the patient received GnRH agonist treatment prior to the treatment described under 5a and b, there must be evidence of a period without GnRH agonist treatment for a minimum of 2 months prior to starting the present treatment as is seen, for example with intermittent treatment regimens.

6. Able to initiate Screening procedures 2 weeks prior to the next scheduled injection with a GnRH agonist
7. Willing to discontinue current ADT regimen for the duration of the study
8. T level less than 50 ng/dL at Screening
9. WHO/ECOG performance status of 0 or 1
10. Life expectancy of at least 1 year
11. Adequate renal function demonstrated by not having elevated blood urea nitrogen (BUN) or Creatinine Screening lab values
12. Willing and able to communicate with the Investigator and study staff, and willing and able to complete all phases and all procedures required of the study
13. Provide voluntarily consent to participate in this study and provide written informed consent prior to start of any study-specific procedures

4.2 Exclusion Criteria

1. History or presence of allergic or adverse response to estradiol
2. Presence of symptomatic metastatic disease, risk of spinal cord compression or presence of clinically significant urinary obstruction as determined by the Principal Investigator

3. History within the past 2 years of deep vein thrombosis (DVT), pulmonary embolism (PE_2), a known thrombophilic disorder (eg.protein C, protein S, or antithrombin deficiency), or cerebrovascular accident (CVA)
4. History within the past 2 years of myocardial infarction or a coronary vascular procedure (e.g. percutaneous coronary intervention, coronary artery bypass graft)
5. History of congestive heart failure
6. Use of any investigational drug, biologic, or device within 28 days prior to the first dose of study drug
7. Use of any of the following known inducers or inhibitors of cytochrome P450 3A4 (CYP3A4): phenobarbital, carbamazepine, rifampin, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, St. John's Wort preparations (Hypericum perforatum), and grapefruit juice
8. Hematological parameters (Hematocrit or Hemoglobin) outside 20% of the upper or lower limits of normal at Screening
9. Active skin rash, sunburn, or other skin disorder on the upper arm(s) that requires treatment or may affect skin absorption of study gel
10. Resting uncontrolled hypertension (HTN) (160/100 mmHg) at Screening
11. Co-existent malignancy or a history of malignancy during the past 5 years, with the exception of basal and/or squamous cell carcinoma of the skin
12. Any other significant concurrent illness or disease or condition that in the opinion of the Investigator might interfere with the patient's ability to receive the treatment outlined in the protocol or might put him at additional risk

4.3 Early Withdrawal of Patients

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

The following are reasons to terminate the participation of a patient in the study:

- The patient is no longer chemically castrated, after 4 weeks of double-blind treatment or anytime thereafter, indicated by a measurement of T ≥50 ng/dL. (*treatment failure*)

- The patient's PSA rises >0.5 ng/mL above the baseline measurement (*treatment failure*)

- Lost to follow-up: patient fails to return to the study site for scheduled visits and does not respond to multiple telephone or written attempts to contact (these attempts should be documented).

- Withdrawal of consent: patient decides to stop participation in the study for any reason or is unable to complete the study as described in the study protocol. Although a patient is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. Every effort will be made to contact a patient who fails to attend any follow-up appointments/contacts in order to complete study assessments.

- Administrative: the Sponsor decides to terminate or discontinue the study (either at the study site or the entire study).

4.4 Patient Replacement

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

5.0 Study Drug

Study drug will only be shipped to Investigators who have provided BHR PHARMA, LLC (or an authorized representative) all required study documents, including Institutional Review Board (IRB) approval, have executed a clinical trial agreement (CTA), and have been approved by BHR PHARMA, LLC to begin the study. Study drug will be provided by BHR PHARMA, LLC (or authorized representative) as blind-labeled ready-to-use canisters containing BHR-200 (0.36% transdermal estradiol gel) or placebo.

5.1 Blinding and Unblinding

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

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

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

If the treatment assignment is unblinded, study drug may be discontinued at the Investigator's discretion.

5.2 Formulation, Packaging, and Labeling

The BHR-200 drug product consists of [redacted]

The placebo drug product is an absorptive hydro-alcoholic gel preparation of the same ingredients as BHR-200, but without 17β-estradiol.

Both drug products are provided in ready-to-use, plastic canisters with a metered-dose pump capable of delivering 1 milliliter of gel, and labeled 'For Investigational Use Only'. A resealable polypropylene cap tops the canister to protect the pump. Each individually packaged canister is capable of delivering at least 90, 1mL metered doses of gel.

