CLINICAL TRIAL PROTOCOL: V72203

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Protocol Title:	Randomized, double-blind, placebo controlled, dose finding Phase 2 study comparing oral daily dosing of VERU-944 after a week of loading (daily dosing) with placebo to ameliorate the vasomotor symptoms resulting from androgen deprivation therapy in men with advanced prostate cancer
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1.0 LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CTX	C-Telopeptide cross-links of type I collagen
eCRF	Electronic Case report form
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
ES	Elastic stockings
FXaI	Factor X inhibitor
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
hERG	Human ether-à-go-go related gene
IEC	Independent ethics committee
IMP	Investigational medicinal product
IPC	Intermittent pneumatic compression
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LDUH	Low dose unfractionated heparin
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone
LMWH	Low molecular weight heparin
MedDRA	Medical dictionary of regulatory activities
MRI	Magnetic resonance imaging

MMRM	Mixed Models Repeated Measures
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the Counter
PCWG2	Prostate Cancer Working Group 2
PRN	*Pro re nata* – As Needed
PSA	Prostate specific antigen
SAE	Serious adverse event
SHBG	Sex hormone binding globulin
SRE	Skeletal related event
T½	Plasma concentration elimination half-life
TNM	Tumor staging, T = primary tumor, N = lymph nodes, M = distant metastases

2.0 PROTOCOL SUMMARY

Study Number: V72203

Title: Randomized, double-blind, placebo controlled, dose finding Phase 2 study comparing oral daily dosing of VERU-944 after a week of loading (daily dosing) with placebo to ameliorate the vasomotor symptoms resulting from androgen deprivation therapy in men with advanced prostate cancer

Primary Objective: To determine an effective dose of VERU-944 (from among 10 mg, 50 mg, and possibly 100 mg PO q day), after a loading dose, for the treatment of vasomotor symptoms commonly known as hot flashes by assessing its effect on:

1. the frequency of moderate to severe hot flashes at week 6

Secondary Objectives:

To assess the effect of VERU-944 on:

1. the severity of moderate to severe hot flashes at week 6
2. the frequency of moderate to severe hot flashes at week 8
3. the frequency of moderate to severe hot flashes at week 10
4. the frequency of moderate to severe hot flashes at week 12
5. the severity of moderate to severe hot flashes at week 8
6. the severity of moderate to severe hot flashes at week 10
7. the severity of moderate to severe hot flashes at week 12
8. the frequency of moderate to severe hot flashes at week 4
9. the severity of moderate to severe hot flashes at week 4
10. bone turnover markers

Exploratory Objectives:

To assess the effect of VERU-944 on:

1. serum PSA concentrations
2. serum total and free testosterone concentrations
3. serum SHBG concentrations

Safety Objective:

To assess the safety and tolerability of VERU-944

Design: This study is a multicenter, randomized, double-blind, placebo controlled, dose finding study of VERU-944 to treat hot flashes (vasomotor symptoms) in men with advanced prostate cancer on ADT. The study will be conducted as a staged study with Stage 1 being a three-arm evaluation of placebo, 10 mg and 50 mg of VERU-944. When all subjects have completed Week 6 (Day 42) of dosing, an evaluation of the efficacy of the doses administered in Stage 1 will be made (safety will be assessed in a blinded review) and Stage 2, a two-arm evaluation of placebo and 100 mg VERU-944 may be initiated. Stage 1 of the study will have three arms (placebo, 10 mg VERU-944, and 50 mg VERU-944) and Stage 2 of the study will have two arms (placebo and 100 mg VERU-944) with approximately 30 subjects per arm. The subjects participating in the study will have advanced prostate cancer and will be undergoing androgen deprivation therapy (ADT) with a luteinizing hormone releasing hormone (LHRH) therapy (agonist or antagonist) for at least the three months prior to randomization and be experiencing regular moderate to severe hot flashes while on ADT. Subjects will all continue to receive ADT and will be randomized to receive, for the first four days, a loading dose followed by daily doses of placebo or VERU-944 (10 mg, 50 mg or 100 mg) orally for a total period of 12 weeks.

Subjects: Approximately, ninety (90) subjects will be randomized into Stage 1 of this study and approximately 60 subjects are planned to be randomized into Stage 2 of this study. Subjects with advanced prostate cancer who have experienced moderate to severe vasomotor symptoms (hot flashes) for at least one month prior to study entry will be enrolled. Subjects must have been maintained on ADT with an LHRH agonist or antagonist for at least the 3 months prior to randomization will be screened for the study and if these subjects meet the other inclusion/exclusion criteria, will be randomized into the study.

Treatments: Subjects will be maintained on ADT with an LHRH agonist or antagonist while on the study. In addition to ADT, each subject will be orally administered either placebo, 10, or 50 mg of VERU-944 daily after they have completed a four day loading dose as outlined in Section 7.3 in Stage 1 of the study. Each subject in Stage 2 of the study will receive either placebo or 100 mg of VERU-944 daily after they have completed a four day loading dose as outlined in Section 7.3.

Procedures: Potential study participants will undergo a series of screening evaluations within 28 days prior to randomization. Subjects who give written informed consent and satisfy the selection criteria will be enrolled into the study.

The frequency and severity of hot flashes will be recorded daily beginning with screening and through week 12 (Day 84). Assessments of serum total and free testosterone, serum SHBG and serum PSA will be made at baseline (Day 1), Days 30, 60 and 84. Bone turnover markers will be assessed at baseline (Day 1) and Day 84.

Safety evaluations including assessment of adverse events, serum PSA, periodic monitoring of vital signs, 12-lead electrocardiogram (single) and clinical laboratory results (including hematology, serum chemistry (including LDH) will be conducted at every visit.

Patients that have been previously screened for this study and could not complete screening for reasons other than not meeting the inclusion and exclusion criteria, may be rescreened into the study. Laboratory testing conducted under this protocol (Appendix A) within 45 days prior to randomization into this study, may be used as the baseline laboratory values for this study and repeat laboratory testing is not required unless new coadministered medication(s) has been started, unless the investigator determines that retesting is warranted.

Stage 2 dosing evaluation: After the last subject has completed Day 42 of Stage 1, an unblinded assessment of the Week 6 (Day 42) hot flashes frequency (primary endpoint), hot flash severity (first secondary endpoint),and a blinded assessment of safety of VERU-944 will be conducted.

If an effective dose of VERU-944 has been identified in Stage 1, Sponsor reserves the right to not initiate Stage 2 of this protocol.

If an unacceptable safety profile is observed in Stage 1, Sponsor reserves the right to not initiate Stage 2 of this protocol.

3.0 INTRODUCTION

3.1 Background

Veru Inc. is developing VERU-944 (cis-clomiphene), a nonsteroidal estrogen, as a hormonal therapy for the alleviation of vasomotor symptoms, commonly known as hot flashes in men undergoing ADT. Cis-clomiphene is one of two geometric isomers of clomiphene, which is approved as Clomid® (clomiphene citrate oral capsules, 50 mg; NDA 016131; Sanofi Aventis US) for the treatment of ovulatory dysfunction in women desiring pregnancy. While trans-clomiphene is anti-estrogenic, cis-clomiphene is an estrogen agonist at pharmacologic concentrations (Turner et al., 1998; Fitzpatrick et al., 1999; Kaminetsky et al., 2013). Furthermore, cis-clomiphene has a half-life of 5–7 days (Mikkelson et al., 1986; Mürdter et al., 2012). VERU-944 is expected to be effective and safe in men with prostate cancer undergoing ADT based on the established efficacy of low dose estrogens in the treatment of vasomotor symptoms (hot flashes) and safety of off-label clomiphene use for male infertility.

3.2 Target Indication and Pharmacologic Activity

Introduction

Prostate cancer is the most common cancer in men with over 160,000 new cases expected in 2017 (American Cancer Society. Cancer Facts & Figures 2017). As advanced prostate cancer is hormone sensitive, androgen deprivation therapy (ADT) is the standard of care for patients with metastatic or locally advanced prostate cancer, either alone or in combination with other drug treatments or radiation (National Comprehensive Cancer Network, 2016). The main objective of ADT is to lower the serum testosterone level to castrate level of approximately 1.7 nmol/L (< 50 ng/dL) (Djavan et al., 2012). ADT is usually achieved either by surgical orchiectomy (castration) or by medically administering LHRH (luteinizing hormone releasing hormone) agonists and antagonists.

One of the main side effects of low testosterone levels in men is vasomotor symptoms, commonly known as hot flashes. Hot flashes are experienced by about 75% of men receiving ADT (Holzbeierlein et al., 2004) and are a significant component in men's perception of their quality of life (Holzbeierlein et al., 2004). One study found 38% of men who had experienced hot flashes over the past four weeks were distressed about them (Holzbeierlein et al., 2004). These hot flashes can have a long duration. For example, in men experiencing hot flashes while on ADT, 70% of them continued to experience them five years later (Karling 1994). Men describe their experience of hot flashes with physical as well as emotional descriptors (Isbarn et al., 2008). Up to 80% of men have described hot flashes that range from mild to very severe, lasting up to 30 minutes and accompanied by feelings of anxiety, irritability and being out of control. (Schow 1998). Hot flashes for men, as for women, often require some sort of action such as changing clothes or taking a shower (Isbarn et al., 2008). Hot flashes in men who have advanced prostate cancer being treated by ADT have detrimental effects on overall quality of life such that cancer-related distress caused by hot flashes are a contributing factor in the discontinuation of ADT (Engstrom, 2008; Ulloa et al., 2009; Frisk, 2010).

