The Protocol
for
Complementary and Alternative Medicine For Urological Symptoms (CAMUS)

A Multi-center Double-blind Clinical Trial of *Serenoa Repens* for Benign Prostate Hyperplasia

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Saw Palmetto
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SCHEMA

TITLE: Complementary and Alternative Medicine for Urological Symptoms (CAMUS).

DESIGN: Randomized, double-blind, two arm trial with equal allocation to *Serenoa Repens* or placebo.

POPULATION: Males ≥45 years old with peak urinary flow rate >4 ml/sec, voided volume >125 ml, AUA symptom score ≥8 and ≤24.

REGIMEN: Participants will be randomized to one of the treatment arms:

- *Serenoa Repens* 320 mg once daily for 24 weeks followed by *Serenoa Repens* 640 mg once daily for 24 weeks followed by *Serenoa Repens* 960 mg once daily for 24 weeks.
- Placebo for 72 weeks.

DURATION: Participants will continue on study treatment until they meet a protocol defined reason for treatment discontinuation or complete 72 weeks of follow-up at the assigned treatment.

SAMPLE SIZE: 350 participants randomized in a 1:1 allocation to *Serenoa Repens* or placebo.

PRIMARY OBJECTIVE: To determine if *Serenoa Repens* reduces the AUA symptom score compared to placebo over 72 weeks of treatment and is well tolerated.

SECONDARY OBJECTIVES:

1. Determine if *Serenoa Repens* has a beneficial effect on subjective global assessment.
2. Assess the impact of *Serenoa Repens* on the following measures over time:
   a. BPH Impact Index
   b. Quality of Life item score from the IPSS
   c. Nocturia item score from the IPSS
   d. Peak uroflow
   e. Post-void residual volume
   f. Prostate Specific Antigen (PSA) level
   g. Erectile and ejaculatory function
   h. ICS*male* Incontinence scale
   i. Jenkins Sleep Dysfunction scale
   j. NIH Chronic Prostatitis Symptom Index
3. Assess the impact of the assigned treatments on complete blood counts and basic blood chemistries.

1.0 INTRODUCTION

1.1 Study Rationale

The long-term efficacy and side effects of over-the-counter phytotherapies for men with lower urinary tract symptoms attributable to BPH are unknown, despite wide use of these agents by older men for maintaining "prostatic health." The overall goal of this study is to compare the efficacy of a widely available phytotherapy, extract of *Serenoa Repens*, against placebo in terms of impact on lower urinary tract symptoms. The phytotherapy selected for study has demonstrated short-term efficacy at relieving lower urinary tract symptoms with minimal side effects in a number of clinical trials. However, a recent NIDDK/NCCAM supported trial of *Serenoa Repens* at the 320 mg daily dose versus placebo did not demonstrate efficacy in terms of symptom reduction over 12 months of follow-up. As a result, this study is being conducted to compare higher-than-standard (double and triple) doses of this agent to determine its short-term effect on lower urinary tract symptoms and other parameters of BPH disease severity, and whether there is sufficient short-term efficacy and tolerability to merit testing for long-term efficacy in a long-term trial focused on the prevention of BPH progression. Because the study arm will use doses of this agent higher than generally used, participants will be monitored closely for toxicity/tolerability and have their doses slowly increased at 24-week intervals.

1.2 Background

Benign prostatic hyperplasia (BPH) is a common cause of morbidity among older men in the United States and other developed countries. Although BPH is actually a histological process with an exact cause that is unknown, this condition confers its morbidity through potentially bothersome lower urinary tract symptoms (LUTS). In addition, men with BPH, and particularly those men with larger prostates as a result of BPH, are at increased risk for complications such as acute urinary retention and may progress to requiring surgical treatment for BPH. In fact, though the availability of effective medical therapy has reduced the need for transurethral resection of the prostate (TURP), the traditional surgical treatment for BPH, 132,000 TURPs were still performed in the U.S. in 2000,

according to the Centers for Disease Control's National Hospital Discharge Survey. Although there is debate about the working epidemiologic definition of symptomatic BPH, there is general agreement that the clinical manifestations of BPH are common. If an American Urological Association (AUA) symptom score of greater than 7 points (moderate to severe lower urinary tract symptoms) and a depressed peak uroflow rate (<15 mL/sec) are considered reflective of clinically important BPH, the condition affects 17% of men age 50-59, 27% of men age 60-69, and 35% of men age 70-79 (Jacobsen, 1995)[1].

Men with bothersome lower urinary tract symptoms of BPH may choose from a spectrum of traditional medical treatments, including two classes of medications, alpha blockers and 5-alpha reductase inhibitors, minimally invasive therapies that generally use heat administered in different ways to damage or destroy prostate tissue, or a variety of surgical therapies, including TURP (AUA Practice Guidelines Committee, 2003).[2] For men with symptoms that are not particularly bothersome at present, medical therapy may be a particularly attractive way to prevent the progression of symptoms, and even avoid future BPH complications, including the need for surgery.

The NIDDK sponsored Medical Treatment of Prostatic Symptoms (MTOPS) trial compared the ability of representatives of the two classes of medication for BPH, alone or in combination, to prevent BPH progression (McConnell, et al, 2003)[3]. In this trial, BPH progression was defined as a confirmed increase in AUA symptom score of 4 or more points, acute urinary retention, incontinence, urinary tract infection or urosepsis, or new renal insufficiency (in reality, almost all the progression events in the trial were in the first two categories). The drugs used were Finasteride, a 5-alpha reductase inhibitor, and doxazosin, an alpha-blocker. Finasteride blocks the conversion of testosterone to dihydrotestosterone, the major intraprostatic androgen, and reduces prostate size. Doxazosin blocks alpha-adrenergic receptors in the lower urinary tract, resulting in a reduction in smooth muscle tone in the prostate and bladder neck. Both of these drugs have been documented to be effective at reducing LUTS in men with a clinical diagnosis of BPH in previous trials (AUA Practice Guideline Committee, 2003)[2]. Combination

therapy with these two drugs over the long-term is an attractive concept, given their different mechanisms of action.

In the MTOPS trial, over a mean follow-up of 4.5 years, Finasteride and doxazosin were equally effective at reducing the rate of BPH progression, while combination therapy was significantly more effective than either agent alone (McConnell, 2003)[3]. The effectiveness profile of the two drugs was different. Doxazosin was more effective than Finasteride at reducing lower urinary tract symptoms, while Finasteride was more effective than doxazosin at reducing the rate of acute urinary retention and progression to surgery (although the latter was not part of the prespecified composite endpoint). Each drug had a side-effect profile similar to what would be expected from previous studies.

Another potentially promising class of medical therapies for the prevention of BPH progression is phytotherapy. Plant extracts are widely used in the United States (where they are sold as dietary supplements) and Europe (where they are often prescription drugs) by men with lower urinary tract symptoms. One of the best studied of these phytotherapies is extract of the fruit of *Serenoa Repens*, the Saw palmetto dwarf palm that grows in the Southeastern U.S.

Saw palmetto preparations of many varieties are widely used in the United States and Europe. The proposed mechanisms of action for Saw palmetto include 5-alpha reductase inhibition, intraprostatic androgen receptor blockage, and adrenergic receptor antagonism as well as an anti-inflammatory effect (Gerber, 2000)[4]. In a 2002 Cochrane meta-analysis of the effectiveness of Saw palmetto extracts for men with BPH, 21 randomized trials of 4 to 48 weeks duration were identified with 3193 subjects. Data from the trials indicated that compared to placebo, Saw palmetto reduced nocturia by 0.76 times per night (10 trials), increased the odds of self-rated improvement 1.76 fold (6 trials), and improved peak flow rates by 1.86 mL/sec (9 trials) (Wilt, 2002)[5]. Adverse effects were mild and infrequent. Methodological problems noted within the trials included lack of use of standardized symptom scores and short study durations. While trials have most

commonly used a dose of 160 mg twice daily, a comparative trial showed similar effectiveness with the more convenient dose of 320 mg once daily (Stepanov, 1999)[6].

The STEP (Saw palmetto Treatment for Enlarged Prostates) study was a randomized, double-blind, placebo-controlled clinical trial of a saw palmetto extract for reducing BPH-related symptoms. Two hundred twenty-five men, aged at least 50 years old with baseline AUASI score ≥8, were randomized to saw palmetto 160 mg BID or a matching placebo (the saw palmetto extract used for this trial was manufactured by Indena and the placebo used was PEG-400). Participants were seen at quarterly intervals over a one-year follow-up period. The primary outcome was change in the AUASI score; secondary endpoints included changes in peak urine flow, post-void residual and detailed safety assessments (Bent, 2005).[7]

Visit and medication adherence during the trial were excellent (97.5% of all study visits were kept and 91.6% of all study medications were returned by the participants). Analysis of the STEP data by mixed-effects models revealed no differences between study groups in changes in any of the primary or secondary endpoints. In particular, the between-group differences in the change scores (calculated as change in active-group scores minus change in placebo-group scores) were small and non-significant for the AUASI (0.04, 95% CI: -0.93 to 1.01), peak urine flow (0.43, 95% CI: -0.52 to 1.38), and post-void residual urine volume (-4.51, 95% CI: -24.44 to 15.42). The quality of the blinding appeared adequate as similar proportions of participants in the active and placebo study groups presumed they were on the active study medication at the end of the trial (40% *vs.* 46%, $p = 0.38$). No toxicity was observed with the saw palmetto extract in terms of serious adverse events, non-serious symptomatic adverse effects, or changes in laboratory parameters.

Extract of *Serenoa Repens* appears to have modest favorable effects on lower urinary tract symptoms and uroflow rates with few side effects. However, the trials documenting both the effectiveness and safety of this agent have many methodological problems, and the mechanisms of their clinical effect remain undefined. It is not clear if the results of

the STEP trial, which contradict the results of previous trials, reflect the play of chance or call into question the efficacy of *Serenoa Repens*, at least at the standard dose. Nonetheless, this agent is widely used, and if it is indeed effective at reducing lower urinary tract symptoms, might be preferred by many men based on the "natural therapy" appeal, its side-effect profile, and its cost, relative to the prescription medications for BPH.

The Saw palmetto product selected for use in CAMUS is produced by Madaus/Rotta-Pharm, and is an ethanol extract of Saw palmetto berries sold in Europe known as Prosta Urgenin. The same product is available in the United States, where it is sold under different brand names. The active ingredients are unknown, but the composition of this extract appears similar to other widely used Saw palmetto extracts, including the most intensively studied hexane extract. The extract method for the CAMUS product differs from the Saw palmetto product tested in the STEP trial, which was produced with a CO_2 extraction process. The CAMUS Saw palmetto product is available in dark-colored gelcaps containing 320 mg of the extract, and the company will provide placebo gelcaps with an identical appearance.

1.3 Study Design

CAMUS is a double-blind, randomized, multi-center trial to determine if *Serenoa Repens* reduces lower urinary tract symptoms compared to placebo. Participants will be randomized equally to one of two treatment arms: extract of *Serenoa Repens* 320 mg once daily for 24 weeks (one gelcap); followed by 640 mg daily for 24 weeks (two gelcaps) followed by 960 mg daily for 24 weeks (three gelcaps) or placebo. To maintain the double blind, all participants will take one gelcap daily for the first 24 weeks, two gelcaps daily during the second 24 weeks and 3 gelcaps daily during the next 24 weeks. Protocol treatment will be discontinued if the participant develops unacceptable toxicity, or meets one of the protocol-defined reasons for treatment discontinuation.