5.3 Storage

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

5.4 Dispensing

The Investigator (or designee) will only dispense the specific numbered canisters of the study drug as allocated by central pharmacy to the patient. Two (2) canisters will dispensed at a time.

5.5 Dosage and Administration

Patients will self-apply either BHR-200 or placebo as a metered unit dose (one actuation or multiples thereof, Table 2) of gel daily to clean, dry, intact skin of the upper arms and shoulders as shown in the shaded areas in Figure 2. The gel should not be applied to any

other parts of the body, including the abdomen or genitals. The area of application should be limited to the area that would be covered by a short sleeve t-shirt. It is advised to apply study drug in the morning after showering. Night-time application is acceptable, but caution should be taken to limit transfer to other individuals. Application should occur approximately at the same time daily. A patient study drug administration guideline is provided in Appendix 2.

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

Table 2

Study Drug Dose and Application Sites

Total Number of Pump Actuations*	Pump Actuations Per Upper Arm and Shoulder	
	Upper Arm and Shoulder: #1	Upper Arm and Shoulder: #2
1 actuation	1	0
2 actuations	1	1
3 actuations	2	1

*1 actuation of the pump dispenses [redacted]

Figure 2

Application Sites for BHR-200 and Placebo gel

5.6 Study Drug Administration Precautions

- Only the patient should apply the study drug. Others (study staff and/or patient's family members) should not apply the study drug to the patient.

- The patient should not make contact with the area of skin where the study drug was applied for at least 1 hour after the application.

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

No skin-to-skin transfer studies with BHR-200 (estradiol gel) have been conducted. However, a study conducted in women with a similar FDA-approved product, EstroGel® (0.06% estradiol gel), showed that skin-to-skin contact between treated and non-treated women 1 hour after application of the gel, neither resulted in a statistically significant or clinically important transfer of estradiol gel to the non-treated women nor was there subsequent absorption of estradiol by the non-treated women (ZumBrunnen et al. 2006). Use of lotions and creams on the application site is not allowed. Use of sunscreen products is allowed 1 hour after application. Although no studies have been performed with BHR-200, a study with repeated daily application of sunscreen for 7 days at 1 hour after the administration of EstroGel® (0.06% estradiol gel) decreased the mean AUC and Cmax of estradiol by not more than 16% (EstroGel® Package Insert Rev. 08/2014).

5.7 Assessment of Compliance

Study drug compliance will be performed at each study visit. If the study drug is discontinued or interrupted, the reason(s) will be recorded.

Study drug canisters will be weighed after priming of the canister and when the canister is returned. The canister weight(s) will be recorded in grams.

5.8 Drug Accountability

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

5.9 Prior and Concomitant Medications

All medications, on-going and new, administered or taken by the patient during the study (from time of consent through Week 24) are to be recorded on the CRF. Information should

be recorded for: name of drug, dose, route of administration, start and end dates and time (for i.v. drugs), and indication.

Any therapeutic or surgical procedure performed for concurrent conditions through Study Week 24 should be recorded, including the date, description of the procedure, and clinical findings.

5.10 Prohibited Concomitant Medications/Therapies

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

- Administration of any of the following prostate cancer treatments:
  - Immunotherapy (e.g., antibody therapies, tumor-vaccines)
  - External radiotherapy
  - Brachytherapy
  - Chemotherapy
  - Biological response modifiers (e.g., cytokines)
  - GnRH agonists (e.g. Lupron®, Eligard®, Viadur®, Vantas®, Trelstar®, Zoladex®)
  - GnRH antagonists (e.g. Firmagon®)
  - Antiandrogens (e.g. Casodex®, Eulexin®, Nilandron®)
  - Androgen inhibitors (e.g. Zytiga®, Xtandi®)
- Any of the following prostatic or other related surgery :
  - Transurethral resection of the prostate
  - Radical prostatectomy
  - Orchiectomy
  - Adrenalectomy
  - Hypophysectomy
- Application of prescription or over-the-counter (OTC) topical products (including but not limited to: gel, patch, cream, ointment, lotion, or spray) to the study drug application site(s), i.e. on the upper arm(s) and shoulder(s). An exceptions is the use of sunscreen products > 1 hour after application of the study drug.
- Prescription or OTC treatments that are known/suggested to have an estrogenic or anti-androgenic effect.
- Any of the following known inducers or inhibitors of cytochrome P450 3A4 (CYP3A4): phenobarbital, carbamazepine, rifampin, erythromycin, clarithromycin,

ketoconazole, itraconazole, ritonavir, St. John's Wort preparations (Hypericum perforatum), and grapefruit juice.