The precise mechanism of hot flashes in men is not fully understood, but appears to be similar to postmenopausal hot flashes in women. Studies in postmenopausal women and women undergoing breast cancer treatment who experience hot flashes have shown that abrupt withdrawal of sex hormones leads to a dysfunctional hypothalamic thermoregulation resulting in vasomotor flushing (Kaplan and Mahon, 2014). In women, hormones (usually estrogen combined with progesterone), selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenalin reuptake inhibitors (SNRIs), clonidine, and gabapentin have been effective in treating hot flashes. Similar treatments have been attempted in men with inconsistent activity; overall, hormonal treatments (cyproterone and medroxyprogesterone) are generally thought to be more effective than non-hormonal treatments at reducing hot flashes in men on ADT (Loprinzi et al., 1994; Frisk, 2010; Irani et al., 2010; Vitolins et al., 2013). Hot flashes in men on ADT are typically treated by off-label treatments such as an SSRI, whereas hormones such as estrogen and megestrol are reserved for refractory cases (Smith and Crawford, 2017).

Hot Flash Treatment for Men

There are no approved therapies for the treatment of moderate to severe vasomotor symptoms in men with advanced prostate cancer on ADT. There have been few placebo controlled, multicenter studies evaluating possible drug interventions for hot flashes these men. Megestrol acetate, 20 mg twice a day (Loprinzi et al., 1994), depomedroxyprogesterone 400 mg IM (Brosman S 1995), and venlafaxine 12.5 mg twice a day has been investigated as a tool to address hot flashes in men (Loprinzi et al., 1999). A very small randomized trial was completed with 12 men after orchiectomy with cyproterone acetate (100 mg three times a day) which appeared to reduce hot flashes (Eaton and McGuire, 1993). In addition to hormonal approaches, in women, the norepinephrine reuptake inhibitor, venlafaxine, has been studied and shown to be an effective non-hormonal treatment for hot flashes (Evans et al., 2005) although there is no evidence that this approach will work in men.

Another drug that has received some pilot testing, specifically in men, is sertraline as reported in a series of case studies (Roth and Scher 1997). Five men who were being treated with androgen ablation therapy for prostate cancer exhibited symptoms of hot flashes, symptom distress, trouble sleeping, worsening mood, fatigue and illness concerns. Patients were treated with sertraline, starting with 25 mg daily, and titrated up to 100 or 150 mg daily. From these five cases, it appeared that improvement in hot flashes was not experienced until the dose was at least 50 mg daily and side effects were experienced at a dose of 150 mg daily. Specific reductions in hot flashes were not provided for every case, but one man experienced a 75 % reduction in hot flashes while another experienced a 50% reduction. In addition to hot flash reduction, the author reports improvement in mood and irritability (Roth and Scher 1997). Doses from 50 mg to 100 mg appeared to be tolerated very well in this small group of cases.

Gabapentin for the treatment of hot flashes

To date, there has only been one placebo-controlled, Phase 3 study of an agent to control hot flashes in men with prostate cancer on ADT. This study, albeit non-regulatory, investigated the anti-seizure medication, gabapentin. In this trial, men with bothersome hot flashes as

defined as the occurrence of at least 14 times per week, were evaluated and of sufficient severity to make the patient desire therapeutic intervention, with the hot flashes being present for at least 1 month before study entry. The study duration was four weeks and during this time, the patients on the highest gabapentin dose arm (900 mg/day) demonstrated a significant decrease in hot flash frequency (p=0.02) and a trend towards lower scores (p=0.10) (Loprinzi 2009). In a continuation phase of this study, those effects were maintained (Moraska et al., 2007). Although these results were promising, gabapentin is not widely used for the treatment of hot flashes in this male population and the unmet medical need remains.

Estrogens for the treatment of hot flashes in men with advanced prostate cancer on ADT

As stated briefly above, vasomotor symptoms (hot flashes) occur in a majority of men receiving ADT for advanced prostate cancer. Since decreasing estrogen levels as a result of the ADT are a contributing cause of the hot flashes, the off-label use of estrogenic compounds have historically been used. For example, low doses of diethylstilbestrol (0.25 mg/day) appears to have efficacy but can result in significant breast swelling and tenderness along with an increase in cardiovascular side effects (Smith JA 1994; Smith JA 1996; Glashan 1981). Transdermal estrogen patches are another route of off-label administration of estrogens for this indication. In a study of twelve men with moderate to severe hot flashes who were randomized to receive either low dose (0.05 mg) of high dose (0.10 mg) estrogen twice weekly for four weeks. Although no placebo group was included in this study, a significant reduction in the severity and frequency of hot flashes was observed in the high dose arm and in severity only in the low dose arm (Gerber 2000).

In conclusion, while the off-label use of estrogens appears to have benefit for the treatment of hot flashes in men with advanced prostate cancer, the type of most efficacious estrogen or estrogen preparation as well as dosing route or schedule is not known. Furthermore, the potential for safety issues with potent steroidal estrogens remains a significant limitation to their clinical utility. These published data support the evaluation of VERU-944 to determine the optimal dose for efficacy and safety of a nonsteroidal estrogen to treat hot flashes in men with advanced prostate cancer on ADT.

3.3 Study Rationale

Veru is evaluating cis-clomiphene (zuclomiphene), a nonsteriodal estrogen, as a hormonal therapy for the amelioration of hot flashes in men undergoing ADT for advanced prostate cancer. Cis-clomiphene is one of two geometric isomers of clomiphene, which is approved as Clomid® (clomiphene citrate oral tablets, 50 mg; NDA 016131; Sanofi Aventis US) for the treatment of ovulatory dysfunction in women desiring pregnancy. While trans-clomiphene is anti-estrogenic, cis-clomiphene is an estrogen agonist at pharmacologic concentrations (Turner et al., 1998; Fitzpatrick et al., 1999; Kaminetsky et al., 2013; Section 7.4.1.1). Furthermore, cis-clomiphene has a half-life of 5–7 days (Mikkelson et al., 1986; Mürdter et al., 2012). VERU-944 is expected to be effective and safe in men with prostate cancer undergoing ADT based on the established efficacy of low dose estrogens in the treatment of vasomotor symptoms (hot flashes) and safety of off-label clomiphene use for male infertility.

4.0 STUDY OBJECTIVES

4.1 Primary Objective

To determine an effective dose of VERU-944 (from among 10 mg, 50 mg, and possibly 100 mg PO q day), after a loading dose, for the treatment of vasomotor symptoms commonly known as hot flashes by assessing its effect on:

1. the frequency of moderate to severe hot flashes at week 6
2.

4.2 Secondary Objectives

To assess the effect of VERU-944 on:

1. the severity of moderate to severe hot flashes at week 6
2. the frequency of moderate to severe hot flashes at week 8
3. the frequency of moderate to severe hot flashes at week 10
4. the frequency of moderate to severe hot flashes at week 12
5. the severity of moderate to severe hot flashes at week 8
6. the severity of moderate to severe hot flashes at week 10
7. the severity of moderate to severe hot flashes at week 12
8. the frequency of moderate to severe hot flashes at week 4
9. the severity of moderate to severe hot flashes at week 4
10. bone turnover markers

4.3 Exploratory Objectives

To assess the effect of VERU-944 on:

1. serum PSA concentrations

2. serum total and free testosterone concentrations

3. serum SHBG concentrations

4.4 Safety Objective

To assess the safety and tolerability of VERU-944

5.0 STUDY DESIGN

5.1 Treatment Groups and Allocation of Subjects

This randomized, multicenter, double blind, placebo controlled clinical study consists of three treatment arms along with a placebo arm with approximately thirty (30) subjects enrolled in each of three treatment arms in a 1:1:1 fashion (placebo, 10 and 50 mg) in Stage 1 and

approximately thirty (30) subjects randomized in a 1:1 fashion to each of two treatment arms (placebo and 100 mg) in Stage 2. Each subject will be randomized, and after a four-day daily loading dose, outlined in Section 7.3, will receive either placebo, 10 mg VERU-944 or 50 mg VERU-944 daily in Stage 1 and either placebo or 100 mg VERU-944 daily in Stage 2.

5.2 Study Duration

The study will require that each subject receive a loading dose followed by a daily oral dose of placebo, 10 mg VERU-944, 50 mg VERU-944 or 100 mg VERU-944 for 12 weeks (84 days).

5.3 Efficacy Endpoints

5.3.1 Primary Endpoints

Patients will record frequency and severity of hot flashes using an electronic diary (eDiary) at home to ensure attributable, time stamped data collection in an unsupervised environment. This instrument will be used to assess the:

1. Percentage change in frequency of moderate to severe vasomotor symptoms from baseline to Week 6 (Day 42)

5.3.2 Secondary Endpoints

1. Percentage change in severity of vasomotor symptoms from baseline to Weeks 6 (Day 42)
2. Percentage change in frequency of moderate to severe vasomotor symptoms from baseline to Week 8 (Day 56)
3. Percentage change in frequency of moderate to severe vasomotor symptoms from baseline to Week 10 (Day 70)
4. Percentage change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12 (Day 84)
5. Percentage change in severity of vasomotor symptoms from baseline to Week 8 (Day 56)
6. Percentage change in severity of vasomotor symptoms from baseline to Week 10 (Day 70)
7. Percentage change in severity of vasomotor symptoms from baseline to Week 12 (Day 84)
8. Percentage change in frequency of moderate to severe vasomotor symptoms from baseline to Week 4 (Day 28)
9. Percentage change in severity of vasomotor symptoms from baseline to Week 4 (Day 28)
10. Percentage change in bone turnover marker concentrations at Day 84 compared with baseline

5.3.3 Exploratory Endpoints

1. Percentage change in serum PSA concentrations at Days 30, 60, and 84 compared with baseline

2. Percentage change in serum total and free testosterone concentrations at Days 30, 60, and 84 compared with baseline

3. Percentage change in serum SHBG concentrations at Days 30, 60, and 84 compared with baseline

6.0 SUBJECT POPULATION

6.1 Number of Subjects

Approximately ninety (90) subjects will be enrolled into Stage 1 of the study, with approximately thirty (30) subjects in each of three treatment arms (placebo, 10 and 50 mg). Approximately sixty (60) subjects will be enrolled into Stage 2 of the study, with approximately thirty (30) subjects in each of two treatment arms (placebo and 100 mg).