2.0 OBJECTIVES

2.1 Primary objective

- The primary objective of CAMUS is to determine if *Serenoa Repens* reduces the AUA symptom score compared to placebo over 72 weeks of treatment and is well tolerated.

2.2 Secondary Objectives

Secondary objectives of the study are to:

1. Determine if *Serenoa Repens* has a beneficial effect on subjective global assessment.
2. Assess the impact of *Serenoa Repens* on the following measures over time:
    a. BPH Impact Index
    b. Quality of Life item score from the IPSS
    c. Nocturia item score from the IPSS
    d. Peak uroflow
    e. Post-void residual volume
    f. Prostate Specific Antigen (PSA) level
    g. Erectile and ejaculatory function
    h. ICS*male* Incontinence scale
    i. Jenkins Sleep Dysfunction scale
    j. NIH Chronic Prostatitis Symptom Index
3. Assess the impact of the assigned treatments on complete blood counts and basic blood chemistries.

2.3 Subgroups

The primary and secondary outcome measures may vary by subgroups. Subgroup analyses will be conducted based on the following baseline measurements:

1. AUA Symptom Index and BPH Impact Index
2. Peak uroflow
3. Post-void residual volume

4. Prostate Specific Antigen (PSA) level
5. NIH Chronic Prostatitis Symptom Index

For each variable #1 - #4, three ordered categories will be created based on textiles of the respective distributions, and the relationship of the ordered categories to the outcome variables would be examined. For #5, the NIH-CPSI, the score will be dichotomized into two ordered categories, the threshold considered to indicate significant symptoms of chronic prostatitis.

Subgroup analyses of primary and secondary endpoints will be performed for subgroups defined by ethnicity and racial category.

2.4 Substudies

Serum for Banking

As a substudy of the CAMUS trial, participant's serum will be stored on a voluntary basis in the Central Repository of the NIDDK located in Germantown, Maryland. The purpose of this serum bank is to allow future studies specific to BPH progression in this population. Specific ancillary studies will be guided by the study outcomes. No genetic analyses will be performed. Because the samples are stored in the NIDDK Central Repository, investigators unrelated to this trial may eventually have access to these samples in accordance with NIDDK policies.

Serum samples will be obtained from participants after giving proper consent specific for blood storage and maintaining a database for future research. A maximum of 2 samples will be obtained. The first will be obtained at screening visit #1 and the second at the conclusion of the trial (72 week visit).

The participant's health care information will be maintained in an anonymous database maintained by the Data Coordinating Center. It will be provided to the Central Repository after the database has been locked. Both the serum samples and database will

be stripped of all identifiers so that the participant's confidentiality will be maintained. The details of serum banking and confidentiality are located in the Manual of Operations.

Studies using the serum samples will be performed in accordance with NIH Policy.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

To be eligible for the study, potential participants must meet all of the following eligibility criteria:

1. Male at least 45 years of age.
2. Peak urinary flow rate at least 4 ml/sec with a voided volume of at least 125 ml.
3. AUA symptom score ≥ 8 and ≤ 24 at both screening visits.
4. Voluntarily signed informed consent agreement prior to the performance of any study procedures.

3.2 Exclusion Criteria

Potential participants that meet any of the following exclusion criteria will be excluded from the full-scale trial:

1. Any prior invasive intervention for BPH.
2. Phytotherapy for BPH or a 5-alpha reductase inhibitor within 3 months.
3. Alpha blocker within one month.
4. Reported allergic reaction to *Serenoa Repens.*
5. Taken an oral alpha agonist, tricyclic antidepressants, and anticholinergic or cholinergic medication within 4 weeks of the first screening visit, with the following exception: topical anticholinergic eye drops used for glaucoma or inhaled anti-cholinergic used for COPD.
6. Taken an estrogen, androgen, or any drug producing androgen suppression, or anabolic steroids within 3 months.
7. Known clinically significant renal impairment (i.e., creatinine greater than 2.0 mg/dl).

8. ALT (SGPT), AST (SGOT) or GGT value greater than 3 times the upper limit of normal in the clinical center lab at SV1.0; confirmed on a second measurement.
9. Prothrombin time greater than 3 seconds above the upper limit of normal, or more than 3 seconds above the control value in the clinical center at SV1.0; confirmed on a second measurement.
10. ECG reading at the clinical center at SV1.0 or SV2.0 suggesting active ischemia or recent myocardial infarction until appropriate consultation confirms the absence of an acute coronary syndrome.
11. PSA level greater than 10 ng/ml at the first screening visit.
12. Requires the daily use of a pad or device for incontinence, or ICS*male*IS score >14 at screening.
13. Unstable medical condition within the past 3 months.
14. History or current evidence of carcinoma of the prostate, pelvic radiation, urethral stricture, or prior surgery for bladder neck obstruction.
15. Active urinary tract disease or has undergone cystoscopy or biopsy of the prostate within one month prior to the first screening visit or has an imminent need for urologic surgery.
16. Known primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function.
17. Documented bacterial prostatitis within the past year.
18. Two documented independent urinary tract infections of any type in the past year.
19. Known severe bleeding disorder or need for ongoing therapeutic anticoagulation with Coumadin, Heparin, or Plavix.
20. Cancer, which is not considered, cured (except basal cell or squamous cell carcinoma of the skin). Men with a prior diagnosis of cancer are excluded unless the principal investigator at the site considers the individual cured or at low risk of recurrence. In general 5 years from the diagnosis of the cancer should have elapsed without recurrence to be considered cured or at low risk

of recurrence. The exception is for basal cell or squamous cell skin cancers. Men with a history of prostate cancer regardless of curability are not eligible.

21. Unable to follow protocol directions due to organic brain or psychiatric disease.
22. History of alcoholism or any other substance abuse, which, in the opinion of the investigator, would affect compliance with the protocol.
23. Any serious medical condition likely to impede successful completion of the study.
24. New diuretic prescription or change in diuretic dose within the last month.

3.3 Randomization and Stratification

Following a successful screening period, the participant will be officially randomized to one of the two treatment groups:

- *Serenoa Repens*
- Placebo

This study will use a stratified randomization scheme with equal numbers of participants in each treatment group. Stratification will be by clinical center and AUA Symptom Score (8-15; 16-24). Within each stratum, the method of randomly permuted blocks will be used to ensure that an equal number of participants are assigned to each treatment group.

Clinical Centers will randomize participants to treatment groups using a centralized, data-based system. Password protection will be implemented to ensure that only certified clinical center personnel are allowed to randomize patients. At the time of randomization, each participant will be assigned a unique medication kit identification number that will be used throughout the duration of the study.

4.0 TESTS AND OBSERVATION

See Schedule of Evaluations - Appendix I

4.1 Informed Consent

Prior to screening visit #1 (SV1.0), potential participants will undergo pre-screening procedures (e.g., chart review, telephone interview) to identify candidates for screening visits; this pre-screening is identified as SV0.0. If a potential participant is identified during SV0.0, then SV1.0 will be scheduled. During SV1.0, the trial and procedures will be thoroughly explained and the participant will be asked to sign an informed consent form. The informed consent form developed by the Steering Committee will be used as a model (see Appendix III). Each center will develop its own modification of the consent form based on the requirements of its own institutional review board.

4.1.1 Screening Visit #1 (SV1.0)

During Screening Visit #1, after the participant has signed the informed consent document, the participant will undergo the following procedures to determine eligibility:

4.1.1.1 Medical History, including:

- History of urinary retention, gross hematuria and microscopic hematuria
- Prior biopsy of the prostate
- Family history of BPH
- Family history of prostate cancer
- Date of vasectomy, if applicable
- History of sexual dysfunction or incontinence
- History of BPH symptoms
- Demographics and social characteristics

4.1.1.2 Physical Exam, including (could be done at SV2.0)

- Vital signs (pulse rate and blood pressure)
- Height and weight
- Digital rectal examination

4.1.1.3 Assessment of all medications

4.1.1.4 Laboratory Tests

- Prostate Specific Antigen (PSA). The PSA measurements will be determined by a central laboratory. Please refer to the manual of operations, Chapter 7, for specimen collection and shipping instructions.
- Urinalysis, including dipstick. If dipstick is positive (greater than 0) for blood or leukocyte esterase, a specimen will be sent for microscopic analysis.
- Complete blood count (CBC), prothrombin time (PT) and serum chemistry profile: serum creatinine, sodium, potassium, chloride, glucose, bicarbonate, ALT (SGPT), AST (SGOT) and GGT.
- Serum for Banking
- 12-lead electrocardiogram (with a copy of the tracing and interpretation stored in the participant's study record). Can be performed at SV1.0 or SV2.0.

4.1.1.5 Urinary Function:

- Uroflow measurement to include: voiding time, flow time, time to maximum flow, peak flow rate, mean flow rate, voided volume and post void residual (PVR).

4.1.1.6 International Prostate Symptom Score (IPSS). Note: IPSS=AUA Symptom Score plus IPSS Quality of Life question.

4.1.2 Screening Visit #2 (SV2.0)

If the participant successfully satisfies the inclusion/exclusion criteria based on the measurements during SV1.0, he will be scheduled for screening visit #2 (SV2.0). During SV2.0, the following procedures will be performed:

4.1.2.0. Physical Exam, including (could be done at SV1.0)

- Vital signs (pulse rate and blood pressure)
- Height and weight
- Digital rectal examination

4.1.2.1 Uroflow measurement to include: voiding time, flow time, time to maximum flow, peak flow rate, mean flow rate, voided volume and post void residual (PVR).

4.1.2.2 IPSS (this value will be considered the participant's baseline value).

4.1.2.3 BPH Impact Index

4.1.2.4 Bladder Function (this value of the ICS*male*IS will be considered the participant's baseline value).

4.1.2.5 Vital signs (pulse rate and blood pressure).

4.1.2.6 12-lead electrocardiogram (with a copy of the tracing and interpretation stored in the participant's study record). Note: test at SV2.0 if this was not obtained in SV1.0.

The screening process ends with either documentation of participant ineligibility and dismissal or documentation of participant eligibility and randomization.

4.2 Randomization and Baseline Evaluation

Randomization can be combined with screening visit #2 for the participant's convenience.

4.2.1 Eligibility determination and Randomization.

4.2.2 Provision of assigned study medications.

4.2.3 Baseline questionnaires: Jenkins Sleep Dysfunction Scale, Erectile Function, Ejaculatory Function, NIH- Chronic Prostatitis Symptom Index (CPSI).

4.3 Evaluations during Treatment and Follow-Up

4.3.1 Focused physical examination (including height and weight) and digital rectal examination at the 72 week visit.

4.3.2 Medical follow-up to include new diagnoses, treatments, hospitalizations, life events at the 4, 12, 24, 28, 36, 48, 52, 60 and 72 week visits.