6.0 Study Evaluations

6.1 Laboratory Tests

Laboratory tests will be performed by a central laboratory. The following test results will be reported to the Investigator: hematology, blood chemistry, urinalysis, coagulation factors, hormones (including total Testosterone), and PSA. The Investigator will assess all abnormal lab values for clinical significance; if categorized as adverse events, they will be collected and recorded similarly to other AEs. All clinically significant abnormal lab values will be followed until resolution. If resolution is not seen, a justification as to the cause for such an abnormality, such as due to an underlying pre-existing condition, associated co-morbidity, etc., will be recorded.

The following laboratory assessments will be performed for this study.

Hematology:	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, Cholesterol HDL, Cholesterol LDL, 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) – bone resorption

	Alkaline Phosphatase, Bone Specific (BSAP) – bone formation
Prostate:	Prostate specific antigen (PSA)
Efficacy:	total Testosterone
Pharmacokinetic:	Estradiol, Estrone

6.2 Electrocardiogram

The electrocardiogram (ECG) will be a complete, standardized 12-lead recording. ECGs will be evaluated by the Investigator or a qualified designee. Any significant findings, present prior to the first dose of Study Drug (Study Day 1), must be reported on the ECG CRF. Significant findings made after the start of study drug which meet the definition of an AE must be recorded on the Adverse Event CRF.

6.3 Physical Exam

Any significant findings present prior to the first dose of Study Drug (Study Day 1) must be reported on the Physical Exam CRF. Significant findings made after the first dose of Study Drug (Study Day 1) which meet the definition of an AE must be recorded on the Adverse Event CRF. The physical exam (PE_1) will include an assessment of all body systems as well as measurement of height and weight. The exam should include inspection of the thorax for the presence of gynecomastia.

6.4 Vital Signs

Any significant findings present prior to the first dose of Study Drug (Study Day 1) must be reported on the Vital Signs CRF. Sitting vital signs to be measured are: heart rate (beats/minute), respiration rate (breaths/minute), systolic and diastolic blood pressure (mmHg), and body temperature.

6.5 Quality of Life Questionnaire

The Expanded Prostate cancer Index Composite (EPIC) was developed by researchers at University of Michigan and UCLA to measure health related quality of life among men with prostate cancer (Wei et.al. 2000). EPIC has been validated in men with localized prostate cancer who underwent surgery, external beam radiation, or brachytherapy with or without the use of hormonal adjuvants. EPIC assesses the disease-specific aspects of prostate cancer and its therapies and comprises four summary domains (Urinary, Bowel, Sexual and Hormonal). In this study, only the Sexual and Hormonal domains of the questionnaire will be used.

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).

6.5.1 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.

6.5.2 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.

7.0 Study Visits

7.1 Screening

The assessments listed below will be conducted no more than 14 days prior to the first dose of Study Drug (Study Day 1).

- Informed Consent
- Review of inclusion/exclusion criteria
- Demographics: gender, age, race, and, ethnicity
- Review of relevant medical history within past 5 years
- Review of relevant medication/procedure history within past 2 years
- ECG
- Full physical examination including:
    - Height
    - Weight
    - BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Central laboratory assessments (see Section 6.1 for details):
    - Hematology
    - Blood Chemistry
    - Urinalysis
    - Coagulation Factors
    - Efficacy Assessment

7.2 Study Day 1 (Week 1): Baseline

The evaluations and assessments listed below will be performed within 2 hours prior to dosing with Study Drug on Day 1. An overnight fast is required for the central

laboratory assessments. It is recommended to collect blood samples in the morning (8-10 AM).

- Reaffirmation of participation
- Affirmation of eligibility criteria
- Review of medical history
- Physical exam, including:
  - Height
  - Weight
  - BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
  - Hematology
  - Blood Chemistry
  - Urinalysis
  - Coagulation Factors
  - Endocrine Assessment
  - Hormone Assessment
  - Biomarkers: Bone & Prostate
  - Efficacy Assessment
  - Pharmacokinetic Assessment
- Administer Quality of Life Questionnaires:
  - EPIC – Hormonal Component
  - EPIC – Sexual Component
- Randomization
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Record study drug administration
- Issue patient's study drug administration diary
- *Optional* – Low Dose Radiation for the prevention of gynecomastia*

*Timing is at the discretion of the Investigator.