6.2 Selection Criteria

6.2.1 Inclusion Criteria

Subjects accepted for this study must:

1. Be over 18 years of age
2. Be able to communicate effectively with the study personnel
3. Have histologically confirmed prostate cancer
4. Have been treated with an LHRH agonist or LHRH antagonist for at least the 2 months prior to randomization
5. Be continued on an LHRH agonist or LHRH antagonist throughout this study (must be continuous therapy)
6. Have experienced hot flashes for at least one month prior to study entry
7. Have moderate or severe vasomotor symptoms (hot flashes) (defined as a minimum of 4 moderate to severe hot flashes per day or 12 per week at baseline)
8. ECOG performance status of 0 to 2
9. Be willing to uses electronic data capture for the relevant medical events
    - Must be at least 80% compliant during the screening period (for the 14 contiguous day hot flash assessment that is required during screening)
10. Subjects must agree to use acceptable methods of contraception
    - If their female partners are pregnant or lactating, acceptable methods of contraception from the time of the first administration of study medication until 6 months following administration of the last dose of study medication must be used. Acceptable methods are: Condom used with spermicidal foam/gel/film/cream/suppository. If the subject has undergone surgical sterilization (vasectomy with documentation of azospermia), a condom with spermicidal foam/gel/film/cream/suppository should be used
    - If the male subject's partner could become pregnant, use acceptable methods of contraception from the time of the first administration of study medication until 6 months following administration of the last dose of study medication. Acceptable methods of contraception are as follows: Condom with spermicidal

foam/gel/film/cream/suppository [i.e., barrier method of contraception], surgical sterilization (vasectomy with documentation of azospermia) and a barrier method {condom used with spermicidal foam/gel/film/cream/suppository}, the female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone or subdermal implants and a barrier method (condom used with spermicidal foam/gel/film/cream/suppository)
- If the female partner has undergone documented tubal ligation (female sterilization), a barrier method (condom used with spermicidal foam/gel/film/cream/suppository) should also be used
- If the female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS), a barrier method (condom with spermicidal foam/gel/film/cream/suppository) should also be used

11. Subject is willing to comply with the requirements of the protocol through the end of the study

6.2.2 Exclusion Criteria

Any of the following conditions are cause for exclusion from the study:

1. Have a serum total testosterone concentration > 50 ng/dL at screening
2. Known hypersensitivity or allergy to estrogen or estrogen like drugs
3. Any disease or condition (medical or surgical) which might compromise the hematologic, cardiovascular, endocrine, pulmonary, renal, gastrointestinal, hepatic, or central nervous system; or other conditions that may interfere with the absorption, distribution, metabolism or excretion of study drug, or would place the subject at increased risk
4. Subjects with a personal history of abnormal blood clotting or thrombotic disease, including venous or arterial thrombotic events such as a history of stroke, deep vein thrombosis (DVT), and/or pulmonary embolus (PE)
5. Any subjects, as determined by a central laboratory, that have a:
    - Factor V Leiden gene mutation
    - Prothrombin gene mutation
6. Uncontrolled symptomatic congestive heart failure (NYHA Class III – IV), unstable angina pectoris, cardiac arrhythmia, or uncontrolled atrial fibrillation
7. History of MI in the past 12 months
8. The presence of consistently abnormal laboratory values which are considered clinically significant. In addition, any subject with liver enzymes (ALT or AST) above 2 times the upper limit of normal, total bilirubin above 2 times the upper limit of normal, or serum creatinine above 1.5 times the upper limit of normal will NOT be admitted to the study
9. Received an investigational drug within a period of 90 days prior to enrollment in the study
10. Received the study medication (VERU-944) previously
11. Have previously taken within 3 months prior to screening or are currently taking diethylstilbestrol, other estrogens;

12. Currently taking gabapentin, estrogen, diethylstilbestrol, medroxyprogesterone acetate, clomiphene, selective serotonin reuptake inhibitors (SSRIs), other treatments for hot flashes
13. Recent hospitalization for more than 24 hours (within 30 days of screening)
14. Recent surgery (within 30 days of screening)
15. Have been previously diagnosed or treated for active cancer (other than prostate cancer or non-melanoma skin cancer) within the previous five years
16. Have a BMI >40

17. Have been randomized into Stage 1 of this protocol

7.0 STUDY MEDICATION

7.1 Enrollment and Blinding

Stage 1 of the study will be a randomized (1:1:1) double blind, placebo controlled study with approximately thirty (30) subjects in each of the three treatment arms: Subjects will be randomized (1:1:1) to receive oral doses of placebo, 10 mg VERU-944, or 50 mg VERU-944 daily for 12 weeks.

Stage 2 of the study will be a randomized (1:1) double blind, placebo controlled study with approximately thirty (30) subjects in each of the two treatment arms: Subjects will be randomized (1:1) to receive oral doses of placebo or 100 mg VERU-944 daily for 12 weeks

An emergency code break will be available to the investigator / pharmacist / investigational drug storage manager. This code break option in IWRS may only be disclosed in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break for a patient is opened, the sponsor and CRO will be informed immediately via IWRS notification. The reason for the IWRS unblinding of the subject must be documented on the appropriate eCRF page along with the date and the initials of the person who broke the code.

7.2 Drug Supply

7.2.1 Placebo Capsules

Placebo capsules are formulated with standard pharmaceutical excipients, such as pregelatinized starch and/or lactose monohydrate and will be supplied in a capsule that matches the VERU-944 capsules. The placebo should be stored at room temperature, 15°C to 25°C (59°F to 77°F).

7.2.2 VERU-944 Capsules, 10, 50 and 100 mg

VERU-944 capsules, 10, 50 and 100 mg, are formulated with micronized VERU-944 drug substance and standard pharmaceutical excipients, such as pregelatinized starch and/or lactose monohydrate. The study drug will be supplied in 30-day kits. The study drug should be stored at room temperature, 15°C to 25°C (59°F to 77°F).

7.2.3 Drug Dose Justification

The doses of VERU-944 (cis-clomiphene) selected in this dose finding study are 10, 50 and 100 mg daily. Support for the utilization of these doses results from published studies as well as additional work that the Sponsor has performed.

In mouse studies, 40 mg/kg/day cis-clomiphene for 90 days results in a significant reduction in testicular weight as well as testicular degeneration (Fontenot GK et al., BJUI Int, 117:344-350, 2016). Using the FDA published guidance on conversion from animal studies to humans (FDA, Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers), the 40 mg/kg dose is multiplied by 0.08 resulting in an equivalent human dose of 3.25 mg/kg. For an average weight adult (70 kg) this would correspond to 227 mg. In the same study, at 4 mg/kg/day there were no effects on testicular degeneration but seminal vesicle weights were somewhat reduced. This dose would correspond to a 22.7 mg in humans. From this study, it appears that the efficacious range for cis-clomiphene will be above 22.7 mg with a maximum of 227 mg.

In a study in baboons, administration of 1.5 mg/kg for 12 days resulted in mild reduction of total serum T levels, an estrogenic signal (Fontenot, unpublished 2001). Utilizing the FDA conversion from a baboon to a human dose (multiplication by 0.54), in an average adult, this would correspond to 56.7 mg further supporting our proposed dose range for the Phase 2 study.

In ovariectomized female rats 3 mg/kg cis-clomiphene for 90 days results in the restoration of uterine weight to the pre-ovariectomized state similar to a 0.1 mg/kg dose of estradiol (Turner RT et al., Endo, 139:3712-3720, 1997). A 3 mg/kg dose in rats would correspond to 33.6 mg daily dose in an average human.

When hypogonadal men were treated with 25 mg daily clomiphene citrate for 6 weeks, the median steady state level of cis-clomiphene was 44.0 ng/ml (Helo S et al., BJUI Int 119:171-176, 2017). Assuming that clinically available clomiphene citrate contains 30% cis-clomiphene, that would equate to 7.5 mg daily cis-clomiphene resulting in these steady state levels. Extrapolating the daily doses that will be used in this study, a 10 mg dose will result in steady state level of 59 ng/ml, a 50 mg dose would result in 293 ng/ml and a 100 mg dose would result in 1,173 ng/ml.

In order to determine if these concentration ranges would result in estrogenic activity, in vitro assays were utilized. In a transactivation assay, the effective concentration of cis-clomiphene appears to be in the range of 1.2 μM which correspond to a level 717.6 ng/ml. Based upon the Helo 2017 study, this blood level would be achieved within the dose finding range of 50 mg and 100 mg. In a separate in vitro study utilizing a in a rat hypothalamic cell line they observed an EC_{50} of cis-clomiphene of 100 nM corresponds to a level of 60 ng/ml (Fitzpatrick SL Endo 140:3928-3937, 1999). This concentration is lower than that observed in the Sponsor's study and may reflect, as the authors point out, cell type specific differences.

Low doses of estrogens have been shown to ameliorate vasomotor symptoms (hot flashes) in men who underwent bilateral orchiectomy or on ADT for advanced

prostate cancer. A daily dose of 1 mg diethylstilbestrol (DES) over 12 weeks eliminates the hot flashes in 86% of these men (Atala A et al., Urology, 1992). VERU-944 is 400X less potent of an estrogen as DES based on the transactivation in vitro study, but does have a much longer half-life supporting the selected dose range to evaluate the activity of VERU-944 for the treatment of hot flashes in men who have advanced prostate cancer on ADT.

VERU-944 is intended for daily maintenance dosing following a 4-day loading period. Due to the relatively long half-life of cis-clomiphene, the loading doses were included in the protocol to shorten the time to steady-state cis-clomiphene plasma levels in order to determine whether that dose level will have efficacy at Day 28 to treat hot flashes, the primary endpoint of the proposed study. During the first 4 days of treatment, the subjects will receive a loading dose that is determined by their maintenance dose (10, 50, or 100 mg). On day 1, subjects will take 5 times their maintenance dose at a single time; on days 2–4, subjects will take 3 times their maintenance dose at a single time.