4.3.3 Hematology: CBC and PT at the 12, 24, 36, 48, 60 and 72 week visits.

4.3.4 Serum chemistries: serum creatinine sodium, potassium, chloride, bicarbonate, glucose, ALT (SGPT), AST (SGOT) and GGT at the 12, 24, 36, 48, 60 and 72 week visits.

4.3.5 Urinalysis, including dipstick at the 72-week visit. If dipstick is positive (greater than 0) for blood or leukocyte esterase, then a specimen will be sent for microscopic analysis.

4.3.6 PSA at the 24, 48, and 72 week visits. The PSA measurements will be determined by a central laboratory. Please refer to the Manual of Operations for specimen collection and shipping instructions.

4.3.7 Vital signs at the 4, 12, 24, 28, 36, 48, 52, 60 and 72 week visits. (Visits 4, 28 and 52 can be optional phone interviews. A blood pressure monitor will be provided to participants to record blood pressure at home. The participant must agree to give 2 sitting readings to the study personnel.)

4.3.8 Uroflow measurement to include: voiding time, flow time, time to maximum flow, peak flow rate, mean flow rate, voided volume and post void residual at the 12, 24, 36, 48, 60 and 72 week visits.

4.3.9 Bladder Function, IPSS (AUA Symptom Score plus IPSS Quality of Life questions), and BPH Impact Index questionnaires, at the 12, 24, 36, 48, 60 and 72 week visits.

4.3.10 Erectile Function, Ejaculatory Function, NIH-CPSI, Jenkins Sleep Dysfunction Scale and Subjective Global Assessment, and participants' perception about whether they are on active therapy or placebo at the 24, 48, and 72 week visits.

4.3.11 Treatment compliance by pill count and provision of assigned study medication at the 12, 24, 36, 48, 60, and 72 week visits.

4.3.12 Adverse event assessment at the 4, 12, 24, 28, 36, 48, 52, 60, and 72 week visits. .

4.3.13 Assessment of all medications, including over-the-counter medications, at the 4, 12, 24, 28, 36, 48, 52, 60 and 72 week visits, or when and adverse event occurs. (Visits 4, 28, and 52 can be omitted if optional phone interview chosen.)

4.3.14 Serum for banking at SV1.0 and 72 week visit.

4.3.15 12-lead electrocardiogram (with a copy of the tracing and interpretation stored in the participant's study record) at 24, 48 and 72 weeks visit.

Optional phone interview or office visit at 4, 28 and 52 weeks. A participant has the option of either an office visit or phone interview for visits 4, 28 and 52. Medical follow-up, height, weight and medications review will not be required if phone interview for weeks 4, 28 and 52 only. Still assess any AE if necessary (inquiry). All forms required at the visits will have to be completed during the interview. A blood pressure monitoring device will be provided to the participant to satisfy the BP requirement.

4.4 Separation Visit

The last scheduled visit at 72 weeks represents the final collection of data to be included for the primary and secondary analyses. Subjects will stop coded study medications at

that time. In order to provide participants with a summary of their care, disclose their treatment group and provide future treatment recommendations, a Separation Visit has been planned. Since disclosing the treatment group requires breaking the blind, the Separation Visit cannot be scheduled until the database is locked. It is anticipated that database lock will occur approximately 4 to 6 months after the last participant (study-wide) has completed the last scheduled visit, which may be as long as 18 months after the first study participants have their last scheduled visit.

The Separation Visit will be scheduled after the database has been locked and the treatment groups have been made available to the clinical centers.

The Separation Visit will be optional for the participant. At this visit the participant will be provided with:

1. Treatment group.
2. Graphical history of PSA.
3. Graphical history of the AUA Symptom Score.
4. Recommendations for future treatment.
5. Information on obtaining the eventual published results of the trial.
6. An opportunity to ask questions about the trial.

If the participant prefers, the summary can be mailed to him.

5.0 TREATMENT PLAN

5.1 Summary of Treatment Plan

CAMUS participants will receive a study medication or matched placebo (see Section 3.3). All participants will take one gelcap daily for the first 24 weeks, two gelcaps daily in the second 24 weeks and three gelcaps daily in the last 24 weeks. The placebo will be matched for appearance with the therapy.

Serenoa Repens and matching placebo will be supplied as "dark colored" gelcaps in blister packs.

5.2 Retitration and Rechallenge with Study Medications

A participant may experience a symptomatic side effect or other abnormality (e.g., a laboratory abnormality) that either he or the investigator believes may be related to the study medication and require withdrawal. Investigators will consider the possibility of a study medication side effect especially in the event of a new, persistent abnormality in any blood test, particularly one that would have excluded a participant's enrollment at baseline, or in the event of new evidence of myocardial infarction or ischemia on the periodic study EKGs. In these circumstances, it may be prudent to attempt a rechallenge of study medication in order to ascertain more evidence of causality and to better assess severity of the adverse effect. Whether or not to perform a rechallenge is the decision of the site principal investigator; obviously, it would be inadvisable to rechallenge a patient who had a serious reaction with a high likelihood of being related to the study medication.

In the event that there is an interruption of therapy and the participant does not take the study medication for at least 14 days (e.g. due to compliance problems, lost medication, physician stopping drug for mild intolerance or minor adverse event), the participant may be retitrated on the medication.

In the event that the participant experiences a moderate or severe adverse event and it is the physician's medical judgment that the participant should be restarted on the study medication and the physician has contacted the Clinical Review Committee and received approval, the participant may be rechallenged.

Retitration or re-challenge should utilize the same kit of medication that the participant has been using or a new kit for that participant may be issued (contact the Drug Distribution Center to request an additional kit if necessary). The participant should be dosed in the following manner. The participant should start at the lowest dose (1 capsule daily) for at least 1 week (longer if physician/participant desires) and then add 1 capsule per day each week until the previous maximum dose (2 gelcaps/day or 3 gelcaps/day) is

reached or the participant becomes intolerant of the medication. Investigators may suggest that participants spread doses out over the day to increase tolerability. If, in the medical judgment of the physician (as in the case of a severe adverse event or reaction) medication should not be continued, or in the event that a participant does not want to continue the medication, the medication does not have to be restarted.

It should also be noted that, under the principle of intention-to-treat, even if a participant will no longer continue to take his study medication, he should be encouraged to continue his study visits and all data (with the exception of pill counts) should be collected.

The procedure for re-challenge will vary with the specific clinical situation, but should follow the general guidelines below:

1) The date of last study medication use by the participant should be recorded on the study drug administration form. All study medications should be discontinued.
2) The site principal investigator should determine if it is safe to re-challenge the participant. If so, re-challenge should be discussed with the participant.
3) If the participant agrees, he should remain off study medication until all symptoms or abnormalities have stopped (it may be very useful to create a daily diary for the participant to use during this time). The participant should remain off study medication for at least one additional week (to ensure that there is stability in the absence of the symptoms).
4) The participant should be followed closely (at least weekly) for recurrence of the symptoms or abnormalities; he should also be advised to contact study staff if his symptoms recur. Again, it may be useful to continue use of a daily diary for the participant. If symptoms recur after restarting the study medication, the investigator should consider withdrawing the participant permanently from study medication. If the symptoms/abnormalities do not recur, the participant may continue in the study following usual study procedures.

5) NOTE: If, after withdrawing the study medication, the participant's symptoms/abnormalities do not diminish, the investigator may wish to discuss re-challenge with the participant (since the symptoms may have been due to some cause other than the study medication). Careful monitoring of the participant should be observed during this re-challenge period. When assessing the potential causal relationship between the symptom/abnormality and the study medication, remember that the phytotherapy contains many fat-soluble constituents, so that the participant may have detectable tissue levels for several weeks after the medication is discontinued.

If subjects do not redevelop the side effect on re-challenge, they can remain on the final dose for that phase of the study until they have completed 24 total weeks of therapy at that dose, and then be escalated as called for in the protocol, unless they are already at triple dose, in which case they will be at the end of the study.

If on re-challenge, a participant once again develops the same side effect at a higher dose of study medication, but has tolerated a lower dose, he can be dropped back to the lower, tolerable dose for the rest of the study.

5.3 Measures of Compliance

Participants will be instructed to bring their packaged coded medication to each follow-up visit. Capsule counts will be conducted to assess the participant's level of compliance with the treatment regimen. The use of blister packs will greatly facilitate keeping CAMUS study personnel blinded to the treatment assignments of their participants.

Participants will be supplied ample study capsules at each visit and assured that they should have capsules left over at the following visit. Participants will be asked to return their remaining blister-pack cards with remaining capsules at each visit for pill count and compliance check. Participants demonstrating consistently inadequate adherence (>20% of capsules remaining on at least two consecutive visits) will be counseled regarding measures to improve adherence (including regular telephone or mail reminders) and will

have a visit with the site principal investigator or co-investigator, if necessary. If participants miss a dose of their study medication, they will be instructed *not* to take an extra dose the next day.

There are no known serum markers for *Serenoa Repens* that would permit assessment of whether participants in the active or control groups are taking the study medicine obtained from non-study sources. Visit adherence will be monitored carefully. Participants demonstrating frequent missed visits or out-of-window visits will be contacted by the Site Coordinator or PI to discuss barriers to keeping scheduled study visit appointments.

5.4 Packaging of Medications and Supplies *Serenoa Repens* 320 mg capsules and matching placebo will be supplied in blister cards.

A kit will be prepared that will contain enough blister cards to allow for a 12-week supply plus 2 weeks. All blister cards and kits will be labeled in a manner to maintain the blind. The kits will be prepared as per section 5.1 for each of the two treatment assignments.

Each site will be sent an initial supply of kits. Kits will be assigned to participants at randomization. Additional kits will be sent to replace those assigned to participants and for the next visit for randomized participants. Additional kits will be available to be assigned to participants in the event of lost or damaged medication.

Participants will be instructed to take one capsule from the study drug package daily for the first 24 weeks, two capsules from the study drug package daily for the 2nd 24 weeks, and three capsules from the study drug package daily for the last 24 weeks. Participants will be instructed to return all used, partially used and unused blister cards to the study coordinator at the next visit, to allow for compliance counts. Medication returned by participants will be documented in their case report forms. Returned medication once documented may be destroyed on site according to site-specific procedures on file with the Data Coordinating Center.

Kits that expire or kits from participants who are dropped permanently from the study will be disposed of at each clinical site according to site-specific procedures on file with the Data Coordinating Center.

Unmasking of kits should not be necessary but in the event of a medical emergency the site should contact the Data Coordinating Center.

All medication kits will be shipped with an invoice, which should be checked to ensure the shipment is complete and undamaged. Any missing, or incorrect or damaged kits should be documented on the invoice and the Drug Distribution Center contacted immediately. The invoice should be signed by an authorized site representative and returned to the Drug Distribution Center (by Fax or Mail); a copy should be maintained in the site drug inventory record book. All kits assigned to participants should be signed out of the drug accountability records.

5.5 Masking Procedure and Labeling

In order to preserve the double-masking of the trial, only the Data Coordinating Center and the drug distribution center will be unmasked. The Drug Distribution Center will be provided with the randomization sequence and treatment assignment directly by the Data Coordinating Center.

