

NCI Protocol #: WFU 08 08 09

WFU Protocol #: CCCWFU 98110

IND #: N/A

A Randomized Phase II Dose Finding Study of ArginMax for Its Effect on Erectile Function and Quality of Life in Survivors of Prostate Cancer Previously Treated with Radiotherapy

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Protocol Version Date: September 15, 2010

Approval Dates: **PRC:** 01/26/2010 **NCI:** 03/26/2010
FDA: **IRB:** 09/29/2010

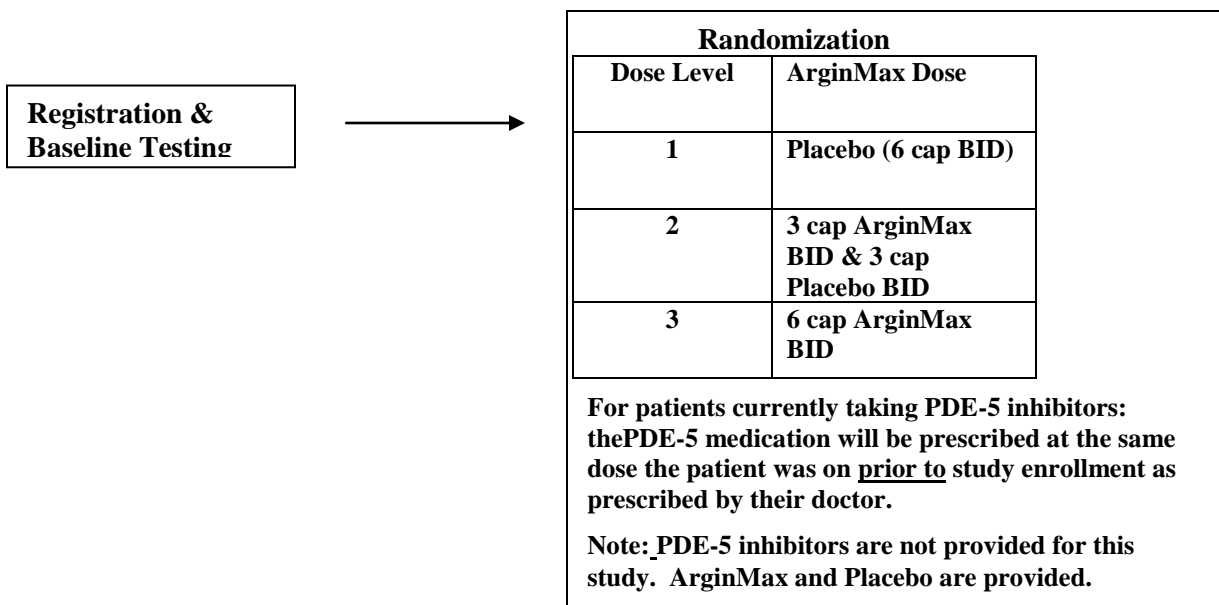
Activation Date: **WFU:** 10/18/2010
Sites: 10/18/2010

NCI Version Date: 9/15/2010

Renewal Dates:

Amendment/Update # & Date:

SCHEMA



STRATIFICATION FACTORS:

- Age: < 65 years of age vs. \geq 65 years of age.
- Currently taking phosphodiesterase-5 inhibitors (PDE-5 inhibitors) vs. not taking PDE-5 inhibitors.

Study Sample Size: 140 patients (approximately 47 per dose level)

Study Duration: 8 weeks

Brief Eligibility Criteria:

- Male prostate cancer survivor previously treated with radiotherapy and who identifies himself as concerned with sexual quality of life, including erectile dysfunction.
- The patient must describe himself as having had successful sexual activity prior to the commencement of radiotherapy. Erectile dysfunction is defined by the NIH Consensus Development conference as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.
- Must be interested in sexual activity, and agree to make at least one sexual intercourse attempt every week during the study.
- The usage of phosphodiesterase-5 inhibitors (PDE-5 inhibitors) will be voluntary and will serve as a stratification factor. Patients currently taking this class of medication must agree to assume the responsibility for the cost of PDE-5 inhibitor treatment during the protocol period (8 week period) as this cost is not covered by the study. Patients unable or unwilling to take PDE-5 inhibitors will also be eligible for enrollment on study. PDE-5 inhibitor use will be recorded in the patient diaries.
- Patients taking PDE-5 inhibitors as part of this study must be on a stable dose of drug for at least one month prior to study entry.

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1. OBJECTIVES

1.1. Primary protocol objective.

- To determine the “best dose” of ArginMax to be used in a subsequent Phase III trial. The “best dose” will be defined as the dose which shows the greatest improvement in the erectile function domain of the IIEF (Appendix 8) after 8 weeks of therapy

1.2. Secondary protocol objectives.

1. Toxicity Evaluation: Because the combination of PDE-5 inhibitors and ArginMax has not been previously rigorously tested, evaluation for toxicity will be a key component of this study. A dose-limiting toxicity will be defined as any grade 3 or higher toxicity as defined by the CTCAE that is possibly, probably, or definitely related to ArginMax and will result in discontinuation of ArginMax usage in that patient.
2. Estimate trial accrual, retention, adherence, and variability as outlined in section 3.4. These data will be used in the design of a subsequent Phase III trial.
3. Assess changes in quality of life and sexual function as defined by:
 - Changes in the Quality of Life of prostate cancer survivors using the Expanded Prostate Cancer Index Composite (EPIC-26 (Appendix 10))
 - Changes in the other domains of the International Index of Erectile Function (IIEF): orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.
 - Changes in the Sexual Encounter Profile (SEP (Appendix 9))
 - Changes in the percentage of "yes" (positive) responses to either of the two global efficacy questions (from the Global Efficacy Questionnaire (Appendix 11))