As mentioned above, the rationale for the loading dose is to achieve steady state quickly to meet the Food and Drug Administration (FDA) requirement for the demonstration of efficacy at Day 28 of dosing (FDA Draft Guidance for Industry, 2003: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation). Based upon the published 14.2–33.4 day half-life of cis clomiphene (Szutu et al., 1989), without a loading dose, evaluation of efficacy as reflected by the steady state will not be achieved until after Day 28. Therefore, Veru has developed a dosing regimen for this study that includes loading doses (see Table below).

Cis-clomiphene, as part of the FDA approved product Clomid, has been used in men for off-label acute and chronic indications with limited reported safety observations. However, in an ongoing nonclinical toxicology study of VERU-944 in rats and beagle dogs, preliminary indications are that the dose of VERU-944 required to treat hot flashes in men with prostate cancer on ADT is between 10-50 mg (data on file). Moreover, at a high dose of cis-clomiphene of 20 mg/kg/day (a human equivalent dose of 667 mg in a 60 kg human) in male dogs, dose limiting toxicities have been observed. The dose limiting toxicities that have been observed include elevations in liver function tests (AST, ALT, alkaline phosphatase, GGT, and total bilirubin), weight loss and death. No significant toxicities have been observed in the ongoing study in rats. Due to the preliminary information that suggests a dose of VERU-944 up to 50 mg per day will show efficacy and safety in the proposed indication, Protocol V72203 has been amended so that the 100 mg dose of VERU-944 will not be used until and unless the dose of 50 mg VERU-944 has been shown to not be effective for the proposed indication and an acceptable side effect profile is determined at the blinded placebo, 10 mg and 50 mg doses of VERU-944 in Stage 1.

7.2.4 Drug Accountability

Patients should not take a replacement dose if a dose is missed. Study medication should not be taken more than once a day.

The pharmacists or other site personnel as delegated by the Investigator are responsible for accountability of all used and unused study drug supplies. A study drug dispensing log should be kept current and should contain the dates and quantities of drug dispensed to the subject, the subject's identification (i.e., subject number), the initials of the dispensing persons and the date and quantity of drug returned. Drug accountability and reconciliation should be assessed and performed at each outpatient visit. At the end of the study, a final study drug reconciliation statement will be retrieved by the clinical monitor assigned to the site. Veru Inc., shall be immediately notified of any unexpected occurrences during the dispensing of study drug.

7.3 Drug Administration

Dosing should occur greater than (1) hour before or greater than (1) hour after eating. Subjects will take the entire daily dose at once according to the dosing schedule below. Subjects randomized to the placebo group will receive placebo capsules daily. During the first four days of treatment, the subjects will receive a loading dose representing the dose arm that they have been randomized to. On day one they will take five times their maintenance dose at a single time. On days 2-4 they will take 3 times their maintenance dose at a single time each day. Upon completion of the loading dose (Days 1-4), subjects in the 10 mg VERU-944 dose arm will receive one 10 mg capsule of VERU-944 daily. Subjects in the 50 mg VERU-944 dose arm will receive one 50 mg VERU-944 capsule daily. Subjects in the 100 mg VERU-944 dose arm will receive one 100 mg VERU-944 capsule daily.

Dosing Arm	Day 1	Days 2-4	Days 5-84
Stage 1			
Placebo	(5 capsules)	(3 capsules)	(1 capsule)
10 mg dosing arm	50 mg (5 capsules)	30 mg (3 capsules)	10 mg (1 capsule)
50 mg dosing arm	250 mg (5 capsules)	150 mg (3 capsules)	50 mg (1 capsule)
Stage 2			
Placebo	(5 capsules)	3 (capsules)	(1 capsule)
100 mg dosing arm	500 mg (5 capsules)	300 mg (3 capsules)	100 mg (1 capsule)

Amendment 4 of the protocol is implemented to change the primary endpoint from Week 4 (Day 28) to Week 6 (Day 42) due to the potential for some patients to have a longer T½ of cis-clomiphene up to 32 days. Patients with longer T½ will not reach

steady state within the first 2-3 weeks of dosing, even with the loading dose that is currently used in the protocol. Therefore, to adequately assess the effect of VERU-944 on moderate to severe hot flashes at steady state, Week 6 (Day 42) is being named as the timepoint for the primary efficacy endpoint in this Phase 2 study.

8.0 STUDY PROCEDURES

A summary of clinical laboratory tests (Appendix A) and a flow chart describing study procedures (Appendix B) can be found at the end of this document.

8.1 Clinic Visits

Potential study participants will visit the clinical research facility as needed for screening evaluations in the 28 days prior to enrollment. Subjects will have study related visits at Day 1, Day 30, Day 60, and 84. A follow-up visit will be conducted approximately 30 days after the last dose.

8.2 Screening

Potential subjects will be screened for this study in the 28 days prior to enrollment. The following activities will be conducted at screening:

1. Signed informed consent will be obtained prior to any study-specific procedures and a copy of the signed consent form will be given to the subject.
2. Assess subject eligibility for inclusion into this study based on protocol inclusion/exclusion criteria.
3. Medical history will be obtained, including diagnosis of primary disease (date of diagnosis), clinical stage and Gleason score (individual scores and sum) at diagnosis, presence, date and extent of soft tissue and bone metastases, details and dates of primary treatment, and details and dates of prior therapies for prostate cancer, concurrent illnesses and family history.
4. The use of any medications will be recorded (including radiation). This will include medications currently being taken and those taken within the last 30 days. This will also include the type of androgen deprivation therapy (ADT) utilized and when it was initiated. Over-the-counter (OTC) medications as well as medications taken on an as-needed basis (PRN) should be recorded.
5. Vital signs (temperature/pulse/supine blood pressure)
6. Physical examination including height and weight
7. History of hot flash frequency and severity
8. Thromboembolic risk assessment including: a) Factor V Leiden gene mutation; b) Lupus Anticoagulant assessment and Cardiolipin assessment; c) Prothrombin gene mutation; and Protein C and S.

NOTE: detection of lupus anticoagulant, cardiolipin antibody outside the normal range, prolonged PTT-LA, dRVVT and Protein C and/or Protein S deficiency are not exclusionary from the study. However, if a patient has lupus anticoagulant detected, cardiolipin outside the normal range, a prolonged PTT-LA, a prolonged dRVVT or is deficient for Protein C and/or Protein S, and remains eligible for participation in the study, prophylactic anticoagulation therapy should be considered.

For Protein C or Protein S deficiency, consideration should be given to dietary changes to increase Vitamin K intake.

9. Electrocardiogram- 12 lead (single)

10. Caprini Venothromboembolism (VTE) Risk Assessment

    NOTE: Caprini VTE Risk is not an inclusion/exclusion criteria for the study. It is intended to assess the patient's overall risk for VTE and the change of risk over the course of the study.

11. Clinical Laboratory Tests

    - Hematology (Appendix A)
    - Serum hormones (Appendix A)
    - Serum chemistry (Appendix A)
    - Urinalysis

12. Measurement of frequency and severity of hot flashes utilizing electronic device (values over 14 contiguous days in order to establish a weekly baseline)

    - Must be at least 80% compliant during this assessment. This translates into recording frequency and severity of hot flashes at least 11 of the 14 days.

13. Bilateral Doppler ultrasound of the lower extremity (If the subject is diagnosed with a VTE in this assessment, the subject will not be eligible for the study under the exclusion criterion of history of a VTE).

Patients that have been previously screened for this study and could not complete screening for reasons other than not meeting the inclusion and exclusion criteria, may be rescreened into the study. Laboratory testing conducted under this protocol (Appendix A) within 45 days prior to randomization into this study, may be used as the baseline laboratory values for this study and repeat laboratory testing is not required unless new coadministered medication(s) has been started, unless the investigator determines that retesting is warranted.

Patients that failed screening under previous versions of the protocol due to a positive lupus anticoagulant, but in whom lupus anticoagulant was not "detected" may be rescreened under Amendment 2, Version 7.0 of the protocol.

Patients that failed screening under previous versions of the protocol due to indeterminant cardiolipin antibody, may be rescreened under Amendment 2, Version 7.0 of the protocol.

Patients that failed screening under previous versions of the protocol due a finding related to Protein C or Protein S, including patients that were excluded from participation inappropriately due to elevated levels of Protein S and/or Protein C above the upper limit of normal, may be rescreened under Amendment 2, Version 7.0 of the protocol.

For patients that fall into the three categories outlined above, laboratory testing conducted under this protocol (Appendix A) within 45 days prior to randomization into this study, may be used as the baseline laboratory values for this study and repeat laboratory testing is not required unless new coadministered medication(s) has been started or if the investigator determines that retesting is warranted.

8.3 Enrollment

Subjects will be enrolled from 2 to 5 days prior to the Day 1 visit. Enrollment should be done after the subject has completed the screening assessments and after it has been determined that the subject meets all the inclusion and exclusion criteria.

Assess eligibility status for inclusion into the trial based on protocol inclusion/exclusion criteria, including results from screening lab assessments.

8.4 Day 1 Visit

Subjects should fast for at least 8 hours (overnight) prior to this visit. The Day 1 visit assessments will serve as the baseline assessments.