7.3 Study Week 2: +14 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Recording adverse events (AEs)
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)

- Efficacy Assessment
- Pharmacokinetic Assessment

7.4 Study Week 4: +28 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
  - Efficacy Assessment
  - Pharmacokinetic Assessment
  - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.5 Study Week 6: +42 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
  - Efficacy Assessment
  - Pharmacokinetic Assessment

7.6 Study Week 8 – +56 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
  - Efficacy Assessment
  - Pharmacokinetic Assessment
  - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weighing of canister(s)
- Collect/issue patient's study drug administration diary

7.7 Study Week 10: +70 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment

7.8 Study Week 12: +84 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed. An overnight fast is required for the central laboratory assessments. It is recommended to collect blood samples in the morning (8-10 AM).

- ECG
- Height, Weight and BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Hematology
    - Blood Chemistry
    - Urinalysis
    - Coagulation Factors
    - Endocrine Assessment
    - Hormone Assessment
    - Biomarkers: Bone & Prostate
    - Efficacy Assessment
    - Pharmacokinetic Assessment
- Administer Quality of Life Questionnaires:
    - EPIC – Hormonal Component
    - EPIC – Sexual Component
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.9 Study Week 14: +98 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs

- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment

7.10 Study Week 16: +112 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment
    - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.11 Study Week 18: +126 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment

7.12 Study Week 20: +140 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment
    - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.13 Study Week 22: +154 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment

7.14 Study Week 24: +168 days (+/- 2 days) from Baseline

The evaluations and assessments listed below will be performed. An overnight fast is required for the central laboratory assessments. It is recommended to collect blood samples in the morning (8-10 AM).

- ECG
- Height, Weight and BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Hematology
    - Blood Chemistry
    - Urinalysis
    - Coagulation Factors
    - Endocrine Assessment
    - Hormone Assessment
    - Biomarkers: Bone & Prostate
    - Efficacy Assessment
    - Pharmacokinetic Assessment
- Administer Quality of Life Questionnaires:
    - EPIC – Hormonal Component
    - EPIC – Sexual Component
- Obtain informed consent if patient chooses to enter the study extension phase (Study Week 28 – Study Week 52: Extension Study)
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.15 Study Week 28: +196 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature

- Recording AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment
    - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.16 Study Week 32: +224 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment
    - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.17 Study Week 36: +252 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed. An overnight fast is required for the central laboratory assessments. It is recommended to collect blood samples in the morning (8-10 AM).

- ECG
- Height, Weight and BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Hematology
    - Blood Chemistry
    - Urinalysis
    - Coagulation Factors
    - Endocrine Assessment
    - Hormone Assessment

  - Biomarkers: Bone & Prostate
  - Efficacy Assessment
  - Pharmacokinetic Assessment
- Administer Quality of Life Questionnaires:
  - EPIC – Hormonal Component
  - EPIC – Sexual Component
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.18 Study Week 40: +280 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
  - Efficacy Assessment
  - Pharmacokinetic Assessment
  - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.19 Study Week 44: +308 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
  - Efficacy Assessment
  - Pharmacokinetic Assessment
  - Biomarkers: Prostate
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.20 Study Week 48: +336 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed. An overnight fast is required for the central laboratory assessments. It is recommended to collect blood samples in the morning (8-10 AM).

- ECG
- Height, Weight and BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Hematology
    - Blood Chemistry
    - Urinalysis
    - Coagulation Factors
    - Endocrine Assessment
    - Hormone Assessment
    - Biomarkers: Bone & Prostate
    - Efficacy Assessment
    - Pharmacokinetic Assessment
- Administer Quality of Life Questionnaires:
    - EPIC – Hormonal Component
    - EPIC – Sexual Component
- Dispense study drug
- Study drug compliance –weigh canister(s)
- Collect/issue patient's study drug administration diary

7.21 Study Week 52: +364 days (+/- 2 days) from Baseline – Extension Study

The evaluations and assessments listed below will be performed.

- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)
    - Efficacy Assessment
    - Pharmacokinetic Assessment
    - Biomarkers: Prostate
- Study drug compliance –weigh canister(s)
- Collect patient's study drug administration diary

7.22 Study Week 54: +378 days (+/- 2 days) from Baseline or End of Study/Early Termination

The evaluations and assessments listed below will be performed. An overnight fast is required for the central laboratory assessments. It is recommended to collect blood samples in the morning (8-10 AM).