2. BACKGROUND

2.1 Study Disease

As more patients survive cancer diagnosis and treatment, quality of life issues are gaining importance. Sexuality is one of the most important quality of life issues for men and women. Treatment for all types of cancers can have psychosexual consequences. Anderson estimates that sexual functioning morbidity occurs for up to 90% of cancer patients who have the disease at the most prevalent sites.¹ These problems are bothersome to many patients and interfere with a return to normal post treatment life. In a qualitative study of 48 men (130 approached) with erectile dysfunction after treatment for prostate cancer, quality of life was significantly affected, including areas such as the quality of sexual intimacy, everyday interactions with women, sexual fantasy life, and perceptions of their masculinity. The most common sexual problems for men with cancer are loss of desire for sexual activity, erectile dysfunction,² anejaculation, retrograde ejaculation, or the inability to reach orgasm.³

Most often, orgasm remains intact but may be delayed secondary to medications and/or anxiety. Erectile dysfunction is commonly described as changes in voluntary erection in sexual situations, erection on awakening, and spontaneous erections.⁴ For men with prostate cancer, erectile dysfunction has been the primary form of sexual dysfunction investigated. Prevalence rates of erectile dysfunction vary. In general, those studies that have used patients' self-reports have found higher rates of erectile dysfunction ranging from 60% to 90% after radical prostatectomy and between 67% and 85% following external-beam radiation therapy.⁵⁻⁸ Erectile dysfunction is also prevalent with brachytherapy and cryotherapy in the treatment of localized prostate cancer.⁹

Patients in a randomized trial comparing radical prostatectomy with watchful waiting completed a questionnaire regarding symptoms, psychological functioning, and quality of life. Although the frequency of sexual thoughts was similar in both groups, the prevalence of erectile dysfunction was higher in the radical prostatectomy group than in the watchful-waiting group (80% vs. 45%). Among men who underwent radical prostatectomy, 56% were moderately or greatly distressed by the decline in sexual function, as compared with 40% of men in the watchful-waiting group.¹⁰

Sildenafil (Viagra[®]) is an oral medication to treat erectile dysfunction.¹¹ Sildenafil works best in men with the mildest forms of erectile dysfunction. Many men will not be able to achieve adequate erections by taking this drug alone. Sildenafil use allows about 72% of patients with nerve-sparing prostatectomy and 15% of patients with non-nerve-sparing prostatectomy to achieve vaginal intercourse.¹² About 12% of sildenafil responders lose efficacy by 3 years.¹³ In a study of brachytherapy for the treatment of localized prostate cancer, sildenafil improved potency in 62% to 70%.¹⁴ As would be expected, patients who were not being treated with androgen therapy had a significantly better response.¹⁵ Similarly, of men who became impotent after brachytherapy for prostate cancer,¹⁶ 85% to 88% responded with improved erectile function when taking sildenafil. The efficacy of sildenafil has not been limited to this group. Sildenafil also improved erectile function for patients with partial parasympathetic nerve disruption from rectal surgery.^{17, 18} Specifically, relevant to this proposed study are randomized data from a 12 week double-blinded, placebo-controlled cross-over study of men treated with external beam radiotherapy for prostate cancer that demonstrated significant increases in the mean IIEF scores from baseline with the use of sildenafil. Successful intercourse was reported in 55% of patients after sildenafil and 18% after placebo ($p < 0.001$). 90% of the men treated required a dose adjustment of sildenafil to 100mg.¹⁹ This experience, in a nearly identical patient population to the one proposed, has defined the dose of sildenafil to be 100 mg. The same group of investigators also completed a similar trial using tadalafil (Cialis[®]), another PDE-5 inhibitor, and they demonstrated a similar improvement in IIEF scores with treatment. 48% of these patients reported successful intercourse compared with 9% of patients using placebo.²⁰

Sildenafil has been tested for effects on both blood pressure as well as adverse cardiovascular events. A study of 105 men with known or suspected coronary artery disease was reported in which the patients underwent stress echocardiograms 1 hour after receiving placebo or sildenafil. In men with stable CAD, sildenafil had no effect on symptoms, exercise duration, or exercise induced ischemia.²¹ In a post-hoc sub analysis of five prospective randomized trials the acute, short-term effects of oral sildenafil on blood pressure and heart rate in men with erectile dysfunction were small and not likely to be clinically significant in those taking concomitant antihypertensive medication.²²

Priapism, defined as persistent erection of the penis for longer than 4 to 6 hours, has been rarely reported in patients treated with sildenafil for erectile dysfunction.²³ A large meta-analysis of 6659 men treated with sildenafil versus placebo did not report any cases of priapism.²⁴ In post-marketing surveillance, priapism was rarely reported but nearly half of these men reported using sildenafil in combination with other drug therapies for erectile dysfunction.²⁵ However, given the rarity of these events, there is no known contra-indication to the use of PDE-5 inhibitors in combination with other erectile dysfunction therapies. As part of our clinical trial, we will caution men that if they experience a prolonged erection longer than four hours they should seek immediate medical attention. If an incident of priapism occurs, that patient will not receive further PDE-5 inhibitors or ArginMax as part of this protocol. The incident would also be reported to our clinical research oversight committee for review.