1. The medical history should be reviewed and updated to include any changes occurring since the screening visit.
2. Assessment of eligibility
3. Vital signs (temperature/pulse/supine blood pressure)
4. Physical examination (including weight)
5. Hematology (Appendix A)
6. Serum chemistry (Appendix A)
7. Urinalysis
8. Serum hormones (Appendix A)
9. Bone turnover markers (Appendix A)
10. Record the usage of any concomitant medications and ongoing treatments.
11. Adverse events (ongoing on Day 1)
12. Caprini VTE Risk Assessment (Appendix D)
13. Blood samples for pharmacokinetic assessment
14. Assess hot flashes

15. Dispense study drug
16. First dose- Instruct the subject to take his capsule at the same time each day

8.5 Day 14 Visit

The following assessments will be conducted on Day 14 (± 3 days):

1. Vital Signs
2. Serum Chemistry – (Appendix A)
3. Record the usage of any concomitant medications and treatments
4. Adverse events

8.6 Day 30 and Day 60 Visit

Subjects should fast for at least 8 hours (overnight) prior to these visits. The following assessments will be conducted on Day 30 (± 7 days) and Day 60 (± 7 days):

1. Vital Signs (temperature/pulse/supine blood pressure)
2. Serum chemistry – (Appendix A)
3. Hematology – (Appendix A)
4. Serum hormones– (Appendix A)
5. Blood samples for pharmacokinetic assessment
6. Record the usage of any concomitant medications and treatments.
7. Assess hot flashes (see Appendix C)
8. Caprini Venothromboembolism Risk Assessment (Appendix D)

- It is important to note that it is expected that the patient population included in this study will have some risk of VTE due to age, presence of a malignancy, and BMI. The purpose of this assessment is a change in risk from baseline. Also, while the questionnaire is designed for the patient to complete, in this study, the Caprini VTE risk assessment should be filled out by study personnel with information from the patient and patient's chart.

  If there is an increase in risk from baseline (Day 1) in this assessment, appropriate preventative actions should be taken. The subject should be consulted about the risk for VTE and actions that would increase their risk further such as long periods of inactivity and surgery. Prophylactic anticoagulation therapy should be considered.

  Prolonged PTT-LA, dRVVT and Protein C and/or Protein S deficiency are not exclusionary from the study. However, if a patient has a prolonged PTT-LA, a prolonged dRVVT or is deficient for Protein C and/or Protein S, and remains eligible for participation in the study, prophylactic anticoagulation therapy should be considered.

For Protein C or Protein S deficiency, consideration should be given to dietary changes to increase Vitamin K intake.

9. Adverse events

10. Collect capsule bottles and perform capsule accountability/compliance assessment

11. Dispense study drug

8.7 Day 84 Visit (End of Study Visit)

Subjects should fast for at least 8 hours (overnight) prior to this visit. The following assessments will be conducted on Day 84 (± 7 days):

1. Vital Signs (temperature/pulse/supine blood pressure)
2. Physical examination (including weight)
3. Serum chemistry (Appendix A) (central laboratory)
4. Hematology (Appendix A) (central laboratory)
5. Serum hormones (Appendix A) (central laboratory)
6. Blood samples for pharmacokinetic assessment
7. Bone turnover markers
8. Record the usage of any concomitant medications and treatments
9. Adverse events
10. Assess hot flashes (see Appendix C)
11. Caprini Venothromboembolism Risk Assessment (Appendix D)

- It is important to note that it is expected that the patient population included in this study will have some risk of VTE due to age, presence of a malignancy, and BMI. The purpose of this assessment is a change in risk from baseline. Also, while the questionnaire is designed for the patient to complete, in this study, the Caprini VTE risk assessment should be filled out by study personnel with information from the patient and patient's chart.

  If there is an increase in risk from baseline (Day 1) in this assessment, appropriate preventative actions should be taken. The subject should be consulted about the risk for VTE and actions that would increase their risk further such as long periods of inactivity and surgery. Prophylactic anticoagulation therapy should be considered.

12. Collect capsule bottles and perform capsule accountability/compliance assessment

8.8 Follow-up Visit

The following assessments will be performed 30 days (± 7 days) after the End of Study visit (Day 84):

1. Vital Signs (temperature/pulse/supine blood pressure)
2. Physical examination (including height and weight)
3. Adverse events

8.9 Pharmacokinetic Sampling

8.9.1 Blood Samples

Samples of venous blood for the determination of trough plasma concentrations of VERU-944 and related metabolites will be obtained on Days 1 (prior to dose), 30, 60 and 84. The sample should be taken prior to dosing with VERU-944 on these days. The time of the last dose of study drug prior to the clinic visit (day before visit) and the time of the blood samples should be carefully recorded.

The blood samples should be collected in a 6 mL K_2EDTA blood collection tube at each collection time.

Immediately after collection, the tubes will be gently inverted several times to mix the anticoagulant with the blood sample. Blood samples may be kept on wet ice (the use of ice packs in a water bath is also acceptable) for up to 20 minutes until processed. The plasma fraction will be separated by placing the collection tube into a centrifuge for 10 minutes at 1,500 x g. The plasma fraction will be withdrawn by pipette and divided into two polypropylene freezing tubes (with each tube receiving approximately equal aliquots). All plasma samples will be placed into a freezer at -20ºC (or below) within 1 hour after collection. (NOTE: A flash freezing in dry ice or liquid nitrogen is NOT required under this protocol but may be used.)

Any remaining plasma samples after completion of the protocol outlined pharmacokinetic analysis may be used to identify and quantify the metabolites of VERU-944 or measure other biomarkers of safety or efficacy.

8.9.2 Plasma Sample Labels

The plasma freezing tube labels will contain the following information:

- Subject Number
- Study Number
- Site Number
- Nominal Day Collection
- Aliquot Number: Aliquot A or B
- Species and Matrix: Human Plasma
- Sample Sequence Number

- Barcode Number

Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing.

All plasma samples will be stored frozen (-20°C or below). Details of the method validation and sample analysis will be included with the final report.

8.10 Rules for Subjects that Become at High Risk for the Development of Venous Thromboembolic Events during the Study

If a subject has any of the events listed below during the study, they are considered to have an increased risk of development of a VTE. The subject should be monitored closely and prophylactic anticoagulation therapy should be used if clinically indicated. These subjects are not required to discontinue the study if these events occur:

1. Surgery
2. Hospitalization
3. Trauma, such as a broken long bone
4. Radiation therapy to prostate for cancer control (radiation to bone to relieve pain is acceptable)
5. Prolonged immobilization

If a subject is expecting to have a prolonged immobilization such as a long car ride or plane ride or sitting at a desk for a long period of time, the subject should be instructed carefully about proper steps to take to prevent VTEs. Specifically, subjects should be instructed to, whenever possible, get up and walk around (at least every two hours) and flex your feet up and down while sitting by alternating raising your toes off the floor while keeping your heels on the floor and then pointing your toes. Subjects should also wear compression stockings if long periods of inactivity are expected.

The Caprini Venothromboembolism Risk Assessment (Appendix E) rules and instructions should be followed. However, it is important to note that it is expected that the patient population included in this study will have some risk of VTE due to age, presence of a malignancy, and BMI. The purpose of this assessment is to monitor for increased risk from baseline. The events listed above will increase the risk of VTEs in these patients.

8.11 Subject Stopping Rules

If, in the opinion of the investigator, the participation in the study is or is becoming detrimental to the well-being of a particular subject, this issue should be discussed with the Medical Monitor for this study and dosing may be discontinued.

Subjects that experience a Grade 3 or greater toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4

(https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) that is deemed to be possible, probably or definitely related to study drug will be discontinued from the study. Prior to discontinuation from the study, the grading of the event and causal relationship should be discussed with the Medical Monitor for the study.

Subjects will be discontinued from dosing if AST or ALT levels are >5 times the upper limit of normal, or if AST or ALT levels are >3 times the upper limit of normal along with a total bilirubin elevation of >2 times the upper limit of normal.

8.12 Early Discontinuation of Study Treatment

A subject will be considered to have completed the trial if they received at least 84 days of treatment with VERU-944 or the study is terminated by the sponsor. Subjects may prematurely discontinue study treatment for any of the following reasons:

1. Consent Withdrawn (specify the reason).
2. Significant and unacceptable adverse event – specify the adverse event leading to discontinuation
3. Investigator decision (specify the reason), must be approved by the Medical Monitor
4. Non-compliance by subject with protocol requirements, must be approved by the Medical Monitor
5. Lost to follow-up (record the date of last contact)
6. Death (specify the following information)
    a. Date of death
    b. Death due to primary disease? Yes or no
    c. Death due to study drug? Yes or no
    d. Death due to adverse event? Yes or no
7. Study terminated by the Sponsor
8. Other reason (specify the reason) should be approved by the Medical Monitor

The reason for discontinuation of study treatment will be documented for each subject. Subjects who discontinue prematurely will not be replaced. If a subject is discontinued from the study, he will be asked to complete all End of Study visit assessments and return all study materials (study medication and electronic device). At the time of discontinuation, please fill out the End of Study case report forms (eCRFs) and subject disposition eCRF pages.

8.13 Adverse Events

An adverse event (AE) is any unfavorable or unintended change in body structure (signs) or body function (symptoms), abnormal laboratory result that is associated with symptoms or requires treatment, or worsening of a pre-existing condition. This includes all such events regardless of the presumed relationship between the event and the study medication(s).

Any AE that occurs after the informed consent is signed but prior to dosing on Day 1 will be captured as part of the medical history and will be documented on the appropriate eCRF. This would include AEs resulting from concurrent illnesses, reactions to concomitant medications or progressive disease states. These AEs will be captured as part of the medical history.

Each subject will be assessed for the development of any adverse events. Adverse events should be assessed at each visit to the clinic. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of the study personnel or spontaneous reports from the subjects.

Any AEs such as complaints, signs, or symptoms that occur during the course of the study or designated follow-up periods will be recorded on the subject's case report form (eCRF). This would include AEs resulting from concurrent illnesses, reactions to concomitant medications, or progressive disease states.

Whenever possible, the AE will be described on the case report form using standard medical terminology consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4 in order to avoid the use of vague, ambiguous or colloquial expressions. The investigator will evaluate all adverse events as to their intensity, relation to test medication, outcome and action taken.