5.6 Unmasking

Treatment assignment may be revealed only for reasons relating to the participant's safety or when critical therapeutic decisions are contingent on knowing the assigned study medication. Except in the most pressing circumstances, a decision to unmask must be submitted to the Steering Committee Chair or Clinical Review Committee Chair and permission in writing must be obtained before unmasking. Withdrawal of a participant from the study is not a sufficient reason to unmask.

If a treatment assignment is unmasked, the DCC will record the following key information at the time of unmasking: participant number and initials, medication kit number, date of unmasking, reason for unmasking, the name of the site investigator who requested unmasking, and the name of the Data Coordinating Center member who revealed the treatment assignment to the site investigator after authorization was received regarding that the blind be broken. This information will be forwarded to the Clinical Review Committee, DSMB and funding agency within 5 business days of unmasking.

5.7 Restrictions on use of Concomitant Medications

5.7.1 Exclusionary Medications

The purposes of defining exclusionary medications are: to protect participant safety by avoiding inappropriate and unsafe use of concomitant medications; and to maintain the integrity of the trial by restricting the use of medications or other agents that may affect the primary outcome measures.

The following medications are not permitted while participating in the trial. The absence of a particular medicine from this list does not imply it is not an exclusionary drug. All concomitant medications that a participant is taking should be checked to determine that the medications are not exclusionary. When there is a doubt, please consult the Physician's Desk Reference (PDR), a pharmacist, or the Chairman of the Clinical Review Committee.

5.7.2 Medications not Permitted:

The following classes of medications may alter lower urinary tract symptoms or function, interfering with study measurements. Participants should be instructed to not take these classes of medications, and to call the study coordinator if they start any new medications (including over-the-counter medications). If they are taking a prohibited over-the-counter medication at the time of a study follow-up visit, they should be instructed to stop the medication. If they are taking

prohibited prescription medication, the prescribing clinician should be contacted to determine if stopping the medication would be unsafe (for example, spironolactone prescribed for congestive heart failure might not be safe to discontinue). In that case, a repeat visit should be scheduled after a two-week "washout" period (four weeks for medications with estrogenic or androgenic effects) to obtain the necessary measurements.

Oral Alpha-agonists (pseudoephedrine and others)

Anti-cholinergics

Anti-depressants with anticholinergic effects

Anti-emetics

Anti-Parkinsonian Agents

Anti-spasmodics

Cholinergics Agents

Agents for Myasthenia Gravis

Estrogen Preparations

Androgens

Anti-Androgens

Anabolic Steroids

5.8 Criteria for Treatment Discontinuation

Participants may discontinue assigned CAMUS therapy before the planned completion of study for the following reasons:

- Noncompliance. Participants who are non-compliant with respect to keeping appointments or completing required tests for the evaluation of treatment safety and efficacy may be discontinued from study treatment voluntarily, or at the discretion of the investigator.
- Voluntary withdrawal. Participants may decline to receive further therapy, or decline any study intervention at any time.

- Investigator discretion. The investigator has the right to discontinue any component of study treatment or procedures that the investigator believes could be harmful to the participant.

CAMUS participants must discontinue their assigned CAMUS therapies pursuant to the following events:

- Diagnosis of prostate cancer
- Diagnosis of bladder cancer
- The need for ongoing therapeutic anti-coagulation with Coumadin, Plavix or Heparin.
- Crossover to any open-label therapy for BPH (including phytotherapies for BPH)
- Crossover to any invasive therapy for BPH
- Unacceptable treatment toxicity
- Death

CAMUS participants who elect to or must stop their assigned study medications will be encouraged to continue scheduled follow-up visits regardless.

5.9 Criteria for Study Discontinuation

All participants should be followed for 72 weeks from the date of randomization, and should be encouraged to undergo all protocol procedures. Participants may withdraw from the study at any time.

6.0 ADVERSE EVENTS REPORTING

This study will utilize the NCI's Common Toxicity Criteria for Adverse Events (CTCAE) v3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html).

6.1 Classification of Adverse Events by Severity and Relationship to Study Drug Administration

- **Adverse Event** – Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease regardless of whether it is considered related

to the study medications (attribution of unrelated, unlikely, possible, probable, or definite).

- **Life-Threatening Adverse Event** – Any adverse event that places the participant, in view of the investigator, at immediate risk of death from the reaction.

- **Serious Adverse Event (SAE)** – Any adverse event occurring that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse experiences when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

- **Hospitalization -** All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE grade 3, 4 or 5 must be reported.

- **Attribution** – The determination of whether an adverse event is related to a study treatment. Attribution categories:

    - Definite – The adverse event *is clearly related* to the study medication.
    - Probable – The adverse event *is likely related* to the study medication.
    - Possible – The adverse event *may be related* to the study medication.
    - Unlikely – The adverse event *is doubtfully related* to the study medication.
    - Unrelated – The adverse event *is clearly NOT related* to the study medication.

6.2 Reporting of Adverse Events

All clinically significant adverse events regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the Case Report Form. Participants withdrawn from the study due to adverse events will be followed by the investigator until the outcome is determined and, when appropriate,

additional written reports and documentation will be provided. All grade 3, 4 and 5 adverse events will be reviewed by the Clinical Review Committee.

All adverse events will be tabulated by treatment arm, severity grade and reported to the CAMUS Data Safety and Monitoring Board. Adverse events will be tabulated by severity grade and reported to the site. It will be the responsibility of the site principal investigator to disclose this information to the site's institutional review board.

6.3 Expedited Adverse Event Reporting

All serious adverse events or unexpected adverse events that are life threatening or fatal regardless of attribution, including death within 30 days of the last dose of study treatment, should be reported to the DCC within 24 hours or by the next business day.

7.0 BPH OUTCOME EVENTS

The following BPH outcome events will be tracked on CAMUS subjects. Although not part of the primary outcome, their occurrence should prompt reconsideration of the advisability of continuing coded study medication.

- Acute urinary retention.
- Recurrent symptomatic urinary tract infections or urosepsis.
- New incontinence or progression of minor incontinence (confirmed on two successive visits).
- Initiation of active, unblinded therapy for BPH, including phytotherapy, alpha-blockers, 5-alpha reductase inhibitors, or any invasive therapy for BPH.

If participants initiate active unblinded therapy for BPH, they must be withdrawn from coded study medication, but should continue scheduled follow-up. If a study participant reports one of the BPH outcome events (either at a regular visit or in between visits) such as an episode of acute retention, a urinary tract infection, or initiation of open-label treatment for BPH, the study coordinator would review his medical records to confirm whether the reported event meets the definition for an outcome event.

Definitions of acute urinary retention, new incontinence or progression of minor incontinence, and recurrent symptomatic urinary tract infections are as follows:

- *Acute urinary retention* is the inability to urinate requiring catheterization. If the participant has an obvious cause of acute retention other than BPH (such as alpha sympathomimetic medications or anesthesia), he should have a trial period of catheter removal. If he is still unable to void, he meets the definition of acute urinary retention.
- *New incontinence* is a new requirement for daily use of a pad or device for incontinence. *Progression of minor incontinence* is an increase of six or more points from SV2.0 on the ICS*male*IS.
- *Recurrent symptomatic urinary tract infection* is two or more symptomatic urinary tract infections documented by positive culture, separated by curative antibiotic therapy, within one year. Curative therapy must be documented by a negative interim culture obtained at least one week after completion of the course of antibiotics. *Urosepsis* is a severe urinary tract infection with the same bacterial pathogen isolated from both the participant's blood and urine.
- *Initiation of active, unblinded therapy for BPH* is defined as the participant knowingly taking a phytotherapy, alpha-blocker, or a 5-alpha reductase inhibitor specifically for BPH for more than 30 days; or undergoing an invasive therapy specifically for BPH. Examples of medications for BPH are provided in Section 5.5. Invasive procedures for BPH include open and transurethral prostatectomy, transurethral electrovaporization, transurethral incision, laser therapy (coagulation, vaporization, or holmium resection), transurethral microwave heat therapy, and transurethral needle ablation (TUNA). If participants begin a BPH medication unknowingly or for another purpose (for example, an alpha-blocker prescribed for hypertension), they can be withdrawn from the medications usually in consultation with the prescribing clinician without being considered to have reached a BPH outcome event. They should be "washed out" before additional study measurements are taken (see Section 5.5). Similarly, participants who take a brief course (up to 30

days) of a BPH medication before they stop should not be considered to have reached a BPH outcome event.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample size estimation

The primary goal of this study is to determine the efficacy and safety profile of treatment with *Serenoa Repens* compared to placebo. The primary end point of the study is change in AUA symptom score from baseline to 72 weeks. The sample size estimate is based on the following assumptions: a difference in the change in the AUA symptom score from baseline to 72 weeks of 2 points between the placebo arm and the phytotherapy arm, a common standard deviation of the AUA symptom score of 6 points, a two-group t- test, a one-sided significance level of 0.05 and a statistical power of 90%. A one-sided statistical test will be used since an improvement in the AUA symptom score with therapy (i.e., efficacy of therapy) is of primary interest. To detect the hypothesized difference in the change in the AUA symptom score, a sample size of 157 participants per arm will be required. Therefore, a total of 314 participants will be required for the study. To allow for a 10% dropout rate over the course of the study, 350 participants will be recruited to the study.

To determine the power for evaluating safety by measuring hematology and serum chemistry levels, it is assumed that the underlying probability of a severe or life-threatening adverse event detected by laboratory results for placebo is < 2.5%. With 157 participants in each treatment arm, the power to detect a severe or life-threatening adverse event that occurs with frequency $\geq$ 10% in the phytotherapy arm at the one-sided 0.05 significance level is 80%.

8.2 Statistical Analysis Plan

8.2.1 Analysis Populations

The primary analysis will be performed on the modified-intent-to-treat (MITT) population. The MITT population includes all randomized participants who meet

major eligibility criteria and who receive at least one dose of study therapy. The intent-to-treat (ITT) population will also be analyzed as a confirmatory measure.

8.2.2 Analyses of the Primary Study Endpoint

The primary endpoint of this study is efficacy as determined by the change in AUA symptom score at 72 weeks. A two-group t-test will be used to compare the phytotherapy arm against placebo. A one-sided significance level of 0.05 will be used.

Mixed models repeated measures analysis will be performed to compare the phytotherapy arm with placebo over time (baseline, 24 weeks, 48 weeks and 72 weeks). This technique will control for intra-patient variation. The final covariance structure to be used in these models will be selected after all of the data have been collected. A significance level of 0.05 will be assumed for these longitudinal comparisons. Regarding multiple comparisons, differences between the two treatment groups with respect to the change in the primary endpoint from baseline to 24 weeks, baseline to 48 weeks, and baseline to 72 weeks will be examined to determine if they are significantly different from zero. If these differences are significantly different from zero, comparisons between specific timepoints (48 weeks versus 24 weeks, 72 weeks versus 48 weeks, and 72 weeks versus 24 weeks) for the primary endpoint will be performed. The Hochberg step-up method will be used for each set of these multiple comparisons. (Hochberg, 1990)[8]

An additional analysis that will be performed using the primary endpoint is a comparison between the phytotherapy and placebo arms with respect to the proportion of participants who achieve at least a 3 point difference (improvement) in the AUA symptom score. These proportions will be compared using Fisher's exact test. A one-sided significance level of 0.05 will be used for this comparison.