2.2 Study Agent

ArginMax (Daily Wellness Company) is a proprietary nutritional supplement consisting of extracts of L-arginine, ginseng, ginkgo, multivitamins, and minerals. Both men and women have reported benefit with this supplement. Arginine is believed to be required to carry out the synthesis of nitric oxide that relaxes blood vessels and allows more blood to flow through the arteries and may also be responsible for orgasmic sensations.²⁶ It has been hypothesized that taking extra arginine will increase nitric oxide levels and increase blood flow to the penis.²⁷ This has been demonstrated in animal models. Benelli et al. found that administration of L-arginine increased the percentage of copulation and indexes of sexual performance in rats.²⁸ Moody et al. further explored the effects of long-term administration (8 weeks) of L-arginine on the rat erectile response, finding that L-arginine supplementation improves the erectile response in aging rats.²⁹

Two human studies have been reported including a double-blind placebo controlled trial of 50 men with erectile dysfunction. This study tested arginine at dose of 5 grams per day and 33% of participants showed improvement compared to 10% in the placebo arm.³⁰ This study only included men with ED of organic causes. In contrast to this, Klotz and colleagues reported negative results in controlled crossover study by using a much lower dose of 1500 mg/day of L-arginine. This study, with a small sample size of 32 patients, showed a 17% improvement in erectile function with L-arginine supplementation and a 20% improvement with placebo. No drug related adverse events were reported. Importantly, this study was potentially confounded by the inclusion of patients with mixed type erectile dysfunction (psychogenic and organic).³¹ Given that our trial will only include patients that had been treated with radiotherapy and were having successful sexual activity prior to the commencement of radiotherapy we will assume that the overwhelming cause of their ED will have been their cancer treatment rather than psychogenic causes.

The recommended daily dosage of L-arginine used in the ArginMax preparation is 3000 mg/day. This dosage is supported in part by the placebo controlled human trials noted above including a negative experience noted at a dosage of 1500 mg/day and a positive experience noted at a dosage of 5000 mg/day.³⁰ Two additional series provide further supporting data. The dose escalation trial of Orzalesi et al studied the effect of 3 dosages of L-arginine D,L-pyroglutamate (1000-1500-2000 mg/day) on 35 male subjects under forty and 35 males over sixty years of age.³² No improvement in sexual frequency was noted in those under forty. However, a 40 to 180% increase in frequency in sexual activity was noted in the older subjects, and the recovery was dose-related. In addition, Zornotti and Lizzi conducted a study on 15 men under age 65 with erectile dysfunction.²⁷ The men were given a placebo for 2 weeks followed by

2800 mg l-arginine for 2 weeks. Following the 2 weeks of l-arginine, six of the 15 men reported a marked improvement in their ability to perform sexually (40%). Specifically, their erections were improved and they were now able to achieve vaginal penetration. The mean age of the responders was 37.5 vs. 55.4 for non-responders. Penile vascular findings for the older group suggest some degree of vascular impairment. None of the men reported any unpleasant side effects.

Some additional data regarding the safety of l-arginine is available. Supplementation levels of l-arginine in the literature range from 1200 mg to 30 grams per day, the higher dose levels are usually given in two or three doses over short periods. Long term studies such as Lerman, et al. utilized a dosage of 9,000 mg/day (3 gm given TID).³³ Arginine had no toxic effect, even at very high doses, and very few side effects were reported. An earlier experience in heart failure patients using even higher doses also suggested safety at high daily doses including over 12 grams per day.³⁴ Therefore based on these safety data as well as the efficacy data outlined above, there is some rationale for both the current manufacturer recommended dose (3 grams/day) and for a higher dose in the setting of a clinical trial. The highest dose level on this trial will use a total of 6 grams per day.

It is also possible that the efficacy of ArginMax is in part derived from the ingredients other than l-arginine. The two other primary ingredients within ArginMax are Korean ginseng (Panax Ginseng) and ginkgo biloba.

The efficacy of Korean ginseng in treating erectile dysfunction was demonstrated in a randomized trial involving 90 patients randomized to placebo, trazadone, or ginseng. Although frequency of intercourse, ejaculations, and morning erections were not improved with ginseng, the erectile parameters of girth, early detumescence, and rigidity showed significant improvement with ginseng.³⁵ A review of the use of Korean red ginseng for the treatment of erectile dysfunction was recently published. Seven randomized trials met the inclusion criteria. Based on the Jadad score, the methodological quality was low on average. Meta-analysis of these data showed a significant effect (RR 2.40, $p < 0.00001$) and subgroup analysis showed a beneficial effect in psychogenic erectile dysfunction. However given the small sample sizes and low methodological quality the overall conclusion was that more rigorous study is needed.³⁶ Ginsenosides from ginseng have been shown to increase NO production in endothelial cells.^{37, 38} An observed mechanism for the increase in NO production is the up-regulation of NOS activity by ginsenosides.³⁹ The effect of ginsenosides on NO production has implications for improved sexual function, and may partly account for the aphrodisiac effect of Panax ginseng used in traditional Chinese medicine. In the hypertension literature, there has been some concern about a possible link between the use of ginseng and the development of hypertension. Stavro and colleagues recently reported a placebo controlled randomized trial to determine the effect of 12 weeks of ginseng intake on 24-hour blood pressure and renal function. Participants received 3 grams of ginseng per day. Overall ginseng use had no effect on 24-hour blood pressure and renal function in hypertensive individuals.⁴⁰ Similarly, a review of the literature by Buettner and colleagues did not support the use of ginseng to treat cardiovascular risk factors.⁴¹ The total daily dose of ginseng will be well below that used in the above experiences for both efficacy and toxicity even at the highest dose level on this trial (400 mg daily dose). The effects of ginkgo biloba on microvascular circulation may also lead to improvements in erections. This has been shown in a study of the effect of ginkgo biloba on human and rabbit corpus cavernosum tissue.⁴² Sikora et al. (1989) demonstrated that Ginkgo biloba (60 mg daily) could be used to successfully treat erectile dysfunction, as measured by sonographs of penile arterial flow.⁴³ After 6 months of therapy, 50% of patients regained potency, 45% improved