Each AE will be evaluated for duration, intensity, and relationship to (or association with) the study treatment (or other causes). Additionally, the actions taken (e.g., reduction of dosage, discontinuation of study medication, administration of treatment, etc.) and the resulting outcome of the AE will be indicated on the case report form.

Any subject who is withdrawn from the study due to an adverse event will be followed until the outcome of the event is determined, and the investigator will prepare a written summary of the event and document the available follow-up information on the case report form.

8.13.1 Intensity of Adverse Events

The intensity of the AEs will be graded according to CTCAE version 4. For any adverse event that is not specifically covered in CTCAE version 4, the following criteria should be used:

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

If the intensity (Grade) changes within a day, the maximum intensity (Grade) should be recorded. If the intensity (Grade) changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each grade).

8.13.2 Test Medication Causality

The relationship (or association) of each AE to the test medication will be assessed by the investigator according to the following definitions:

Unrelated: There is no chance that the study medication caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event.

Unlikely: There is little chance that the study medication caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event.

Possible: The association of the AE with the study medication is unknown; however, the AE is not clearly due to another condition.

Probable: A reasonable temporal association exists between the AE and treatment administration and, based on the investigator's clinical experience, the association of the AE with the study treatment seems likely.

Definite: The association of the AE with the study medication has a direct relationship.

For the purpose of safety analyses, all AEs which are classified as "Possible," "Probable" or “Definite” will be considered treatment-related events.

8.13.3 Serious Adverse Events

A **serious adverse event (SAE)** is defined as any experience that suggests a significant clinical hazard, contraindication, side effect, or precaution. This includes any event which:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.
- Results in congenital abnormality/birth defect.
- Requires intervention to prevent permanent impairment or damage

An SAE also may include other events, based on medical judgment, which jeopardize the patient or subject and require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE, including death due to any cause, which occurs during the study or within 30 days following cessation of study medication, whether or not related to the study medication, must be reported immediately via telephone (within 24 hours) to Veru Inc. Drug Safety.

In addition, the investigator must immediately complete a Serious Adverse Event eCRF report form and electronically submit the form. The investigator will promptly notify the Institutional Review Board (IRB).

If additional information regarding a previously submitted SAE is obtained, a follow-up SAE eCRF report should be completed and submitted as indicated above. Supporting source documentation should be provided to Worldwide Clinical Trials Drug Safety at the contact information below.

Worldwide Clinical Trials Drug Safety Contact Information:

- Fax number: 1-866-387-5539 or +44 (0) 115 922 0960
- E-mail:
  drugsafety@worldwide.com

Worldwide Clinical Trials Medical Monitor:

Noor Khaskhely, MD, PhD *Sr. Medical Director,* Medical Affairs Worldwide Clinical Trials
Office +1 610 632 8151Mobile +1 919 324 4351
noor.khaskhely@worldwide.com

8.13.4 Initial Reports

SAEs will be collected from the time of first study drug administration through 30 days after receipt of final dose of study drug. SAEs and events of clinical interest must be reported to the Sponsor (or designee) within 24 hours of the knowledge of the occurrence.

In the event an SAE is observed or reported, the SAE report will be completed as thoroughly as possible including all available details about the event and the signature of the Investigator. If the Investigator does not have all information about an SAE, the Investigator will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received.

8.13.5 Precautions

Adverse events should be treated in accordance with standard medical practice. During the course of the study, the overall safety, tolerability and pharmacokinetics of all study treatments will be reviewed by the sponsor and the investigator.

8.13.6 Reporting of Adverse Events Associated with Study Drug Overdose, Misuse, Abuse or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose: Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose

Misuse: Intentional and inappropriate use of study drug not in accordance with the protocol

Abuse: Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error: Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as non-serious on the SAE form and the Adverse Event eCRF.

8.14 Concomitant Medications and Concomitant Therapies

Any medication (including OTC medications) taken by a subject within 30 days prior to the Screening Visit and during the course of the study and the reason for use of the medication will be recorded on the eCRF. Upon entering the study, each subject will be instructed to report the use of any medication (including OTC medications) to the investigator.

Any radiation therapy (linear beam or seeds) taken by the subject within 30 days prior to the Screening Visit and during the course of the study, including type of treatment, and duration of the treatment will be recorded on the eCRF.

8.15 Prohibited Medications

The following medications are prohibited with the appropriate washout period, if any, for each prohibited medication:

- All anabolic steroids and supplements containing anabolic steroids are prohibited from use during the study. This includes, but is not limited to, testosterone and testosterone-like compounds. Use of anabolic steroids and supplements containing anabolic steroids >6 months prior to screening into the study is allowed.
- Medroxyprogesterone acetate is prohibited from use during the study. Use of medroxyprogesterone >6 months prior to screening into the study is allowed.
- Clomiphene (Clomid® or a generic equivalent to Clomid) is prohibited from use during the study. Use of clomiphene >6 months prior to screening into the study is allowed.
- Diethylstilbestrol and estrogen therapy are prohibited from use during the study. Use of diethylstilbestrol and estrogen therapy >6 months prior to screening into the study is allowed.
- Initiation of treatment with selective serotonin reuptake inhibitors not allowed during the study and 6 months prior to the study is not allowed. However, if a patient is on stable sSSRI for >6 months prior to screening and is still qualifies for the study, this is allowed.
- Cytotoxic chemotherapy is prohibited from use during the study.
- Saw Palmetto, Black Cohosh, soy pills and PC-SPES are prohibited from use during the study. However, a washout period of >90 days prior to screening is allowed.
- Gabapentin is prohibited from use during the study. A washout period of >60 days from screening is allowed.
- Other experimental study medications are prohibited from use during the study. A washout of > 90 days prior to screening is allowed.

8.16 Withdrawal of Subjects

a. Any subject found to have entered the study in violation of the protocol will be withdrawn from the study.
b. An effort must be made to determine why any subject discontinues the study prematurely. This information will be recorded on the case report form.
c. All subjects reserve the right to withdraw from the study at any time. The investigator will encourage all subjects who decide to withdraw from the study to complete all evaluations which may be necessary to assure that the subject is free of untoward effects and to seek appropriate follow-up for any continuing problems.
d. Any subjects who develop a clinically significant medical condition, as judged by the investigator, so that the subject no longer meets the inclusion/ exclusion criteria.
e. Any subject who requires the use of an unacceptable concomitant medication will be withdrawn from the study.

The investigator will withdraw any subject from the study if, in the investigator's opinion, it is not in the subject's best interest to continue. No subject that discontinues from the study for any reason will be replaced.

The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the case report form. When a subject fails to return for scheduled study visits, the investigator will make a reasonable effort to contact the subject and determine why the subject failed to return. This information will be documented on the study records. When a subject is withdrawn from the study (regardless of the reason), all evaluations required at the final study visit should be performed.

9.0 STATISTICAL ANALYSIS

9.1 Sample Size Calculation

The proposed trial sample size, n=30 per arm, total N=90 in Stage 1, is based on the mean change in hot flash frequency from baseline to Week 4 (Day 28) (the planned primary endpoint at the time of the original study design). Other assumptions include: one-sided α=0.10; β=0.10 (i.e., power=0.9), equal variances, the variance is equal to the mean of the active arm, and a frequency in at least one treated arm that is 40% less than that of the placebo arm on Week 4 (Day 28). The same assumptions hold for Stage 2 as well with proposed trial sample size of n=30 per arm, N=60 in Stage 2. Total enrollment if both stages are completed will be approximately N=150.

All patients in screening at the time that the 90th patient is randomized into Stage 1 of the study that qualify for the study will be randomized into the study up to a maximum of 120 patients (40 per arm). In Stage 2, all patients in screening at the time the 60th patient is randomized into Stage 2 of the study that qualify for the study will be randomized into the study up to a maximum of 80 patients (40 per arm).

9.2 Populations

Intent-to-Treat (ITT) population: All enrolled subjects who have taken at least one dose of study drug.

Efficacy Evaluable (EE) population: All subjects in the ITT population who have analyzable baseline data and 12 weeks of hot flash data. Subjects must also be at least 80% compliant with taking study drug with no major protocol deviations, including no major inclusion/exclusion deviations.

Efficacy Evaluable Interim Analysis (EEIA) population: All subjects in the ITT population who have analyzable baseline data and 6 weeks of hot flash data. Subjects must also be at least 80% compliant with taking study drug with no major protocol deviations, including no major inclusion/exclusion deviations.

Safety population: All subjects that receive at least one dose of study medication. The safety analyses will be conducted on this population.

9.3 Efficacy Analyses

The primary efficacy analyses will be among the EE (EEIA) population. The comparison of percentage change in frequency from baseline to Week 6 between the placebo arm and each

of the 10 mg and 50 mg dose arms will be of primary interest in Stage 1. In Stage 2, the comparison of percentage change in frequency from baseline to Week 6 between the placebo arm and the 100 mg dose arm will be of primary interest.

Subjects will record events of hot flashes (frequency and severity) utilizing an application on an electronic device (i.e. smartphone). An example of the specific questions asked and definitions of severity are included in Appendix C

9.3.1 Primary Analyses

9.3.1.1 Hot Flash Frequency, Week 6 (Day 42)

Mixed models repeated measures (MMRM) analyses that incorporate, treatment, time, and the treatment*time interactions will be the primary analytical method for the percentage change in the frequency of moderate to severe hot flashes. The percentage change from baseline in frequency of moderate to severe hot flashes in each active arm will be compared to the placebo arm at Week 6 (Day 42). The analysis will be handled in two ways within the MMRM framework: (1) the means analysis comparing the change from baseline to Week 6, and (2) the slope analysis comparing the rate of change from baseline to Week 6.

The primary endpoint in the study will be analyzed when the last patient reaches Day 42. However, the clinical site and patients will remain blinded through the completion of the Day 84 efficacy assessments and the follow up safety visits.