8.2.3 Analyses of the Secondary Study Endpoints

Secondary endpoints of this study include the following: subjective global assessment, BPH Impact Index, quality of life measure from the IPSS, nocturia item score from the IPSS, peak uroflow, residual volume, prostate specific antigen (PSA) level, erectile and ejaculatory function, ICS*male* Incontinence scale, Jenkins Sleep Dysfunction scale, and the NIH Chronic Prostatitis Index (pain, urinary, and quality of life impact).

Responses for the four questions on the subjective global assessment form are ordinal with lower values reflecting a better outcome. Responses for each of these questions will be transformed to 0 to 100 with higher scores reflecting better outcomes. A similar transformation will be used for the quality of life and nocturia items from the IPSS.

Since each participant will be on each dose level for 24 weeks, longitudinal analyses will be performed on each of the above measures to compare the phytotherapy arm with the placebo arm while accounting for the changes over time (baseline, 24, 48 and 72 weeks). The primary statistical technique that will be used is mixed models repeated measures analysis (in SAS, PROC MIXED will be used). This technique will control for intra-patient variation. The final covariance structure to be used in these models will be selected after all of the data have been collected. A significance level of 0.05 will be assumed for all longitudinal comparisons. Regarding multiple comparisons, differences between the two treatment groups with respect to the changes in the secondary endpoints from baseline to 24 weeks, baseline to 48 weeks, and baseline to 72 weeks will be examined to determine if they are significantly different from zero. If these differences are significantly different from zero, comparisons between specific timepoints (48 weeks versus 24 weeks, 72 weeks versus 48 weeks, and 72 weeks versus 24 weeks) for the secondary endpoints will be performed. The Hochberg step-up method will be used for each set of these multiple comparisons.

The statistical distributions of all of the above measures will be checked for normality. Appropriate transformations will be considered for any measure appearing to have a distribution that deviates greatly from a normal distribution.

Complete blood counts and serum chemistry measurements will be categorized by severity grade from the NCI Common Toxicity Criteria. For each participant and each time period on a dose level (1-24 weeks = level 1, 25-48 weeks = level 2, 49-72 weeks = level 3), the most severe grade of a laboratory level will be taken. For each dose level and laboratory measure, the proportions of participants who have abnormalities of severity grade 3 or greater will be compared between the phytotherapy and placebo arms using Fisher's exact test. A two-sided 0.05 significance level will be used for these comparisons.

8.2.4 Safety Analysis

Adverse event data will be summarized by treatment arm to capture the proportion of participants reporting at least one episode of a specific adverse event (incidence table), incidence of adverse events causing withdrawal, and incidence of serious adverse events. The total number of episodes for each event reported (frequency table), and the severity and attribution to treatment arm of each episode reported within body system (severity and attribution table), will also be displayed by treatment arm. Listings of adverse events by participants and event will also be provided. Comparisons of incidence of each adverse event between treatment and placebo will be performed using the two-group chi-square test, or Fisher's exact test when the assumptions for the chi-square test are not tenable. A two-sided statistical test with a significance level of 0.05 will be used for these analyses. In addition, 95% confidence intervals will be computed for differences in proportions of adverse events between study arms.

8.2.5 Subgroup Analysis

It is anticipated that the primary and secondary outcomes will be evaluated for racial/ethnic groups. Differences between the phytotherapy and placebo arms will be examined separately for each racial/ethnic group.

8.3 Data Quality Control

8.3.1 Training Workshop and Manual of Operations

The DCC will establish procedures to train and certify personnel at the clinical centers in the procedures and data processing requirements for CAMUS. Prior to recruitment of participants into the trial, a training session will be held for clinical center personnel. This session will cover participant recruitment, adherence to study interventions, phytotherapy distribution, data acquisition, and other study procedures. The DCC will provide additional training on an as-needed basis for clinical center personnel.

A manual of operations will be made available for each clinical site in order to provide detailed information about procedures, specimen collection and shipping, and case report form submission.

8.3.2 Periodic Performance Reports

During the study, the DCC will monitor clinical center performance with respect to accrual, retention, timeliness of data submission and other measures of protocol performance.

8.3.3 Error checking and Resolution

The DCC will run delinquency programs to identify data collection forms that are overdue for a participant. The list of delinquent forms will be provided to each clinical center. Clinical centers are expected to maintain a delinquency rate below a threshold defined by the Steering Committee. Failure to do so may result in action by the Steering Committee or the Executive Committee.

Range checks will be incorporated to prohibit the entry of out-of-range of unacceptable values for a field, and to force the entry of required fields. In addition, the DCC will develop a query program to identify logical, range, and inconsistent data. These data items will be submitted to clinical center personnel for resolution. All changes to the database as a result of these queries will be entered into the database by DCC personnel. The query rate will be determined for each site and monitored throughout the study.

8.4 Data Security and Confidentiality

To maintain confidentiality of participant-related information, participant identification numbers are used in the database to identify patient data. Data backup procedures are performed in accordance with the Data Coordinating Center's normal operating procedures. Incremental backups are performed daily and complete backups are performed every three weeks.

There are few medical risks for participants associated with the DCC since the DCC does not interact with participants, collect samples or prescribe treatments or medical procedures. The potential risks to patients from the DCC are related to breaches in confidentiality or security. All data received at the DCC is identified only by ID number and name acrostic. All data files at the DCC are password-protected. All DCC personnel are instructed on the necessity for maintaining patient confidentiality. All participant data forms received at the DCC will be kept in a locked file cabinet in the DCC space. Discarded paper forms relating to individual participants will be shredded.

8.5 Data Safety and Monitoring Plan

A Data Safety and Monitoring Board, a group of individuals not affiliated with any of the institutions in the cooperative agreement, has been established by the NIDDK. The DSMB will serve as external reviewers and advisors to NIDDK and the Steering Committee. The DSMB will review and approve the protocol with respect to ethical and safety standards. Its primary responsibility will be to monitor participant accrual and

safety. The Chair of the Steering Committee and the NIH Project Officers are *ex officio* members of the DSMB. The DSMB will determine the content and frequency of safety reports it will be review and will periodically review data collected on this study.

It is expected that summaries of accrual, retention, and adverse events will be disseminated to the clinical centers periodically. To maintain the blind, adverse events will be aggregated across treatment arms.

9.0 ETHICAL AND REGULATORY CONSIDERATION

9.1 Informed Consent

The principles of informed consent described in Food and Drug Administration (FDA) regulations (21CFR part 50) must be followed. IRB approval of the protocol and the informed consent form must be given in writing. This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or Ethics Committee responsible for oversight of the study. Written informed consent will be obtained from the participant (or parent or legal guardian of participants who cannot consent for themselves). The participant's assent must also be obtained if he is able to understand the nature, significance and risks associated with the study. The informed consent will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form will be given to the participant.

9.2 Subject Confidentiality

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the phytotherapy sponsor, the CAMUS Data Coordinating Center, or the NIH.

9.3 Inclusion of Minorities

This study is being conducted by the NIH sponsored Complementary and Alternative Medicine in Urological Symptoms (CAMUS) Group. As part of their responsibilities,

each participating site within the CAMUS Group and the CAMUS Group as a whole are required to assure that the participation of minority participants reflects the percentage representation of these populations in their geographic region and, for the CAMUS Group, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

10.0 STUDY ADMINISTRATION

CAMUS is being conducted by a cooperative effort among NIDDK, NCCAM, the Office of Dietary Supplements, Clinical Centers, MADAUS and the Data Coordinating Center. The mechanism of funding is a cooperative agreement from NIH.

10.1 NIH (National Institutes of Health)

NIH will file the IND.

10.2 Clinical Centers

There are 11 clinical centers participating in the cooperative agreement. The Principal Investigators representing the clinical centers have agreed to abide by the study protocol.

10.3 Data Coordinating Center

The Data Coordinating Center is responsible for all aspects of biostatistical design, analysis and data processing of the study. In collaboration with the Steering Committee, the DCC is responsible for preparation and distribution of the protocol, manual of operation and data collection forms. The DCC monitors protocol performance, and generates the interim and final statistical analyses, and works with the Steering Committee members in the preparation of presentations and publications emanating from the study results.

10.4 Committees

10.4.1 Steering Committee

The Steering Committee is the policy and decision making group and will oversee the administrative aspects of the trial. The Steering Committee is comprised of a Principal Investigator from each of the Clinical Centers and the Data Coordinating Center, and the NIDDK, NCCAM, and ODS Project Scientists. The Steering Committee Chairperson is a non-voting member. Representatives of the phytotherapy provider, Madaus, and of the Drug Distribution Center are non-voting members of the Steering Committee.

10.4.2 Executive Committee

The Executive Committee has been appointed to direct day-to-day activities. The Executive Committee includes the Chair of the Steering Committee, the Principal Investigator of the Data Coordinating Center, and the NIDDK, NCCAM, and ODS Project Scientists. The committee will meet by conference call as needed.

10.4.3 Clinical Review Committee

The Clinical Review Committee will review all grade 3, 4 & 5 adverse events, retrospectively adjudicate all primary study endpoints, and consult with investigators on re-titration and re-challenge of study medication. The Chairman of this committee will also respond to queries regarding exclusionary medications.

10.4.4 Recruitment, Retention and Medication Adherence Committee

The Recruitment, Retention and Medication Adherence Committee will develop and disseminate materials for recruitment of subjects to CAMUS, including study brochures and advertisements. This Committee will also monitor participant retention and medication adherence. A special focus of this committee will be recruitment of minority subjects.

10.4.5 Publications Committee

The Publications Committee will review all plans and timetables for study abstracts and manuscripts, and set policies for authorship for study publications.

10.4.6 Protocol Adherence Committee

The Protocol Adherence Committee will be responsible for responding to protocol queries.

11.0 REFERENCES

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APPENDIX I - Schedule of Evaluations (Screening Visit 1 - Week 24)

		Screening Visits					
	PROCEDURE	1	2 (2)	Baseline (2)	Week 4 (7)	Week 12	Week 24
FORM	Informed Consent	X					
CAM01	Eligibility & Randomization			X			
CAM21	Medical History	X					
CAM22	Medical Follow-Up				X	X	X
CAM23/24	Assessment of all medications (1)	X		X	X	X	X
CAM31	Vital Signs	X	X		X	X	X
CAM32	Physical & Digital Rectal Exam	X (8)	X (8)				
CAM41	PSA	X					X
CAM42	Uroflow Measurement	X	X			X	X
CAM45	Hematology: CBC/PT/Serum Chemistries	X				X	X
CAM46	Urinalysis	X					
CAM47	Serum for Banking (3)	X					
CAM48	EKG (6)	X (6)	X (6)				X
CAM51	Study Drug Administration & Compliance					X	X
CAM61	BPH Outcome Events			AS NEEDED			
CAM62	Permanent Discontinuation of CAMUS Study Assessment (5)				X	X	X
CAM71	Jenkins Sleep Dysfunction Scale			X			X
CAM72	Erectile Function			X			X
CAM73	Ejaculatory Function			X			X
CAM74	Bladder Function		X			X	X
CAM75	International Prostate Symptom Score	X	X			X	X
CAM76	BPH Impact Index		X			X	X
CAM77	Subjective Global Assessment						X
CAM78	NIH-Chronic Prostatitis Symptom Index			X			X
CAM79	Participant Treatment Perception Form (4)						X
CAM81	Adverse Events				X	X	X

1. Assessment of all medications, including over-the-counter medications, every 12 weeks, plus every 4, 28, and 52 week and when an endpoint or adverse event occurs.
2. Screening Visit #2 and Baseline visit can be combined for participant's convenience.
3. Serum samples will be collected at Screening Visit #1 and the last scheduled visit.
4. Subject's guess at whether on active agent or placebo at 24, 48, 72 weeks.
5. Only complete if participant goes completely off study.
6. EKG can be taken at Screening Visit #1 or Screening Visit #2.
7. Visit 4, 28 and 52 can be either in office visit or via telephone interview.
8. Physical & DRE can be done at Screening Visit #1 or Screening Visit #2.