blood flow or papaverine response, and 5% remained unchanged. The clinical experience of ginkgo biloba for other indications proves to be helpful as we try to determine a safe dosing range. Multiple experiences for the treatment or prevention of dementia have been reported. In a relatively small trial 122 patients age 85 or older evaluating the impact of ginkgo on delaying progression to cognitive impairment, no benefit was seen. No overall difference in toxicity compared to placebo was noted but there was a univariate suggestion of an increased risk of stroke or TIA with a dose of 80 mg TID.⁴⁴ In a much larger experience of over 3000 patients using 120mg BID, the compound again demonstrated no efficacy for the prevention of dementia. More relevant to this proposal is the toxicity profile from this study. No serious adverse events were noted in comparison to placebo and this included risk of stroke.⁴⁵ Patients who were on or subsequently commenced warfarin therapy were excluded from participating due to a concern for possible bleeding with ginkgo use. This is the basis for our exclusion of this group of patients. At our maximum dose level we will be administering a total daily dose of 100 mg ginkgo biloba which is well below the amount delivered safely on the above trials.

The impact of either ginseng or ginkgo biloba supplementation on cytochrome p450 metabolism has been studied in the elderly population. In terms of ginseng, inhibition of cytochrome P2D6 reached the level of statistical significance (7%) but the magnitude of the effect was felt to have little if any clinical relevance. No significant effect was noted for ginkgo biloba. Neither supplement had an impact on cytochrome P1A2 activity.⁴⁶ Separately, the use of ginseng has been studied in combination with warfarin. Ginseng usage did not affect the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin.⁴⁷

Two reported studies have evaluated the effects of ArginMax in humans. A study of 25 men with mild to moderate erectile dysfunction were treated with ArginMax.⁴⁸ All interested participants were allowed to enroll regardless of the etiology of their erectile dysfunction. Assessment of the effect of ArginMax was based on results of a Sexual Function Questionnaire (SFQ) assessed after 4 weeks of treatment with a twice daily ArginMax regimen as compared to baseline. The SFQ was self-administered and was a composite of the IIEF as well as questions regarding the subject's activities, condition during the trial period, and quality of life. After 4 weeks, 21 patients completed the study, 88.9% improved their ability to maintain erection during sexual intercourse and 75.0% had improvement in the overall satisfaction with their sex life. No significant side effects were noted. In addition to the male study, a double-blind placebo-controlled study of ArginMax was open to women over the age of 21 years with an interest in improving their sexual function.⁴⁹ After 4 weeks, 73.5% of the ArginMax group improved in satisfaction with their overall sex life, compared with 37.2% of the placebo group ($p < 0.01$). Notable improvements were also observed in sexual desire, reduction of vaginal dryness, frequency of sexual intercourse, and orgasmic and clitoral sensation. No significant side effects were noted. The results of the female ArginMax trial suggest that the beneficial effects of this supplement may be due to effects either in addition to or instead of its direct effects on erectile function. This later trial formed the basis of the ArginMax study for women that is nearing completion in the Wake Forest University CCOP Research Base. No published clinical data is available for the combination of ArginMax with any phosphodiesterase type 5 inhibitor. Preclinical tissue studies of human corpus cavernosum samples has shown vasodilatory effects of l-arginine treatment and interestingly a possible synergistic effect with the addition of sildenafil to l-arginine treatment.⁵⁰ No significant side effects of ArginMax monotherapy have been reported. The planned daily dose of either 3000mg or 6000mg of l-arginine within Arginmax is well below the doses that have been safely reported for l-arginine supplementation in the cardiovascular literature.⁵¹

As stated before, the hypothesized mechanism of action of ArginMax is through effects on nitric oxide synthesis and that the effects of PDE-5 inhibitors are through similar pathways.^{52, 53}

2.3 Rationale

Limited research is available to support interventions that may be effective in improving erectile dysfunction for prostate cancer survivors and only a small percentage of men with erection problems seek help.^{54, 55} The proposed study will offer an intervention to prostate cancer survivors treated with radiotherapy that have identified themselves as having sexual dysfunction. Assessment of all patients with validated tools will provide information needed to assess the effect that ArginMax may have on these patients. The goal of this study will be to better define the appropriate dose of ArginMax. We plan to evaluate endpoints regarding both efficacy and toxicity. We hope that a positive outcome for this trial will lead to a larger efficacy trial.

The International Index of Erectile Function (IIEF (Appendix 8)) will be used for the assessment of the primary endpoints of this trial.⁵⁶ The IIEF is an international, validated, self administered, 15-item questionnaire. The IIEF questions can be grouped into 5 domains. The EF domain: questions 1 to 5 and 15; orgasmic function (OF) domain: questions 9 and 10; sexual desire (SD) domain: questions 11 and 12; intercourse satisfaction (IS) domain: questions 6 to 8; overall satisfaction (OS) domain: questions 13 and 14. The IIEF will be administered at baseline and 4 and 8 week post-randomization. For statistical purposes, the erectile function (EF) domain will be used as the primary end-point.