Each subject's hot flash frequency will be summed on a weekly basis. Because the MMRM is the primary analytical method, it will be possible to estimate Week 6 changes from baseline by incorporating the preceding weeks' data, e.g., Week 6 estimates will incorporate data from baseline and Week 1 through Week 6. Analyses will be performed for the EE (EEIA) populations.

If the MMRM model does not converge or has poor fit, T-tests or non-parametric tests, if the data are deemed non-normally distributed, will compare changes over time within (Paired T-test or Wilcoxon sign-rank test) an arm and between (T-test or Wilcoxon rank sum test) each active arm and the placebo arm, respectively.

The Hochberg procedure (Hochberg Y, 1988) will be applied to control for the multiple comparisons associated with the comparisons between the two dose arms and placebo and the two different MMRM analyses (means, slope) in the primary analyses of frequency of hot flashes in Stage 1. The analyses for Stage 2 will be treated similarly to address the multiplicity of the MMRM analyses. Note that the placebo arm in Stage 2 comprises a cohort of subjects distinct from those placebo subjects that were enrolled during Stage 1.

9.3.2 Secondary Analyses

9.3.2.1 Hot Flash Frequency (Weeks 4, 8, 10 and 12) and Severity (Weeks 4, 6, 8, 10, and 12)

Mixed models repeated measures (MMRM) analyses that incorporate, treatment, time, and treatment*time interactions will be the primary analytical method for the percentage change in both the frequency and severity of moderate to severe hot flashes: frequency (severity). The percentage change from baseline in frequency (severity) of moderate to severe hot flashes in each active arm will be compared to the placebo arm at Week 4 (Day 28), Week 8 (Day 56), Week 10 (Day 70), and Week 12 (Day 84). Each analysis will be handled in two ways within the MMRM framework, as described for the primary analysis above.

Each subject's hot flash frequency (severity) will be summed on a weekly basis. Because the MMRM is the primary analytical method, it will be possible to estimate Weeks 4, 8, 10, and 12 changes from baseline by incorporating the preceding weeks' data, e.g., Weeks 4, 8, 10, and 12 estimates will incorporate data from baseline and Week 1 through Weeks 4, 8, 10, and 12. Analyses will be performed for the ITT and PP populations.

If the MMRM model does not converge or has poor fit, T-tests or non-parametric tests, if the data are deemed non-normally distributed, will compare changes over time within (Paired T-test or Wilcoxon sign-rank test) an arm and between (T-test or Wilcoxon rank sum test) each active arm and the placebo arm, respectively.

If the MMRM model does not converge or has poor fit, non-parametric tests will compare changes over time within (Wilcoxon sign-rank test) an arm and between (Wilcoxon rank sum test) active arms and the placebo arm, respectively.

The Hochberg procedure (Hochberg Y, 1988) will be applied to control for the multiple comparisons associated with the comparisons between the two dose arms and placebo and the two different MMRM analyses in the analyses of frequency (severity) of hot flashes for Stage 1. The analyses for Stage 2 will be treated similarly to address the multiplicity of the two MMRM analyses. Note that the placebo arm in Stage 2 comprises a cohort of subjects distinct from those placebo subjects that were enrolled during Stage 1.

The severity of hot flash analysis will be the average severity at baseline of only the moderate and severe hot flashes. The severity of hot flashes analysis at Weeks 4, 6, 8, 10, and 12 will be the average severity of all hot flashes, i.e. mild, moderate, and severe hot flashes.

See the Statistical Analysis Plan for the study for full and complete statistical analyses planned for the study.

9.3.2.2 Bone Turnover Markers

Values at baseline and each scheduled assessment (Day 84) for each treatment group will be assessed. The mean, standard deviation, median, minimum, and maximum values will be summarized at each of these time points. The percentage change from baseline to Day 84 will be summarized as well. This will be done for the ITT population. T-tests or non-parametric tests, if the data are deemed non-normally distributed, will compare changes over time within (Paired T-test or Wilcoxon sign-rank test) an arm and between (T-test or Wilcoxon rank sum test) each active arm and the placebo arm, respectively.

9.3.3 Exploratory Analyses

9.3.3.1 Serum PSA

Values at baseline and each scheduled assessment (Days 30, 60, and 84) in each treatment group will be assessed. The mean, standard deviation, median, minimum, and maximum levels will be summarized at each of these time points. The percentage change from baseline to each time point will be summarized as well. This will be done for the ITT population. T-tests or non-parametric tests, if the data are deemed non-normally distributed, will compare changes over time within (Paired T-test or Wilcoxon sign-rank test) an arm and between (T-test or Wilcoxon rank sum test) each active arm and the placebo arm, respectively.

9.3.3.2 Change in Serum Total and Free Testosterone Concentration

Values at baseline and each scheduled assessment (Days 30, 60, and 84) for each treatment group will be assessed. The mean, standard deviation, median, minimum, and maximum lab values will be summarized at each of these time points. The percentage change from baseline to each time point will be summarized as well. This will be done for the ITT population. T-tests or non-parametric tests, if the data are deemed non-normally distributed, will compare changes over time within (Paired T-test or Wilcoxon sign-rank test) an arm and between (T-test or Wilcoxon rank sum test) each active arm and the placebo arm, respectively.

9.3.3.3 Serum SHBG

Values at baseline and each scheduled assessment (Days 30, 60, and 84) for each treatment group will be assessed. The mean, standard deviation, median, minimum, and maximum lab values will be summarized at each of these time points. The percentage change from baseline to each time point will be summarized as well. This will be done for the ITT population. T-tests or non-parametric tests, if the data are deemed non-normally distributed, will compare changes over time within (Paired T-test or Wilcoxon sign-rank test) an arm and between (T-test or Wilcoxon rank sum test) each active arm and the placebo arm, respectively.

9.3.3.4 Pharmacokinetic Assessments

VERU-944 trough concentrations will be determined in each subject and used to calculate the mean, median, standard deviation, coefficient of variation, maxima and minima within each arm of the trough levels of VERU-944.

9.3.4 Safety Analysis

The frequency of adverse events (AEs) will be tabulated by MedDRA term and system organ class. The incidence of AEs and the maximum intensity and frequency of AEs will be summarized. A new onset AE is defined as an AE that was not present prior to treatment with study medication but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a new-onset AE (regardless of the intensity of the AE when the treatment was initiated).

All laboratory results, vital sign measurements, and other safety variables will be summarized using appropriate descriptive statistics. Changes from baseline will be computed and will be summarized using appropriate descriptive statistics.

9.3.4.1 Data Safety Monitoring Board

There will be no formal Data Monitoring Committee for this study. Safety data, including all SAEs, will be reviewed on an ongoing basis by a Safety Review Team comprised of the Medical Monitor, and representatives of the Sponsor. This Safety Review Team will meet at least monthly. Additional ad hoc meetings will be scheduled if required to evaluate the safety and/or thromboembolic events further.

10.0 ADMINISTRATION PROCEDURES

10.1 Study Conduct and Compliance

The study will be conducted in accordance with the Code of Federal Regulations (21 CFR parts 50, 54, 56, 312, and 314), which originates from the ethical principles laid down in the Declaration of Helsinki. Good Clinical Practices (GCPs) and the policies and procedures of the Sponsor and/or its authorized representative will also be followed. This clinical trial will be overseen and managed by a contract research organization (CRO) and the Sponsor. The CRO will be responsible for data management, data handling, statistical analysis, quality assurance and the final study report. The Sponsor will be responsible for project management of the CRO and clinical monitoring.

Sponsor Emergency Contact Info:

K. Gary Barnette, Ph.D. Chief Scientific Officer Veru Inc. Cell: 919-426-3611

Before initiating a trial, the Investigator/Institution should have written and dated approval/favorable opinion from the Independent Ethics Committee (IEC)/IRB for the trial protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g., advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

10.2 Informed Consent

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the investigational medicinal product (IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The Sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the Sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical trial.

10.3 Protocol Amendments

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- **Non-Substantial Amendments** are those that are not considered 'substantial' (e.g., administrative changes) and as such only need to be notified to the IECs/IRBs or Competent Authorities (CA) for information purposes.

- **Substantial Amendments** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:

  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the trial;
  - the conduct or management of the trial; or
  - the quality or safety of the IMP used in the trial.

  Substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the EU member states, approval or 'favorable opinion' can be assumed if the CA has raised no grounds for non-acceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.

- **Urgent Amendments** are those that require urgent safety measures to protect the trial subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.

10.4 Protocol Deviations

It is the responsibility of the Investigator and Sponsor to ensure compliance with the study protocol. When the protocol is not followed, it can put the safety of study subjects at risk as well as jeopardize the accuracy and reliability of the study results which could lead to a rejection of the data by regulatory authorities.

All identified deviations from the protocol must be documented and reported to the Sponsor using the appropriate electronic form to be supplied by the Sponsor. Deviations will be categorized into minor deviations or major deviations; definitions and examples of deviations will be provided by the Sponsor. The Sponsor will be reviewing all deviations on an ongoing basis.

10.5 Data Handling and Recordkeeping

10.5.1 Data Handling

Data will be recorded at the site on the eCRF and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator or assignee.

Data will be processed using a validated computer system conforming to regulatory requirements.

10.5.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.5.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA (version 18.1 or higher) for medical history and AEs, and
- World Health Organization Drug Dictionary Enhanced (Sept. 2015 or later) for prior and concomitant medications.

10.5.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator in order to be considered complete.

10.5.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drugs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.6 Data Quality

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional

electronic manual queries to be raised to the Investigator by the monitor for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

Clinical site personnel must make themselves available for any potential audit by the Sponsor or Sponsor representative and regulatory authorities, such as, but not limited to, United States Food and Drug Administration. The clinical site personnel must be completely responsive and cooperative during these audits.