APPENDIX I - Schedule of Evaluations (Week 28 - Week 72)

	PROCEDURE	Week 28 (7)	Week 36	Week 48	Week 52 (7)	Week 60	Week 72
FORM	Informed Consent						
CAM01	Eligibility & Randomization						
CAM21	Medical History						
CAM22	Medical Follow-Up	X	X	X	X	X	X
CAM23/24	Assessment of all medications (1)	X	X	X	X	X	X
CAM31	Vital Signs	X	X	X	X	X	X
CAM32	Physical & Digital Rectal Exam						X
CAM41	PSA			X			X
CAM42	Uroflow Measurement		X	X		X	X
CAM45	Hematology: CBC/PT/Serum Chemistries		X	X		X	X
CAM46	Urinalysis						X
CAM47	Serum for Banking (3)						X
CAM48	EKG (6)			X			X
CAM51	Study Drug Administration & Compliance		X	X		X	X
CAM61	BPH Outcome Events	AS NEEDED					
CAM62	Permanent Discontinuation of CAMUS Study Assessment (5)	X	X	X	X	X	X
CAM71	Jenkins Sleep Dysfunction Scale			X			X
CAM72	Erectile Function			X			X
CAM73	Ejaculatory Function			X			X
CAM74	Bladder Function		X	X		X	X
CAM75	International Prostate Symptom Score		X	X		X	X
CAM76	BPH Impact Index		X	X		X	X
CAM77	Subjective Global Assessment			X			X
CAM78	NIH-Chronic Prostatitis Symptom Index			X			X
CAM79	Participant Treatment Perception Form (4)			X			X
CAM81	Adverse Events	X	X	X	X	X	X

1. Assessment of all medications, including over-the-counter medications, every 12 weeks, plus every 4, 28, and 52 week and when an endpoint or adverse event occurs.
2. Screening Visit #2 and Baseline visit can be combined for participant's convenience.
3. Serum samples will be collected at Screening Visit #1 and the last scheduled visit.
4. Subject's guess at whether on active agent or placebo at 24, 48, 72 weeks.
5. Only complete if participant goes completely off study.
6. EKG can be taken at Screening Visit #1 or Screening Visit #2.
7. Visit 4, 28 and 52 can be either in office visit or via telephone interview.
8. Physical & DRE can be done at Screening Visit #1 or Screening Visit #2.

APPENDIX II – List of Investigators

Steering Committee Chairperson

Harvard University	Michael J. Barry, M.D.

Site	**Principal Investigator**
Cornell University	Steven A. Kaplan, M.D.
New York University	Andrew McCullough, M.D.
Northern California Kaiser	Andrew L. Avins, M.D.
Northwestern University	Kevin T. McVary, M.D.
Queen's University	J. Curtis Nickel, M.D.
University of Colorado	E. David Crawford, M.D.
University of Iowa	Karl J. Kreder, M.D.
University of Maryland	Michael J. Naslund, M.D.
University of Texas – Southwestern Medical Center	Claus G. Roehrborn, M.D.
Washington University	Gerald L. Andriole, M.D.
Yale University	Harris E. Foster, Jr., M.D.

Data Coordinating Center

University of Alabama at Birmingham	O. Dale Williams, Ph.D.

Appendix III – Consent Form

Principal Investigator: [Add Site PI Name]

Institution Address:

Office/Scheduling Phone Number:
24 hour Telephone Number:

INFORMED CONSENT FORM *TO* PARTICIPATE AND AUTHORIZATION FOR RESEARCH
Complementary and Alternative Medicine for Urological Symptoms (CAMUS).

This study is sponsored by the National Institute of Diabetes and Digestive and Kidney Disease, National Center for Complementary and Alternative Medicine, Office of Dietary Supplements, National Institutes of Health (NIH). Phytotherapy donated by: Madaus.

PURPOSE OF THE STUDY

You are being asked to participate in this study because you have been diagnosed with a condition known as benign prostatic hyperplasia (known as BPH). As you read further, this consent/authorization form includes information about this study. BPH is a non-cancerous growth of the prostate gland that commonly occurs in men as they grow older. The prostate gland is a male sex organ that is located near the urinary bladder. The prostate is related to urination because the urine passage goes through the middle of the prostate as it leaves the bladder. When BPH occurs, the prostate grows in size and partially blocks the urine passage causing bothersome symptoms such as urinating too frequently, waking up at night to urinate, slow urination or other difficulties urinating.

The primary purpose of this study is to determine if the dietary supplement, *Saw palmetto* (*Serenoa Repens*) (also known as *serenoa sarulata* or *sabal*) reduces the urinary symptoms of BPH as compared to a placebo (inactive substance). *Saw palmetto* (*Serenoa Repens*) belongs to a class of therapies known as dietary supplements. They are plant extracts, but are also known as botanicals, herbal therapies or phytotherapies. They are sometimes called "over-the-counter" because anyone can purchase them from a store without the need for a doctor or prescription. This study is being conducted because despite worldwide use of these agents, the effectiveness and side-effects of these dietary supplements for men with BPH are unclear.

SUBJECT PARTICIPATION

We estimate that a total number of 350 male subjects aged 45 years and older will be enrolled in this study. Because of the nature of this study, there are no minors or females. All participants will be enrolled as outpatients. There are 11 sites participating in this study (10 in the United States and 1 in Canada). Your participation will involve several scheduled visits (an estimated 14 visits), but should not exceed 96 weeks. During the study, your appointments will involve screening, baseline evaluations, and visits thereafter at weeks 4, 12, 24, 28, 36, 48, 52, 60 and 72 weeks. There will be a final scheduled visit for close of study and the study staff may

occasionally request additional visits if necessary. This is a long-term study and it is very important for the study that you participate the entire duration even if you are no longer taking the study medicine. If for any reason you feel you cannot participate for the **entire 72 up to possibly 96 weeks,** you should **NOT** sign this form.

Leave this space for
IRB Stamped Approval

DESCRIPTION OF THE RESEARCH

After the study has been explained to you and you have agreed to participate by signing this consent form (SV1.0), you will undergo pre-screening procedures to see if you meet the study criteria. All of the procedures, including risk(s) are more thoroughly described further in this consent.

You will enter the study by a process called randomization. Randomization is a process whereby you are placed into one of the two treatment groups of this study. Neither you nor your doctor will be able to choose which treatment group. In this study you have an equal chance (1 out of 2 chances) of entering 1 of 2 groups. The 2 groups are: 1) *Saw palmetto (Serenoa Repens)* taken by mouth 320 mg once daily for 24 weeks (one gelcap); followed by 640 mg daily for 24 weeks (two gelcaps); followed by 960 mg daily for 24 weeks (three gelcaps). Or 2) placebo (a placebo is an inactive substance that looks like the active medication but has no good or bad effects) taken by mouth one gelcap daily for 24 weeks; two gelcaps daily during the second 24 weeks; and three gelcaps daily during the next 24 weeks.

Prior to screening visit #1 (SV1.0) – As a potential participant, you will undergo pre-screening procedures (e.g., chart review, telephone interview). This pre-screening is identified as SV0.0. If you are designated as a potential participant during SV0.0, the SV1.0 visit will be scheduled.

Screening Visit #1 (SV1.0)

During Screening Visit #1, after you have signed the informed consent document, you will undergo the following procedures to determine eligibility:

Medical history, including:

- History of urinary retention, gross hematuria and microscopic hematuria
- Prior biopsy of the prostate
- Family history of BPH
- Family history of prostate cancer
- Date of vasectomy, if applicable
- History of sexual dysfunction or incontinence
- History of BPH symptoms
- Demographics and social characteristics

Physical exam, including (can be performed at either screening visit 1 or 2)

- Digital rectal examination
- Vital signs (heart rate and blood pressure)
- Height and weight

Assessment of all current medications – this includes prescribed, as well as over-the-counter.

Laboratory tests, including (Approximately 1-2 teaspoons (5-10cc) of blood will be drawn from your vein).

- Prostate Specific Antigen (PSA). The PSA measurements will be determined by a central laboratory. This test will help determine if you have prostate cancer.
- Urinalysis, including dipstick. If dipstick is positive (greater than 0) for blood or leukocyte esterase, a specimen will be sent for microscopic analysis.
- Complete blood count, prothrombin time and serum chemistry profile: serum creatinine, sodium, potassium, chloride, glucose, bicarbonate, ALT (SGPT), AST (SGOT) and GGT.
- Serum for Banking (Please see explanation further in document).
- Electrocardiogram

(All blood drawn for this study will be shipped in accordance with federal and institutional policies for shipping to a central lab for analysis. The lab will generate reports based on your identification number and use this number for reporting purposes to the Data Coordinating Center).

Urinary Function, including Uroflow measurement to include: voiding time, flow time, time to maximum flow, peak flow rate, mean flow rate, voided volume and post void residual (PVR). This is a routine and painless procedure to find out the way your enlarged prostate changes urine flow. While standing, you will be asked to urinate into a cone-shaped collector which will measure your urine flow.

Post-void residual (PVR). This is a routine and painless study done in the work up of patients with BPH. The amount of urine left in the bladder after you urinate, called the post void residual, is measured by an ultrasound device. An ultrasound scanner is gently pressed on the skin of your lower abdomen while you are lying on your back. This will provide the research staff with a number of how much urine is left in your bladder.

International Prostate Symptom Score (IPSS). These are a set of questions which are standard of care that help the research staff determine how your urinary symptoms relate to your BPH impact.

Screening Visit #2 (SV2.0)

If you successfully satisfy the inclusion/exclusion criteria based on the measurements during SV1.0, you will be scheduled for screening visit #2 (SV2.0). During SV2.0, the following procedures will be performed:

Vital Signs (heart rate and blood pressure)

If a physician is not able to see you for a physical examination at SV1.0, the physical exam and EKG will take place at this visit.

Post void residual (PVR) measurement & Uroflow measurement

IPSS

BPH Impact Index – these are questions about quality of life due to urinary symptoms.

ICS*male* IS – these are questions about bladder function.

The screening process ends with either documentation of participant ineligibility and dismissal or documentation of participant eligibility and randomization.

Randomization and Baseline Evaluation

If participant successfully passes all requirements of SV0.0, SV1.0 and SV2.0, the participant will undergo the following procedures:

Randomization and Provision of assigned study medications.