In addition to the IIEF, the Expanded Prostate Cancer Index Composite (EPIC-26 (Appendix 10)) will be used to measure the quality of life of prostate cancer survivors. This is a validated measure that has been used to show differences in quality of life outcomes for prostate cancer survivors after undergoing various local treatment options.⁵⁷⁻⁵⁹ The EPIC-26 will allow for assessment of bowel and urinary function issues that would not otherwise be assessed by the IIEF, but are specifically problematic for prostate cancer survivors after undergoing radiotherapy.

Patients will also be asked to keep a Sexual Encounter Profile (SEP (Appendix 9)) with entries to be made after each sexual attempt. The SEP consists of 5 questions related to erectile quality and overall satisfaction. This metric has previously been used in a study of 60 patients evaluating the efficacy of tadalafil for erectile dysfunction after the treatment of prostate cancer with radiotherapy. For those 60 patients, 767 attempts at sexual activity were recorded and only 42 events (5.1%) occurred where a tablet of either tadalafil or placebo was taken and no sexual intercourse attempt followed. This diary becomes a useful metric of the patients' immediate impression following sexual activity as opposed to the IIEF which has inherent lead time bias. We may also gain a greater understanding of the relationship between PDE-5 inhibitors usage and the completion of an intercourse attempt in this patient population.

3. SUMMARY OF STUDY PLAN

3.1 Study design

A randomized, parallel design will be used to assess the effect of Arginmax on sexual function as quantified by the erectile function domain score of the IIEF. Patients will be stratified by age and PDE-5 use, and randomized within strata to receive various doses of Arginmax with equal probability. Patient evaluations will occur at baseline

and 4 and 8 weeks following randomization. The 8 week evaluation will be used to address the primary objective of the study.

3.2 Number of Participants

140 patients will be enrolled on the study, approximately 47 per dose group.

3.3 Study Population

1. Male prostate cancer survivor previously treated with radiotherapy and who identifies himself as concerned with sexual quality of life, including erectile dysfunction.
2. Patient must describe himself as having had successful sexual activity prior to the commencement of radiotherapy.
3. Must be interested in sexual activity, and agree to make at least one sexual intercourse attempt every week during the study.
4. The use of PDE-5 inhibitors will be a voluntary component of the trial and will serve as a stratification factor. For patients currently taking PDE-5 inhibitors, they must agree to assume the responsibility for the cost of PDE-5 inhibitors treatment during the protocol period (8 week period) as this is not covered in the cost of the trial. Patients unable or unwilling to take PDE-5 inhibitors will also be eligible for enrollment on study. PDE-5 inhibitors use will be recorded in the patients' diaries.
5. Patients taking PDE-5 inhibitors as part of this study must be on a stable dose of drug for at least one month prior to study entry.

3.4 Intervention Plan

Patients will be given ArginMax at one of three dose levels (i.e., Arm 1: 6 capsules placebo bid; Arm 2: 3 capsules ArginMax & 3 capsules placebo BID; Arm 3: 6 capsules ArginMax bid). All patients will take the assigned medications twice daily. Pill diaries will be provided. All patients will take the same number of pills daily.

For patients currently taking PDE-5 inhibitors sildenafil (Viagra[®], Pfizer Pharmaceuticals), tadalafil (Cialis[®], Lilly ICOS, LLC), and vardenafil (Levitra[®], Bayer Healthcare / Schering Plough Corp.) This medication will be prescribed as recommended by the manufacturer and at the discretion of the treating physician.

Involvement of Participant's Partner:

Sexuality is one of the most important quality of life issues for men and women. Erectile dysfunction affects and is affected by not only the patient, but also his partner and their relationship. Despite the fact that pharmaceutical breakthroughs allow for renewed or expanded sexual activity among many couples, the psychosocial impact of these agents on couples has largely been ignored.

For this reason it is recommended the participant's partner be included in the consenting process at the baseline visit. Information provided regarding the study objectives will inform both partners of what is expected in relation to use of medication, side effects, forms required for analysis and the main study objective of improving the overall satisfaction of their sex life.

3.5 Study Assessments

Patients will be asked to complete study assessment forms at trial registration, after 4 weeks of treatment and at the end of the 8 week treatment period.

In order to encourage and assess compliance with the study protocol and pill taking, to document adverse events and concomitant medications, all patients will be telephoned by the study coordinator/nurse during Weeks, 4 and 8.

3.6 Duration of study

Patient participation will be 8 weeks.

4. PARTICIPANT SELECTION

4.1. Inclusion Criteria

- Male prostate cancer survivor previously treated with radiotherapy and who identifies himself as concerned with sexual quality of life, including erectile dysfunction.
- Had successful sexual activity prior to the commencement of radiotherapy.
- Erectile dysfunction, defined as inability to achieve or maintain an erection sufficient for satisfactory sexual performance
- Interested in sexual activity and agrees to make at least one sexual intercourse attempt every week during the study.
- The usage of PDE-5 inhibitors will be voluntary and will serve as a stratification factor. Patients taking PDE-5 inhibitors must agree to assume the responsibility for the cost of PDE-5 inhibitor treatment during the protocol period (8 week period) as this is not covered in the cost of the trial.
- Patients currently taking PDE-5 inhibitors sildenafil (Viagra[®], Pfizer Pharmaceuticals), tadalafil (Cialis[®], Lilly ICOS, LLC), and vardenafil (Levitra[®], Bayer Healthcare / Schering Plough Corp.) must agree to take the medication only as prescribed by their treating physician.
- Patients taking PDE-5 inhibitors as part of this study must be on a stable dose of drug for at least one month prior to study entry.
- Must be able to take oral medications.
- \geq 6 months following completion of all cancer therapy
- No evidence of disease recurrence

- If previously taken LHRH agonist androgen suppression (e.g, Lupron, Zoladex), anti-androgen (e.g., Casodex, Eulexin, Nilandron), or estrogenic (e.g., diethylstilbestrol) agents, serum testosterone must have returned to the laboratory normal range
- No planned surgery while on protocol or for ≥ 4 weeks following completion of protocol.
- Prior cystoscopy is permitted.
- Age ≥ 18
- ECOG performance status 0/1.
- Patients must agree not to start taking an herbal product for erectile dysfunction during the eight weeks of study intervention.