10.7 Regulatory Approval

As required by local regulations, the Sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

10.8 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organizations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multicenter studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

10.9 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on structure and contents of clinical study reports. A final clinical study report will be prepared where any subject has signed informed consent, regardless of whether the trial is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

10.10 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital/institution authorized representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments and other activities in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

10.11 Insurance and Indemnity

The Sponsor will obtain Product Liability insurance providing coverage relating to the clinical study and subjects participating therein.

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12.0 APPENDICES

12.1 Appendix A: Clinical Laboratory Tests (central laboratory)

Hematology:	***Urinalysis:***
Hemoglobin	pH
Hematocrit	Specific Gravity
Red Blood Cell Count	Protein
White Blood Cell Count	Glucose
White Blood Cell Differential	Leucocytes
Platelet Count	Nitrates
Reticulocyte Count	Ketones
	Blood
"Serum Hormones"	Microscopic Examination (only if urinalysis results are abnormal)
LH	
FSH	
Total testosterone (LC-MS/MS)	***Serum Chemistry:***
Free testosterone (LC-MS/MS)	Sodium
Sex Hormone Binding Globulin	Potassium
Serum PSA	Chloride
	Bicarbonate
	BUN
Bone turnover markers	Creatinine
C-telopeptide (CTX)	Calcium
Bone specific alkaline phosphatase	Phosphorus
	Total Protein
	Albumin
Thromboembolic Risk Assessment	Total Bilirubin
Factor V Leiden gene mutation	SGOT (ALT)
Antiphospholipid antibodies for Lupus Anticoagulant and Anticardiolipin	SGPT (AST)
	Alkaline phosphatase
Prothrombin gene mutation	LDH
Protein C and S	GGT
	Glucose

12.2 Appendix B: Schedule of Study Evaluations[e]

Day	Screen[a]	Pre-Randomization during screening period	1	14	30	60	84 End of study	Follow-up
Informed Consent	X							
Medical History	X		X					
Assessment of Eligibility *(For Screening visit capture history of hot flashes frequency and severity*	X	X	X					
Physical Exam	X		X				X	X
Vital signs	X		X	X	X	X	X	X
12-lead ECG (single)	X							
Clinical Laboratory Tests								
Hematology	X		X		X	X	X	
Urinalysis	X		X					
Serum Chemistry	X		X	X	X	X	X	
Serum Hormones	X		X		X	X	X	
Blood sample for pharmacokinetic assessment[c]			X		X	X	X	
Bone turnover markers			X				X	
Thromboembolic risk assessment	X							
Bilateral Doppler ultrasound of the lower extremities		X						
Assess hot flashes (electronic diaries)		X	X		X	X	X	
First dose			X					
Dispense study drug			X		X	X		
Collect capsule bottles (even if empty) and perform accountability/compliance assessment [b]					X	X	X	
Assessment of conmeds	X		X	X	X	X	X	
Assessment of AEs			X	X	X	X	X	X
Caprini VTE risk assessment [d]	X		X		X	X	X	

a Screening evaluations to be conducted within 28 days prior to Day 1.
b. Collect capsule bottles (even if empty) and perform accountability/compliance assessment throughout the participation of the subject in the study.
c. The pharmacokinetic blood samples should be done prior to receiving the dose of study drug for that day.
d. It is important to note that it is expected that the patient population included in this study will have some risk of VTE due to age, presence of a malignancy, and BMI. The purpose of this assessment is a change in risk from baseline. Also, while the questionnaire is designed for the patient to complete, in this study, the Caprini VTE risk assessment should be filled out by study personnel with information from the patient and patient's chart.
e. The same schedule of study evaluations will be used in Stage 1 and Stage 2 of this protocol.

11.3 Appendix C: Hot Flash Assessments

Assessments of hot flashes will be made at baseline (14 contiguous days during screening) and daily from Day 1 (first dose) to the end of the study. Patients will record frequency and severity of hot flashes using an electronic diary (eDiary) to ensure attributable, time stamped data collection in an unsupervised environment. When experiencing a hot flash the subject will indicate on the app that they have had a hot flash and then will assign a severity to the hot flash based upon the following scale:

A. **MILD**: sensation of heat without sweating

B. **MODERATE**: sensation of heat with sweating, able to continue activity

C. **SEVERE**: sensation of heat with sweating, causing cessation of activity

The hot flashes will then be compiled to examine the number of hot flashes during the period and their severity.

12.3 Appendix D: Caprini Venous Thromboembolism Risk Factor Assessment

Illinois State Medical Society

Are You at Risk for DVT?

FOR PATIENTS Complete this risk assessment tool to find out.

Name ❑ Male ❑ Female Today's Date

Only your doctor can determine if you are at risk for Deep Vein Thrombosis (DVT), a blood clot that forms in one of the deep veins of your legs. A review of your personal history and current health may determine if you are at risk for developing this condition. Take a moment to complete this form for yourself (or complete it for a loved one). Then be sure to talk with your doctor about your risk for DVT and what you can do to help protect against it. Your doctor may want to keep a copy in your file for future reference.

Directions:

1. Check all statements that apply to you.
2. Enter the number of points for each of your checked statements in the space at right.
3. Add up all points to reach your total DVT Risk Score.

Then, share your completed form with your doctor.

Add 1 point for each of the following statements that apply now or within the past month:

- ❑ Age 41–60 years ____
- ❑ Minor surgery (less than 45 minutes) is planned ____
- ❑ Past major surgery (more than 45 minutes) within the last month ____
- ❑ Visible varicose veins ____
- ❑ A history of Inflammatory Bowel Disease (IBD) (for example, Crohn's disease or ulcerative colitis) ____
- ❑ Swollen legs (current) ____
- ❑ Overweight or obese (Body Mass Index above 25) ____
- ❑ Heart attack ____
- ❑ Congestive heart failure ____
- ❑ Serious infection (for example, pneumonia) ____
- ❑ Lung disease (for example, emphysema or COPD) ____
- ❑ On bed rest or restricted mobility, including a removable leg brace for less than 72 hours ____
- ❑ Other risk factors (1 point each)*** ____

****Additional risk factors not tested in the validation studies but shown in the literature to be associated with thrombosis include BMI above 40, smoking, diabetes requiring insulin, chemotherapy, blood transfusions, and length of surgery over 2 hours.*

For women only: Add 1 point for each of the following statements that apply:

- ❑ Current use of birth control or Hormone Replacement Therapy (HRT) ____
- ❑ Pregnant or had a baby within the last month ____
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (more than 3), premature birth with toxemia or growth restricted infant. ____

Add 2 points for each of the following statements that apply:

- ❑ Age 61–74 years ____
- ❑ Current or past malignancies (excluding skin cancer, but not melanoma) ____
- ❑ Planned major surgery lasting longer than 45 minutes (including laparoscopic and arthroscopic) ____
- ❑ Non-removable plaster cast or mold that has kept you from moving your leg within the last month ____
- ❑ Tube in blood vessel in neck or chest that delivers blood or medicine directly to heart within the last month (also called central venous access, PICC line, or port) ____
- ❑ Confined to a bed for 72 hours or more ____

Add 3 points for each of the following statements that apply:

- ❑ Age 75 or over ____
- ❑ History of blood clots, either Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE) ____
- ❑ Family history of blood clots (thrombosis) ____
- ❑ Personal or family history of positive blood test indicating an increased risk of blood clotting ____

Add 5 points for each of the following statements that apply now or within the past month:

- ❑ Elective hip or knee joint replacement surgery ____
- ❑ Broken hip, pelvis or leg ____
- ❑ Serious trauma (for example, multiple broken bones due to a fall or car accident) ____
- ❑ Spinal cord injury resulting in paralysis ____
- ❑ Experienced a stroke ____

Add up all your points to get your total Caprini DVT Risk Score ____

What does your Caprini DVT Risk Score mean?

- Risk scores may indicate your odds of developing a DVT during major surgery or while being hospitalized for a serious illness.
- Airplane passengers who fly more than five hours may also be at risk for DVT.
- Studies have shown if you have 0-2 risk factors, your DVT risk is small. This risk increases with the presence of more risk factors.
- Please share this information with your doctor who can determine your DVT risk by evaluating all of these factors.

For more information call ISMS at 1-800-782-4767, ext. 1678
www.isms.org

Adapted with permission. Our thanks to ISMS member, J. A. Caprini, MD, associated with NorthShore University HealthSystem
February 2013

PROTOCOL SIGNATURE PAGE

Protocol Number: V72203

Protocol Date: FINAL/ 09 July 2018
AMENDMENT 1 FINAL/ 29 October 2018
AMENDMENT 2 FINAL/17 January 2019
AMENDMENT 3 FINAL/22 February 2019
AMENDMENT 4 FINAL/30 October 2019

Protocol Title:

Randomized, double-blind, placebo controlled, dose finding Phase 2 study comparing oral daily dosing of VERU-944 after a week of loading (daily dosing) with placebo to ameliorate the vasomotor symptoms resulting from androgen deprivation therapy in men with advanced prostate cancer

SIGNATURE:

10/30/2019

Sponsor Date

K.Gary Barnette,PhD Chief Scientific Officer

Name and Title of Sponsor Representative

This signature of the Sponsor Representative constitutes approval of this protocol.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: V72203

Protocol Title: Randomized, double-blind, placebo controlled, dose finding Phase 2 study comparing oral daily dosing of VERU-944 after a week of loading (daily dosing) with placebo to ameliorate the vasomotor symptoms resulting from androgen deprivation therapy in men with advanced prostate cancer

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AMENDMENT 3 FINAL/22 February 2019
AMENDMENT 4 FINAL/30 October 2019

SIGNATURE:

Principal Investigator:	Date

Name of Principal Investigator ***(Please Print)***

Address of Principal Investigator

The signature of the Principal Investigator constitutes approval of this protocol and an assurance that this study will be conducted according to all requirements of this protocol and according to Good Clinical Practices (GCP).