- ECG
- Physical exam, including:
  - Height
  - Weight
  - BMI
- Vital Signs: blood pressure, heart rate, respiration rate, and body temperature
- Record AEs
- Record concomitant medications & procedures
- Central laboratory assessments (see Section 6.1 for details)*
  - Hematology
  - Blood Chemistry
  - Urinalysis

*If abnormal or not performed within the past 4 weeks, they are to be performed.

- Administer Quality of Life Questionnaires*:
  - EPIC – Hormonal Component
  - EPIC – Sexual Component

*If less than 4 weeks have passed since the EPIC questionnaires were last administered, they are to be omitted.

- Resume ADT of choice

8.0 Statistical Plan

8.1 Statistical Analysis Plan

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

8.2 Sample Size

The sample size for this dose-finding study is a total of 120 patients. Assuming the response rate (the proportion of patients maintaining castrate levels of T (T < 50 ng/dL) for the placebo group is 5%, the response rate for the low dose group of BHR-200 is 50%, the

response rate for the mid dose group is 80%, and the response rate for the high dose group of BHR-200 is 95%, 30 patients per treatment group will provide 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.

8.3 Data Management

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

8.4 Study Populations

Three analysis populations will be defined and analyzed:

(1) Safety population will contain all patients who receive at least one dose of study drug. All safety parameters will be analyzed using safety population.
(2) 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.
(3) Per-protocol population will contain all ITT patients who do not have any major protocol deviation. The major protocol deviations will be described in the SAP and identified by BHR PHARMA, LLC before the database is locked.

8.5 Handling of Missing and Incomplete Data

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

8.6 Methodology and Conventions

Safety and efficacy data will be summarized and presented by treatment group and time point in summary tables. Continuous variables will be presented by descriptive statistics: n, mean,

standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

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

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

8.7 Efficacy Analysis

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 using the Cochran–Mantel–Haenszel (CMH) statistics adjusted for appropriate baseline characteristics.

The following comparisons will be made between active dose levels and placebo, and the study will be considered successful if the first comparison reaches a significance level of $p<0.05$. Subsequent comparisons will be considered significant only if they reach a significance level of $p<0.05$ in addition to the comparison prior to it.

- High dose vs. placebo
- Mid dose vs. placebo
- Low dose vs. placebo
- Low dose vs. high dose
- Mid dose vs. high dose
- Low dose vs. mid dose

Secondary efficacy endpoints will include:

(4) The proportion of the response rate at Week 24. The same statistical analysis method that applied to Week 12 analysis will be used for Week 24.
(5) The Kaplan-Meier curve for time to T > 50 ng/dL at Week 12 for each treatment group.
(6) The Kaplan-Meier curve for time to T > 50 ng/dL at Week 24 for each treatment group.

For the time-to-event analysis, the log-rank test and the Wilcoxon test will be used to compare the median time to event. In addition, a Cox proportional hazard model will be used to analyze the time-to-event, and the model will be stratified by the appropriate baseline characteristics. Treatment effect will be tested for the hazard ratio using the Wald Chi-squared test. In addition, the 95% confidence interval for the hazard ratio (HR) will be estimated

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 EPIC-Hormonal Assessment and the EPIC-Sexual Assessment will be summarized by treatment group at each study visit using descriptive statistics.

9.0 (Serious) Adverse Event Collection and Reporting

9.1 Adverse Event Collection

AEs will be captured for the duration of the study. The reporting period begins with the first dose of Study Drug (Study Day 1) and ends at Week 54 or the End of Study. For this study, an AE is defined as: "Any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not associated with the treatment and study procedures." This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

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

The safety of BHR's transdermal estradiol gel has been studied in 25 healthy volunteers using single doses and in 9 patients in the target patient population, men with androgen-positive prostate cancer, using once daily dosing or twice daily dosing for one week. The tolerability of the drug was very good (for full reference, see the Investigator Brochure). In other formulations of transdermal estrogens have been studied in this patient population and the results have been published in peer-reviewed literature. The known side effects of

transdermal estradiol in these study populations, where estradiol was used for up to a year in some cases, include:

- gynecomastia (Bland et al. 2005, Gerber et al. 2000, Ockrim et al. 2003),
- vasomotor symptoms (Hedlund 2000, Spetz et al. 2001),
- loss of libido, and erectile dysfunction (Cox and Crawford 1995, Hedlund 2000, Lycette et al. 2006, Ockrim et al. 2006, Sayed and Taxel 2003)

Particular attention should be paid to the following potential risks previously identified as associated with administration of estradiol in populations of post-menopausal women:

- myocardial infarction
- stroke
- DVT
- pulmonary emboli

9.2 Reporting of Adverse Events

9.2.1 Diagnoses vs. signs/symptoms

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

9.2.2 Laboratory values

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

9.2.3 Pre-existing conditions

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

9.2.4 Preplanned surgeries or procedures

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

9.2.5 Elective surgeries or procedures

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

9.2.6 Overdose

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

9.3 Assessment of Adverse Event Severity

The Investigator will grade the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). All AEs will be recorded on the AE case report form.