4.2 Exclusion Criteria

- No other concurrent erectile dysfunction therapies permitted (i.e. vacuum pump, cavernosal injections, and other drug therapies). Past use of these and other therapies permitted if the patient can meet the inclusion criteria above.
- No testosterone supplementation permitted.
- Use of LHRH agonist androgen suppression (e.g, Lupron, Zoladex), anti-androgen (e.g., Casodex, Eulexin, Nilandron), or estrogenic (e.g., diethylstilbestrol) agents within the last 6 months.
- Prior prostate or lower genitourinary surgery (bladder, penis, urethra, testicles) including transurethral resection of prostate (TURP).
- Serious cardiovascular disease (unstable angina, supraventricular arrhythmia, myocardial infarction, symptomatic congestive heart failure, cardiac arrhythmia, coronary artery bypass surgery within 6 months prior to registration).
- Hypotension (<90/50mm Hg), or uncontrolled hypertension (>170/100 mm Hg)
- Stroke or spinal cord injury within 6 months before registration.
- Patients on Persantine, heparin, Lovenox, warfarin, ginkgo biloba, Aspirin (low dose 81mg ASA allowed) or with a history of bleeding disorders will be excluded.
- Current use of cimetidine, ketoconazole, itraconazole, erythromycin, or ritonavir.
- Major medical or psychiatric illness which, in the opinion of the investigator, would prevent completion of treatment or would interfere with follow-up.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

- Current use of any organic nitrate or as needed nitrates (e.g., use of nitroglycerin)
- May not receive other investigational agents or devices during 30 days prior to start of study drug.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ArginMax (l-arginine, ginseng, or ginkgo biloba)

4.3. Inclusion of Women and Minorities

Women are not included in this trial as by design it is a study of prostate cancer survivors. Members of all races and ethnic groups are eligible for this trial.

Race/Ethnicity

Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	116	21	3	0	0	140
Female	0	0	0	0	0	0
Total	116	21	3	0	0	140

4.4. Recruitment and Retention Plan

The Comprehensive Cancer Center of Wake Forest University Community Clinical Oncology Program Research Base is comprised of 25 CCOPs and 5 non-CCOPs with 117 participating cancer centers (mostly community cancer centers). Currently, the CCCWFU CCOP Research base has 3 open cancer control studies, none of which compete with the proposed trial. One of the recently open studies was a Phase III prospective randomized double blind placebo controlled study of ArginMax for female cancer survivors. The initial 145 patients on this study accrued at rate of 20.9 patients/month, more than three times the anticipated rate. Retention on this protocol was 79% at 8 weeks. Assuming half that accrual rate for this study, i.e., 10 patients/month, we believe that accrual can be completed within 13-14 months. We hope that this trial will provide us with some data on which to base accrual rationale for a possible future larger randomized trial. We will actively encourage minority accrual throughout the study. The protocol plans to stop accrual of nonminority subjects after accrual of 112 subjects so that additional minority subjects can be accrued at the end (the final 28 subjects). Accrual status will be discussed at monthly steering committee meetings to address any perceived recruitment/retention problems.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

There will be 3 dose groups on this study:

- Dose Level 1 will take 6 capsules of placebo twice daily (0 mg l-arginine)
- Dose Level 2 will take 3 capsules of ArginMax twice daily and 3 capsules of placebo twice daily (3000 mg l-arginine)
- Dose Level 3 will take 6 capsules of ArginMax twice daily (6000 mg l-arginine).
- Patients will be stratified according to current use of PDE-5 inhibitors as needed to improve erectile function vs. no current use of PDE-5 inhibitors as well as age < 65 or ≥ 65 and randomized to one of these three groups with equal probability.

5.2 Study Agent Administration

The agents will be administered orally by the patient. Each patient will be given two pill bottle subtypes A and B. Each patient will be asked to take 3 pills from bottle A and 3 pills from bottle B in a twice daily fashion. By using A and B bottles, the presence of placebo will be blinded to both the investigator and the subject. Two bottles of A and B will be given to each patient (for a total of 4 bottles). Each bottle will have a four week supply of medication. This will consist of 168 capsules in each bottle. The size and shape of each pill will be chosen to match the standard configuration of the ArginMax supplement.

The ArginMax or placebo should be taken in a twice daily fashion with the first dose of the day occurring after arising in the morning and the second dose occurring in the late afternoon or early evening. Any PDE-5 inhibitors sildenafil (Viagra[®], Pfizer Pharmaceuticals), tadalafil (Cialis[®], Lilly ICOS, LLC), and vardenafil (Levitra[®], Bayer Healthcare / Schering Plough Corp.) should be taken as prescribed by the patients treating physician in accordance with manufacturer recommended dosing guidelines.

5.3 Run-in Procedures – N/A

5.4 Contraindications

Patients taking Persantine, heparin, Lovenox, warfarin or ginkgo biloba will not be eligible for enrollment. If any of these medications are prescribed to start while on study the patient will be asked to discontinue taking the study medications. This is due to the bleeding concern with taking these medications concomitantly. (low dose 81mg ASA daily is allowed).