Baseline questionnaires that assess different aspects of your urinary tract conditions: Jenkins Sleep Dysfunction Scale, Erectile Function, Ejaculatory Function, NIH-Chronic Prostatitis Symptom Index (CPSI).

Study drug administration and compliance.

Evaluations During Treatment And Follow-Up

Listed are the procedures that the participant should expect for the remainder of the study:

Focused physical examination (including height and weight) and digital rectal examination at the 72 week visit.

Medical follow-up to include new diagnoses, treatments, hospitalizations, life events at 4, 12, 24, 28, 36, 48, 52, 60 and 72 week visits.

Hematology: complete blood count and prothrombin time at the 12, 24, 36, 48, 60 and 72 week visits.

Serum chemistries: serum creatinine, sodium, potassium, chloride, bicarbonate, glucose, ALT (SGPT), AST (SGOT) and GGT at the 12, 24, 36, 48, 60 and 72 week visits.

Urinalysis, including dipstick at the 72 week visit. If dipstick is positive (greater than 0) for blood or leukocyte esterase, then a specimen will be sent for microscopic analysis.

PSA at the, 24, 48, and 72 week visits. The PSA measurements will be determined by a central laboratory.

Vital signs at the 4, 12, 24, 28, 36, 48, 52, 60 and 72 week visits.

Visits 4, 28 and 52 only require vital signs and medical history and may be done over the phone.

In order to measure your blood pressure and pulse at these visits you will be given a home blood pressure monitor when you are randomized. You will be given clear written and verbal instructions on how to use the monitor. The clinic nurse will demonstrate use of the device and make sure you have learnt how to use it before you take it home. You do not have to complete visits 4, 28 and 52 by phone. You may come in to the clinic as you have to for all the other visits. You will get the BP monitor in either case and will be able to keep it after the study.

Uroflow measurement to include: voiding time, flow time, time to maximum flow, peak flow rate, mean flow rate, voided volume and post void residual at the 12, 24, 36, 48, 60 and 72 week visits.

Bladder Function, IPSS and BPH Impact Index questionnaires, at the 12, 24, 36, 48, 60 and 72 week visits.

Erectile Function, Ejaculatory Function, NIH-CPSI, Jenkins Sleep Dysfunction Scale and Subjective Global Assessment, and participants' perception about whether they are on active therapy or placebo at the 24, 48, and 72 week visits.

Treatment compliance by pill count and provision of assigned study medication at the 12, 24, 36, 48, 60, and 72 week visits.

Adverse event assessment at the 4, 12, 24, 28, 36, 48, 52, 60, and 72 week visits.

Assessment of all medications, including over-the-counter medications, at the 4, 12, 24, 28, 36, 48, 52, 60, and 72 week visits, or when an adverse event occurs.

Serum for Banking at screening visit 1 and the 72 week visit.

Electrocardiogram at screening visit 1 or 2 and follow up visits 24, 48 and 72 weeks.

Additional Information for the Serum Substudy

As listed above, you are being asked to volunteer to allow additional blood to be drawn at the beginning and ending of this trial. This blood would be obtained at the same time that your blood is being drawn for other study blood tests and therefore would not require you to have an extra needle stick. An additional tablespoon of blood (approximately 30cc) would be taken from you.

As a substudy of the CAMUS trial, participant's serum will be stored on a voluntary basis in the Central Repository of the NIDDK located in Germantown, Maryland. The purpose of this serum bank is to allow future studies specific to BPH in this population. Specific ancillary studies will be guided by the study outcomes. No genetic analyses will be performed. Because the samples are stored in the NIDDK Central Repository, investigators unrelated to this trial may eventually have access to these samples in accordance with NIDDK policies.

Serum samples will be obtained from participants after signing additional consents specific to blood storage and maintaining a database for future research. A maximum of 2 samples will be obtained. The first will be obtained at screening visit #1 (SV1.0) and the second at the conclusion of the trial.

The participant's health care information will be maintained in an anonymous database maintained by the Data Coordinating Center. It will be provided to the Central Repository after the database has been locked. Both the serum samples and database will be stripped of all identifiers so that the participant's confidentiality will be maintained. Studies using the serum samples will be performed in accordance with NIH Policy.

Please circle and initial only one choice

1. I <u>DO</u> agree to the Serum studies. **Patient Initials_____**

OR

2. I <u>DO NOT</u> agree to the Serum studies. **Patient Initials_____**

Not participating in the Serum Sub-study portion of the CAMUS trial does not exempt you from agreeing to participate in the overall Study (CAMUS).

<u>Separation Visit</u>

The last scheduled visit represents the final collection of data. You will stop taking your coded study medications at that time. At this visit, we will provide you with a summary of your care; tell you which treatment group you were assigned to and provide future treatment recommendations. Since disclosing the treatment group requires breaking the blind, the separation visit cannot be scheduled until the database is locked. It is anticipated that database lock will occur approximately 4 to 6 months after the last participant (study-wide) has completed the last scheduled visit, which may be as long as 18-months after the first study subjects have their last scheduled visit. The separation visit will be scheduled after the database has been locked and the treatment groups have been made available to the clinical centers. At this visit you will be provided with: treatment group; graphical history of PSA; graphical history of the AUA Symptom Score; recommendations for future treatment; information on obtaining the eventual published results of the trial; an opportunity to ask questions about the trial. If you prefer, however, the summary can be mailed to you.

ADDITIONAL INFORMATION

This study is also described as a "blinded study". This means that neither you nor your doctor nor the study staff will know which treatment group you have been assigned. As part of this process, the medications have been specially prepared so that neither you nor your doctor nor the study staff can tell which medications are active or inactive. Disguising the medications is a very important process to ensure that the study results are valid. You will not be told which medication you are receiving until the entire study has been completed. After you have been placed in one of the 2 treatment groups, the appropriate study medication will be given to you with instructions how to take it. A medication code exists so that it is known exactly what medication you are really taking. If an emergency occurs and it is necessary for your health to find out what medication you are taking, this information will be given to you or your doctor. It is very unlikely that this information will ever need to be disclosed. It is important for you to know that the study personnel will make the final determination as to whether or not this information will be released. It is also very important that you:

1) Take the medication exactly as you are instructed.
2) Return all of the unused study medication at **EVERY** visit.
3) Report any side effects.
4) Call the study staff if you have any questions or stop taking the medication, and
5) Do **NOT** break open any of the medication gelcaps.

You will be given several appointments the entire length of the study. **It is very important that you keep the appointment schedule. If you cannot keep the appointment schedule, you should NOT sign this form.**

At the end of the study further healthcare options will be discussed. When the study is finished, a summary of your care and any recommendation for your care will be made to you. At this time there are no plans for continued care by the study once it is completed.

A Data Safety Monitoring Board has also been established for this study. This is a group of people who periodically review the progress of the study, check for safety issues and can make important determinations for the study if needed.

COSTS/REIMBURSEMENTS

You will be receiving medical care as a part of this research study. All **study-related costs** associated with your being in this study will be paid by the study. You or your insurance company will not be charged or held responsible for standard **study-related costs**. For any and all medical care that is not required by the study, you or your insurance company will be charged and/or held responsible for these costs. For example, as a result of testing done during the study, additional medical testing or treatment may be recommended for you that are unrelated to the study. It is anticipated that some patients may require prostate surgery for their condition during the course of the study. Such costs are **NOT** study related. Only the actual medications supplied to you by the study are paid by the study. For medical care that is not required by the study, you or your insurance company will be charged or held responsible for those costs. For example, if non-study medications are prescribed for your prostate condition, you or your insurance company will be charged or held responsible for those costs. No reimbursement for time and

travel is available at this time. **If you are uncertain about costs of the study, you should ask the study staff.** If you do not sign this consent form your standard care will not be affected, however, you will not receive treatment as part of this study.

POTENTIAL RISKS AND DISCOMFORTS

It is not expected that patients will have any or few side effects (unwanted effects or health problems). Other side effects may occur which were not seen before however. Side effects are usually temporary and manageable. If you are currently taking medications for your prostate condition you will be asked to discontinue these for several months prior to qualifying for this study. During that time, you may experience worsening of your urinary symptoms or very rarely the inability to urinate. If you feel you cannot discontinue your current medications you should **NOT** sign this consent.

Saw palmetto(Serenoa Repens). The side effects of *Saw palmetto* have not been critically studied, however, those who have used *Saw palmetto* have rarely reported side effects. Please be aware that there could be side-effects from any of these medications that are unknown, although this is unlikely. In reality there are very few side effects reported in saw palmetto studies. While rare, the most mentioned side effects are GI related (diarrhea and nausea).

Rare
GI disturbances (diarrhea and nausea) and urinary tract infection.

Very Rare
Hypertension
Sexual dysfunction (ejaculatory and impotence) have been reported.

If you think you might be or are allergic or had a bad reaction to any over the counter medications for a prostate condition, you should discuss this with the study doctor or staff before joining this study. Also, there are other medications that are not allowed during the study because they either interfere with the study results or may not be safe for you to take with the study medications. In most cases another medication can be used. If no other choice is possible, you will be allowed to take medication that is in the best interest of your health even if this requires discontinuation of the study medication. You should speak with the study doctor or staff if you have questions about medications during the study. You will be asked to keep track of all medications that you take and report this to the study staff. This includes any prescription or over-the-counter medications as well as any dietary supplements you may use. Keeping track of all medication you take may be an inconvenience that you are not used to but it is very important for this study and your safety. You will also be monitored for changes in your prostate condition throughout the study. If your prostate condition should worsen during this study, you should discuss this with your doctor. You may want to discuss an alternate treatment for your prostate condition. Any alternative treatment can be started, but it would more than likely mean stopping the study medication.

It is very important for you to know that even if you receive other treatment for your prostate condition and are no longer taking your study medication, you should continue to keep your

study appointments. This is important for your health and for the study to have meaningful results.

The following are procedures that may cause some discomfort or risk to you:

1. Blood tests. These are standard blood tests and are obtained by using a needle to puncture a small vein in your arm or hand. There is a small risk of bleeding or bruising from the needle puncture. A small amount of pain also occurs with the needle puncture.

2. Post Void Residual Measurement (PVR). This test is used to measure how much urine remains in your bladder after urinating. A probe is placed on the skin over your bladder and sound waves are used to measure the remaining urine volume. There is no discomfort or risk. The procedure takes about 1 minute.

3. Uroflowmetry. This test is used to measure the speed of your urine stream. You simply urinate into a funnel (machine) as you normally would urinate and the machine measures the flow speed. There is no pain or risk with this procedure and your privacy is maintained. The procedure takes about 1 minute.

4. Questionnaires. You will be asked several personal questions during this study, i.e., urinary condition, sexual function, sleep patterns and general quality of life. Please know that all information is kept confidential. You may chose to skip any questions that make you uncomfortable or that you prefer not to answer.

POTENTIAL BENEFITS

This research study includes procedures that may change the treatment you would otherwise receive. We hope knowledge gained will be of benefit to you, as well as others in the future. This research study is designed to select by chance which treatment you will receive, therefore, it is not known if the treatment you will receive will be of benefit to you.