After careful medical consideration, the Investigator will assess the relationship of the AE to the study gel as follows:

Unrelated - No possible relationship. The temporal association between administration of the study product and the adverse event is unreasonable or incompatible and/or another cause is confirmed.

Possible - There is a reasonable temporal association and causal relationship between the investigational product and the adverse event. Other potential causes may exist that are just as likely or do not fully explain the adverse event. Dechallenge/rechallenge information is unknown or unclear.

Probable - There is a reasonable temporal association and causal relationship between the investigational product and the adverse event. The adverse event responds appropriately to dechallenge. Rechallenge is not necessary. Other causes have been eliminated or are unlikely.

The Investigator must decide whether the AE meets the definition of an SAE.

9.4 Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening. Life-threatening, in the definition of serious, refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered medically significant by the Investigator or requires intervention to prevent any one of the outcomes above. Medically significant are those events considered important in the Investigator's opinion that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

All SAEs will be captured for the duration of the study. The reporting period begins with the first dose of Study Drug (Study Day 1) and ends at Week 54 or the End of Study. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intermittent illness.

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

9.4.1 SAE Reporting

The BHR MedWatch Form should be completed *within 24 hours of the Investigator/Site learning of the event* and sent by fax or as a PDF by email to the BHR Medical Monitor.

Medical Monitor: [redacted]
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

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

10.0 Regulatory and Procedural Requirements

10.1 Ethical Conduct of the Study

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

10.2 Institutional Review Board

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for following the regional law where the study is to be conducted to obtain written approval for the clinical study protocol (including all substantial protocol amendments), the patient informed consent, informed consent updates, patient recruitment procedures (e.g., advertisements) and any other information to be provided to patients from an institutional review board (IRB) that complies with the local regulatory requirements. Written approval of the study must be obtained from the IRB prior to the study being implemented (i.e., shipment of clinical supplies to the Investigator or screening of patients). Copies of the approval documentation will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the designated study documentation files.
The Sponsor (or an authorized representative) or the Investigator (according to national provisions) will submit written reports of the clinical study status to the IRB annually, or more frequently if requested by the IRB. A final study notification should be forwarded to the IRB within 90 days after the study has completed, or in the event of premature termination of the study within 15 days, with the rationale for study termination clearly explained. Copies of all clinical study status reports (including termination) will be

maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

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

10.3 Patient Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent from the patient prior to initiating any study procedures. All consent documentation must be in accordance with applicable regulations and GCP. Each patient is requested to sign the Patient Informed Consent Form after the patient has received an explanation of what the study involves, including but not limited to, the following: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. A copy of the informed consent documentation (Consent Form) must be given to the patient.

10.4 Advisory Board

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

10.5 Investigator Obligations

The Principal Investigator agrees to conduct the clinical study in compliance with this protocol which was approved by the IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol (Page 4) to confirm this agreement.

10.6 GCP compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (FDA 1996) and the applicable regulatory requirements. Copies of these guidelines are available at www.ich.org and will be provided to the site by BHR upon request.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.
The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the

curriculum vitae for the Investigator, sub-investigator(s) and essential study staff, as appropriate, will be provided to BHR (or designee) before starting the study.

10.7 Protocol adherence and investigator agreement

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

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

10.8 Protocol deviations

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

10.9 Monitoring of the study

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

10.10 Financial disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information will be collected: any significant payments of other sorts from BHR PHARMA, LLC, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in BHR-200 or any significant equity interest in BHR PHARMA, LLC as defined in 21 CFR 54 2(b).

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

10.11 Documentation and Retention of Records

10.11.1 Case Report Forms

Data collection for this protocol may be accomplished using paper forms or electronic data records or both. Therefore, the term CRF is understood to refer to a paper form, an electronic data record or both.

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

10.11.2 Recording, access and retention of source data

Source data to be reviewed during this study will include, but is not limited to: patient's medical file, original laboratory reports, and histology and pathology reports. All key data must be recorded in the patient's medical records.

The Investigator must permit authorized representatives of BHR PHARMA, LLC, the respective national, local or foreign regulatory authorities, the IRB, auditors and interested commercial parties to inspect facilities and records relevant to this study.