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include daily dosage for prescription medications.

5.6 Dose Modification

- Dose modifications of ArginMax will not be allowed. If a patient is intolerant of the prescribed dose level, then he will discontinue the medication and the data generated from his participation will continue to be evaluated on an intention to treat basis. Therefore, he will be “Off Treatment” but continue to provide data (refer to Sections 7.6 and 7.7). One of the purposes of this trial will be to test the feasibility of these two specific ArginMax doses in this patient population.

- Dose modification of PDE-5 inhibitors will not be allowed as the usage of this medication is elective on the part of participants and taken on an as needed basis.
- No “drug holidays” are anticipated.

5.7 Adherence/Compliance

- 5.7.1 Compliance with study medication will be an important metric for this trial. Secondary analyses will be conducted on patients who were at least 75% compliant with the twice daily ArginMax or placebo regimen.
- 5.7.2 Pill diaries will be kept by each patient during the course of the study to record intake of the study medications as well as PDE-5 inhibitors use.
- 5.7.3 The patients will receive periodic phone re-enforcement from study coordinators to encourage full participation.

6. PHARMACEUTICAL INFORMATION

6.1 Supplement Information

ArginMax contains ginkgo biloba which is a mild blood thinner. Therefore, ArginMax should not be combined with any strong blood thinners like warfarin (see Section 5.5). It is recommended that ArginMax be discontinued four weeks prior to any surgery. Although the dose in ArginMax is lower than that known to cause problems, it is best to err on the side of caution.

There has been a single study in vitro that showed Herpes needed L-arginine to grow. Studies in humans have never shown that dietary Arginine influences or causes breakouts. A complete literature search has revealed no unusual breakouts. Many people take Lysine to control their herpes. If so, it is recommended taking ArginMax at a different time of day than Lysine since they compete for absorption.

An analysis will be performed and checked by the manufacturer (Daily Wellness Company). Single lot # will be used in this study. The specific specifications and analyses for this single lot # at the time of manufacturing will be provided for the researcher's review.

The company uses only high quality GMP or ISO 9000 suppliers. A Certificate of Analysis (C of A) is sent by the supplier with every lot that shows lab testing for active ingredients and lack of contaminants. These are double checked with outside testing only when approving a new supplier, and then only randomly thereon. There has never been a discrepancy between the company's data and the suppliers' data.

All of the company's label claims have been approved by the FDA (in spite of their disclaimer) and can be proven by their issuance of Certificates of Free Sale (CFS) for all of the company's products.

Supplement Facts

Serving Size: 6 per day

AMOUNT PER SERVING		%DV*
Proprietary Blend	3250 mg	
L-arginine	3000 mg	#
American Ginseng (Panax Quinquefolius) standardized (5% ginsenosides)	100 mg	#
Korean Ginseng (Panax Ginseng) standardized (30% ginsenosides)	100 mg	#
Ginkgo Biloba- standardized (24% flavones glycosides, 6% terpenes lactones)	50 mg	#
Vitamin A (as palmitate)	5000 IU	100%
Vitamin C (as ascorbic acid)	60 mg	100%
Vitamin E (as di-alpha-tocopheryl acetate)	30 IU	100%
Thiamin (as thiamin mononitrate)	1.5 mg	100%
Riboflavin	1.7 mg	100%
Niacin (as niacinamide)	20 mg	100%
Vitamin B-6 (as pyridoxine hydrochloride)	2 mg	100%
Folate (as folic acid)	400 mcg	100%
Vitamin B-12 (as cyanocobalamin)	6 mcg	100%
Biotin	300 mcg	100%
Pantothenic acid (as calcium pantothenate)	10 mg	100%
Zinc (as zinc gluconate)	15 mg	100%
Selenium (as sodium selenate)	70 mcg	100%
* Percent Daily Value (%DV) are based on a 2000 calorie diet.		
# Daily Value not established.		

A third party analysis will be performed by the American Analytical Chemistry Labs Corporation for both content and impurities. This will be similar to the process used for NCI trial: WFU 05-04-01 (the female ArginMax study). We will also have the study drug tested to ensure that it does not contain PDE-5 inhibitors or other similar impurities given the concern raised by the presence of these medications being found in other Chinese herbal products.

Drug will be provided by Daily Wellness Company, and distributed by an independent company, Biologics Inc., with identical labeling and drug appearance for both placebo and drug.

6.2 Reported Adverse Events and Potential Risks

The ingredients in ArginMax have a long history of use in humans and are not known to interact in an adverse way at the recommended dose with any foods. Based on toxicity information is provided by Daily Wellness Company, rare adverse events include the following:

- Stomach upset
- Headache
- Nausea
- Vomiting

6.3 Availability of ArginMax

The study drug will be shipped to Biologics, Inc. in bulk. Biologics, Inc will divide ArginMax in bottles containing a 4-week supply (168 capsules). ArginMax will be stored at room temperature.

Biologics, Inc. will provide shipment to the participating site for each patient enrolled with enough ArginMax to complete the study.

6.4 Ordering and Distribution

ArginMax is manufactured by Daily Wellness Company. It is a nutritional supplement consisting of extracts of l-arginine, ginseng, ginkgo, and multivitamins, and minerals.

ArginMax and matching placebo will be provided free of charge by Daily Wellness Company. The study drug will be shipped to Biologics, Inc. in bulk supply and will be stored at room temperature.