ALTERNATIVES TO PARTICIPATING IN THE STUDY

You should be aware that alternative treatments for BPH exist and that *Saw palmetto* is available to you without participating in this study. You may or may not personally benefit from your participation in this research; however, your participation may provide valuable information to the medical community about the treatments options of BPH. Other alternatives include:

1. Watchful Waiting**.** This is simply monitoring your condition on a regular basis to make sure there is no deterioration in your prostate condition.

2. Behavioral Changes**.** Modifications of your eating and drinking habits as well as changing certain prescription medications (under your physician's direction) can sometimes improve your urinary symptoms.

3. Other Food Supplements/ Health Foods**.** There are many over-the-counter supplements that are used for prostate conditions including those used in this study. They can be

purchased at pharmacies and health food stores. It is not known if any of these supplements are effective for treating BPH.

4. Prescription Medications. In general, 2 classes of medications are used either alone or in combination to treat BPH. The first class is called alpha-blockers. Available alpha-blockers include terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®) or alfuzosin (Uroxatral®). The second class is known as 5 alpha reductase inhibitors and includes finasteride (Proscar®) and dutasteride (Avodart®). These prescription medications are well studied and have been approved by the US Food and Drug Administration for treating BPH.

5. Minimally Invasive Treatments**.** Many different types of minimally invasive procedures exist to treat the symptoms of BPH. The most popular therapies are microwave thermal therapy, radiofrequency ablation and interstitial laser therapy.

6. Prostate Surgery. Surgery is regarded as the most effective method of treating BPH. Generally, surgical procedures are used when medical therapies are ineffective and/or in more severe cases of BPH.

CONFIDENTIALITY

Private information about you that identifies you may be used or shared for the purposes of this research project. This section of the consent/authorization form describes how your information will be used and shared in this research, and the ways in which ***[INSERT INSTITUTION NAME]*** will safeguard your privacy and confidentiality.

If you agree to be in this research program, Dr. ***[PI NAME]*** and ***[HIS/HER]*** study team will ask you to have certain tests. Some of these tests would have been done as part of your regular care. ***[HE/SHE]*** will use these test results both to treat you and to complete this research. The results of these tests will be kept in your medical chart and will be reported to the data-coordinating center at the University of Alabama in Birmingham, Alabama. Results of tests and studies done just for this research study and not as part of your regular care will also be included in your medical record.

Other persons and organizations, including co-investigators, federal and state regulatory agencies, and the Institutional Review Boards overseeing the research may receive your information during the course of this study. Except when required by law, study information shared with persons and organizations outside of ***[INSERT INSTITUTION NAME]*** will not identify you by name, social security number, address, telephone number, or any other direct personal identifier.

When your study information will be disclosed outside of ***[INSERT INSTITUTION NAME]*** as part of the research, the information that can identify you as listed above will be removed and your records will be assigned a unique code number. ***[INSERT INSTITUTION NAME]*** will not disclose the code key, except as required by law.

Confidentiality of Your Medical Records: Your medical records will be kept in accordance with state and federal laws concerning the privacy and confidentiality of medical information. If your participation in this research is for treatment or diagnostic purposes, the facility in which you are treated may ask you to sign a separate informed consent document for specific procedures or treatment, and that informed consent form may be included in the medical record of that facility. The confidentiality of your medical record is also protected by federal privacy regulations, as described below.

Confidentiality of Your Study Information: Your study records include information that identifies you and that is kept in research files. We will try to keep this information confidential, but we cannot guarantee it. However, any identifiable data will not be disclosed if data from this study is published or presented.

Retention of Your Study Information: The study results will be kept in your research record for up to seven years. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at ***[INSERT INSTITUTION NAME]***. Any research information in your medical record will be kept indefinitely.

Your HIPAA Authorization: A new federal regulation, the federal medical Privacy Rule, has taken effect as required by the Health Insurance Portability and Accountability Act (HIPAA). Under the Privacy Rule, in most cases we must seek your written permission to use or disclose identifiable health information about you that we use or create [your "protected health information"] in connection with research involving your treatment or medical records. This permission is called an authorization.

If you sign this form you are giving your authorization for the uses and sharing of your protected health information described below. You have a right to refuse to sign this form. If you do not sign the form you may not be in the research program, but refusing to sign will not affect your health care (or payment for your health care) outside the study. This authorization will not expire unless you withdraw it in writing. You have the right to withdraw your authorization at any time, except to the extent that ***[INSERT INSTITUTION NAME]*** has already relied upon it or must continue to use your information to complete data analysis or to report data for this study. The procedure for revoking your authorization is described below.

By signing this form you authorize the use and disclosure of the following information for this research:
1) Your medical records; 2) your research record; 3) results of your laboratory tests; and, 4) clinical and research observations made during your participation in the research. By signing this form you authorize the following persons and organizations to receive your protected health information for purposes related to this research, included, but not limited to every research site for this study, including this hospital, and each site's research staff and medical staff, i.e., every health care provider who provides services to you in connection with this study, any laboratories and other individuals and organizations that analyze your health information in connection with this study in accordance with the study's protocol, the following research sponsors and the people and companies they use to oversee, administer, or conduct the research: National

Institutes of Health, Madaus, the United States research regulatory agencies and other foreign regulatory agencies, the members and staff of the hospital's affiliated Institutional Review Board, the members and staff of the hospital's affiliated Privacy Board, the Principal Investigators and Co-principal Investigators, study coordinators, members of the research team, the Patient Advocate or Research Ombudsman (GCRC), members of the ***[INSERT INSTITUTION NAME]*** Clinical Trials Office/Office of Research and Sponsored Programs, contract research organization, and the data Safety Monitoring Board/Clinical Events Committee.

If any of the companies or institutions listed above merges or is sold during the course of this research, your authorization will cover uses and disclosures of your protected health information to the new company or institution that assumes responsibility for the research. Please be aware that once your protected health information is disclosed to a person or organization that is not covered by the federal medical Privacy Rule, the information is no longer protected by the Privacy Rule and may be subject to redisclosure by the recipient.

COMPENSATION/TREATMENT IN THE EVENT OF INJURY

All forms of medical (or mental health) diagnosis and treatment – whether routine or experimental – could involve some risk of injury. In addition, there may be risks associated with this study that we do not know about. In spite of all precautions, you might develop medical complications from being in this study. If you sustain any injury during the course of the research or experience adverse reactions to a study drug or procedure, please contact ***[PRINCIPAL INVESTIGATOR'S NAME]*** at the following telephone number ***[INSERT CONTACT INFORMATION HERE].*** If such complications arise, the study doctor will assist you in obtaining appropriate medical treatment but this study does not provide financial assistance for medical or other injury-related costs. You do not give up any rights to seek payment for personal injury by signing this form.

VOLUNTARY PARTICIPATION AND AUTHORIZATION

Your decision as to whether or not to take part in this study is completely voluntary. If you decide not to take part in this study it will not affect the standard care you receive and will not result in any loss of benefits to which you are otherwise entitled. Your decision as to whether to give your authorization for the use and disclosure of your protected health information for this study is also completely voluntary; however, if you decline or withdraw your authorization you may not participate in the study.

WITHDRAWAL FROM THE STUDY AND/OR WITHDRAWAL OF AUTHORIZATION

If you decide to take part in the study, you may withdraw from participation at any time without penalty or loss of benefits to which you would otherwise be entitled. You may also withdraw your authorization for us to use or disclose your protected health information for the study. If you do decide to withdraw your consent, we ask that you contact Dr. ***[PI NAME*]** in writing and let ***[Him/Her*]** know that you are withdrawing from the study. The mailing address is ***[ADDRESS].*** If you wish to withdraw your authorization as well as your consent to be in the study, you must contact Dr. **XXXXXX** in writing. ***[INCLUDE THE PI'S NAME AND FULL MAILING ADDRESS.]*** Remember that withdrawing your authorization only affects uses and

sharing of information after your written request has been received, and you may not withdraw your authorization for uses or disclosures that we have previously made or must continue to make to complete analyses or report data from the research. The Principal Investigator or another member of the study team will discuss with you any considerations involved in discontinuing your participation in the study. You will be told how to withdraw from the study and may be asked to return for a final check-up.

The study doctor may also decide to withdraw you from the study for certain reasons. Some possible reasons for withdrawing you from the study would be worsening health or other conditions that might make it harmful for you to continue in the study. Other reasons include: 1) Failure to keep appointments, follow directions or take medications as instructed; 2) a serious adverse reaction to drug therapy; and/or, 3) termination or cancellation of the study by study sponsor.

PERMISSION TO CONTACT YOU ABOUT FUTURE RESEARCH

I authorize the principal investigator and his or her co-investigators to contact me about future research within the ***[INSERT DEPARTMENT, DIVISION, OR CENTER]*** provided that this future research is approved by the original IRB of record and that the principal investigator and co-investigator are affiliated with the research protocol. If I agree, then someone from ***[PI's NAME]*** research staff might contact me in the future and he or she will tell me about a research study. At that time, I can decide whether or not I am interested in participating in a particular study. I will then have the opportunity to contact the researcher to schedule an appointment to be fully informed about the research project.

Please check one:

☐ I **agree** to be contacted by the Principal Investigator or Co-Investigators for future research.

or

☐ I **do not** want to be contacted by the Principal Investigator or Co-Investigator of future research studies.

Signature of participant or legal representative Date

Your permission to allow us to contact you about future research would be greatly appreciated, but it is completely voluntary. If you choose not to allow us to contact you, it will not affect your care at any of the ***[INSERT INSTITUTION NAME]*** facilities. Please understand that giving your permission to do this is only for the purpose of helping us identify subjects who may qualify for one of our future research studies. It does not mean that you must join in any study.

CONTACT PERSON(S)

For further information about your rights as a research subject, or if you are not satisfied with the manner in which this study is being conducted and would like to discuss your participation with an institutional representative who is not part of this study, please contact the Administrator, Institutional Board of Research Associates, Telephone No. ***[INSERT NUMBER HERE]*** If you have any questions or sustain any injury during the course of the research or experience any adverse reaction to a study drug or procedure, please contact the Principal Investigator ***[PI NAME]*** at the following telephone number ***[INSERT NUMBER HERE].***

AGREEMENT TO PARTICIPATE AND AUTHORIZATION FOR THE USE OR DISCLOSURE OF PROTECTED HEALTH INFORMATION: Part of the consent process includes your Authorization to use Protected Health Information for the purposes of this study, as described above. If you do not want to authorize the use of this PHI, you should not agree to be in this study.

Please check one:
☐ I have read this consent form,

OR

☐ It was read to me by: _____.
Any questions I had were answered by: _____.

Please check one: I ☐ am ☐ am not participating in another research project at this time. I voluntarily agree to participate in this research program at: ***[INSERT YOUR INSTITUTION AND APPROPRIATE LOCATIONS].*** I understand that I am entitled to and will be given a copy of this signed Consent/Authorization Form.

By signing this Consent/Authorization form, I give my authorization for the uses and disclosures of my protected health information as described above. You do not have to participate in this study to receive ongoing care for your condition. You are free to choose not to participate in the study.

_____	_____	_____
Print Name of Participant or Legal Representative*	Signature of Participant or Legal Representative*	Date
_____	_____	_____
Print Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

** When the elements of informed consent are presented orally to the subject or representative, a witness to the oral presentation is required.

_____	_____	_____
Print Name of Witness**	Signature of Witness**	Date