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

As described in the ICH GCP Guidelines, 'essential documents', including CRFs, source documents, consent forms, laboratory test results and Study Drug inventory records, should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Study Drug. These documents should be

retained for a longer period however if required by the applicable regulatory requirements or by an agreement with BHR PHARMA, LLC. The Investigator must obtain written permission from BHR PHARMA, LLC prior to the destruction of any study document.

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

10.12 Disclosure of Data

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

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

10.13 Publication

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

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

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APPENDIX 1: Phase 2 Protocol Schedule of Study Assessments and Procedures: Screening – Study Week 24

Study Assessment or Procedure	Screen[1]	Week 1 - Day 1		Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24
		Pre-Dose[2]	Hour 0												
Informed Consent	X	X													X[6]
Inclusion/Exclusion	X	Affirm													
Demographics	X														
Limited Medical History	X	Review													
ECG	X								X						X
PE / Body Systems Review	X	X													
Height and Weight/BMI	X	X							X						X
Vital Signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X
AEs		X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications & Procedures	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Low-dose radiation (optional)[3]		X	←												X
Dispense Study Drug: BHR-200 Gel/Placebo			X[4]		X		X		X		X		X		X
Study Drug compliance: weigh canisters; issue/collect dosing diary		X			X		X		X		X		X		X
Coagulation Factors (protein C activity and antigen, protein S-activity, protein S-antigen, antithrombin III antigen, and APC resistance)	X	X							X						X
Laboratory Measurements (blood chemistry, hematology, and urinalysis)[5]	X	X							X						X
Endocrine (HbA1C) & Hormone assessment (FSH, LH, SHBG)		X							X						X
Biomarkers: Bone (CTx and BSAP)[5]		X							X						X
PSA		X			X		X		X		X		X		X
Efficacy assessment (serum total T)	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic assessment (serum estradiol and estrone)		X		X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires		X							X						X

1 Up to 2 weeks prior to the next scheduled injection with a GnRH agonist treatment.
2 Within 2 hours of Study Drug Administration (Week 1: Day 1: Hour 0).
3 Timing at Investigator's discretion
4 Initial Study Drug administration will take place in the clinic (Week 1: Day1: hour 0) under the supervision of the PI/Designee, after ALL blood samples are taken.
5 An overnight fast is required, except for screening assessment. Collect specimen in the morning (8-10 a m.)
PE=physical exam; ECG=electrocardiogram; BMI=body mass index; AEs=adverse events; Con Meds=concomitant medications; APC=activated protein c; FSH=follicle stimulating hormone, LH=luteinizing hormone; SHBG=Sex hormone-binding globulin; CTx=C-telopeptide crosslink of type 1 collagen; BSAP=alkaline phosphatase, bone specific (BSAP); PSA=prostate specific androgen; ADT=androgen deprivation therapy; ET=early termination; EOS=end of study
6 Informed consent will again be obtained prior to the patient continuing with the extension phase of the study (Week 28-Week 52)

APPENDIX 1 (cont.): Phase 2 Schedule of Study Assessments and Procedures: Study Week 28 – End of Study

Study Assessment or Procedure	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	ET/EOS Wk 54
ECG			X			X		X
Height and Weight/ BMI			X			X		X
PE / Body Systems Review								X
Vital Signs	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X
Concomitant Medications & Procedures	X	X	X	X	X	X	X	X
Dispense Study Drug: BHR-200 Gel/Placebo	X	X	X	X	X	X		
Study Drug compliance: weigh canisters; collect/issue dosing diary	X	X	X	X	X	X	X	
Coagulation Factors (protein C-activity and antigen, protein S-activity, protein S-antigen, antithrombin III antigen, and APC resistance)			X			X		
Laboratory Measurements (blood chemistry, hematology and urinalysis)[5]			X			X		X[7]
Endocrine (HbA1C) & Hormone assessment (FSH, LH, SHBG)			X			X		
Biomarkers: Bone (CTx and BSAP)[5]			X			X		
PSA	X	X	X	X	X	X	X	
Efficacy assessment (serum total T)	X	X	X	X	X	X	X	
Pharmacokinetic assessment (serum estradiol and estrone)	X	X	X	X	X	X	X	
Quality of Life Questionnaires			X			X		X[8]
Resume ADT of choice								X

1 Up to 2 weeks prior to the next scheduled injection with a GnRH agonist treatment.
2 Within 2 hours of Study Drug Administration (Week 1: Day 1: Hour 0).
3 Timing of administration at Investigator's discretion
4 Initial Study Drug administration will take place in the clinic (Week 1: Day1: hour 0) under the supervision of the PI/Designee, after ALL blood samples are taken.
5 An overnight fast is required. Collect specimen in the morning (8-10 a m.)
PE=physical exam; ECG=electrocardiogram; BMI=body mass index; AEs=adverse events; Con Meds=concomitant medications; APC=activated protein c; FSH=follicle stimulating hormone, LH=luteinizing hormone; SHBG=Sex hormone-binding globulin; CTx=C-telopeptide crosslink of type 1 collagen; BSAP=alkaline phosphatase, bone specific (BSAP); PSA=prostate specific androgen; ADT=androgen deprivation therapy; ET=early termination; EOS=end of study
6 Informed consent will again be obtained prior to the patient continuing with the extension phase of the study (Week 28-Week 52)
7 Laboratory Assessment will only be done if abnormal at previous visit or if performed more than 4 weeks ago.
8 Omit EPIC questionnaires if less than 4 weeks have passed since last administration

APPENDIX 2: PATIENT INSTRUCTIONS FOR USE

BHR-200 gel is provided in a ready-to-use canister with a 1mL metered-dose pump.

BHR-200 gel contains 3 mg of estradiol per dose of 1 mL of gel.

The clear, colorless gel provides delivery of estradiol through the skin of the shoulders and upper arms.

BHR-200 gel is for topical use only. Do not swallow.

For Investigational Use Only

PRECAUTIONS:

1. **BHR-200 is flammable until dry. Do not apply BHR-200 gel near fire, flame or heat.**
2. Be sure to follow your doctor's instructions carefully throughout the course of the study.
3. Inform your doctor about **any** new medicine you take during the study (including dose(s), duration and reason), or any change(s) to medicines you take regularly.
4. Inform your doctor about any unusual symptoms or side effects occurring during the study.

INSTRUCTIONS FOR USE:

Step 1. Applying BHR-200 gel

Do not allow other people to apply BHR-200 to your skin for you.
Apply BHR-200 gel once daily preferably in the morning
Apply BHR-200 gel once daily at the same time of day.
Your study doctor will tell you the number of times to press the pump.

- Apply BHR-200 gel to clean, dry, unbroken skin after your bath or shower.
- Remove the cap from the canister. Hold the canister in one hand and place the palm of your other hand under the pump to catch the gel; see Figure A. Be sure to press down completely on the pump and release it completely to dispense one dose of gel. Repeat to dispense prescribed dose.

Figure A

- Using your hand, apply the BHR-200 gel per the guide in Table 1 and as shown in Figure B. Spread the gel as thinly as possible. Do not massage or rub in BHR-200 gel. Allow the gel to dry for 5 minutes* before you get dressed (BHR-200 gel is colorless and will not stain your clothing). Use the **same** application method every time you apply the gel.

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

Table 1: Dose and Application Guide

Prescribed Dose*	Pump Actuations Per Upper Arm and Shoulder	
	Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
1 actuation	1	0
2 actuations	1	1
3 actuations	2	1

*1 actuation of the pump dispenses 1 mL of gel.

Figure B

Step 2. After applying BHR-200 gel

- Replace the cap on top of the canister after each BHR-200 gel application to protect the pump.
- Wash your hands right away with soap and water after applying the BHR-200 gel.
- Do not let others to make contact with the area of skin where you applied the BHR-200 gel for at least 1 hour after applying the BHR-200 gel.
- Avoid water activities (i.e. swimming) after you apply the BHR-200 gel. If not possible, try to wait at least one (1) hour after applying the BHR-200 gel before participating in the water activity.
- Do not apply any creams, lotions or sprays (i.e. moisturizer) or transdermal patches (i.e. nicotine patch) to your upper arm(s) or shoulder(s) at any time during the study.
- Sunscreen products can be applied one hour after application of the BHR-200 gel.

RECOMMENDATIONS:

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

STORAGE:

- Keep BHR-200 gel at room temperature 68°F to 77°F (20°C to 25°C).
- Keep out of the reach of children.
- Avoid exposure to extreme heat or cold during transportation from the clinic to home.

REMEMBER TO: Record the date, time, and location (which arm/shoulder) you applied the gel to in your dosing diary. Bring this diary and the study drug with you to each clinic visit.

<u>This is very important for the conclusion of the study:</u>

After treatment, be sure to take **all** of the unused study gel back to your doctor. Do not discard your unused study gel.