Upon patient registration Biologics, Inc. will automatically be notified and will call the site for further mailing information. Biologics, Inc. will provide shipment to the participating site for each patient enrolled.

6.5 Study drug and Supplement Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

Participating sites/Institutions are encouraged to document drug accountability using the NCI DARF.

6.6 Packaging and Labels

6.6.1 ArginMax will be packaged and labeled by Biologics, Inc.

Each patient enrolled will receive one shipment of study drug (Biologics, Inc. to ship directly to site). Each patient specific shipment will include 4 – 4 week bottles of study drug with safety labels.

Each patient will be given two pill bottle subtypes A and B. Each patient will be asked to take 3 pills from bottle A and 3 pills from bottle B in a twice daily fashion. By using A and B bottles, the presence of placebo will be blinded to both the investigator and the subject. Two bottles of A and B will be given to each patient (for a total of 4 bottles). Each bottle will have a four week supply of medication. This will consist of 168 capsules in each bottle. The size and shape of each pill will be chosen to match the standard configuration of the ArginMax supplement.

Each patient will take 12 capsules of ArginMax or 12 capsules of placebo or 6 capsules of ArginMax plus 6 capsules of placebo daily for 8 weeks. Each bottle will contain a patient-specific label. In addition to this, and to ensure easy identification, Biologics, Inc. will label each lid with a color-coded sticker entitled: *Bottle A and Bottle B*. Each bottle will contain (168) 168 capsules.

For easy identification at the site, Biologics, Inc. will place a label on the lid of each bottle indicating the week. Bottles will also include a patient-specific label including:

- Patient's name/initials
- Administration instructions/signatures
- Dr.'s name
- Dispense date
- Expiration date
- Storage instructions

Once official notification is received via email that a new patient is enrolled to the study, Biologics, Inc. prepares and ships a "Patient Kit" that includes the entire supply of study drug (or placebo) based on arm assignment provided by the Wake Forest University CCOP Research Base. A clinical pharmacist checks off package for accuracy of contents. 21 CFR Part 11 accountability records including date of dispense, lot number, unique patient identifier, quantity dispensed and remaining inventory balance are completed with each order. All accountability records are stored in a secured area throughout the duration of study.

6.6.2 Expedited Delivery and Logistic Services

Biologics, Inc. ships study drug "same day" for orders received before 4:00 p.m. EST Monday through Friday. Orders received after 4:00 p.m. Monday through Friday will be processed the next business morning. All shipments are sent via Federal Express Second Day Delivery. Biologics, Inc. distribution team monitors packages throughout duration of transit via Federal Express website.

6.6.3 Communications

Upon notification of a new patient registration, Biologics, Inc. places an outbound call to the site contact confirming their shipment is being processed, while providing the courier, date and time of anticipated delivery. Throughout the course of the study, a 24/7/365 clinical hotline support, staffed with clinical pharmacists, is made available in the event an investigator or site coordinator has a question or emergency unblinding is required. Unblinding methods are provided in section 6.9.

6.6.4 Drug Destruction/Disposal

At the conclusion of the study, clinical sites will document remaining drug and destroy remaining study agent on-site using their site's institutional guidelines. Biologics, Inc. will return any remaining study agent to Daily Wellness Company or destroy it per their own guidelines. Destruction of study agent should be documented using the NCI DARF (see Section 6.5).

6.7 Storage and Handling

ArginMax capsules should be stored at 20 to 25°C (between 68 and 77°F).

6.8 Registration/Randomization

6.8.1 Registration Process

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax: (336)716-6275

Fill out Appendix 2, “Eligibility Checklist / Registration Form’. Use this to complete the on-line registration.

Online Registration

Log on to the CCCWFU Research Base registration web site at <<http://www.phsapps.wfubmc.edu/CCRBIS/Login/defaultlogin.cfm>>. Enter your user name and password (which may be obtained by contacting Ping Tan at ptan@wfubmc.edu or June Fletcher-Steede at jsteede@wfubmc.edu.) *In the ‘Patient Registration and Protocol Information’ table, click the ‘Register Patient/Patient Info’, with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the drop down boxes.* If further information is needed by Biologics, Inc. or the Research Base Data Management Center, they will contact you. Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. Print this confirmation sheet for your records. All baseline forms must be completed and faxed to (336)713-6476 or mailed to Data Management (Refer to Section 11.1 data submission schedule):

Research Base Data Management Center
Department of Radiation Oncology
1st Floor Cancer Center
WFUBMC
Medical Center Boulevard
Winston-Salem, NC 27157

These forms should be retained in the patient’s study file. These forms will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base Data Management Center between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-3172 or 713-6507.

6.8.2 Randomization

We will stratify patients based on age and current PDE-5 inhibitors usage and randomized within strata to one of the three treatment groups with equal probability using random permuted block randomization.

6.9 Unblinding Methods

In the event a patient on this study develops a toxicity (adverse event or severe adverse event) for which the patient's physician or other health care professional feels that it is in the patient's best interest to know what drug they are taking (active study drug(s) or placebo), the following procedure should be followed:

- Step 1: the patient's physician or a designated health care professional should call the Research Base clinical nurse or Research Base Protocol Information Office or the Wake Forest University Baptist Medical Center Physician Access Line (336) 716-7654 and ask that Dr. Ed Shaw, Principal Investigator of the CCCWFU CCOP Research Base, be contacted immediately either in his office, by cell phone, or at home. In the event Dr. Shaw cannot be reached, the Research Base clinical nurse, or Research PIO staff or PAL operator should contact Dr. Glenn Lesser, Chair, Cancer Treatment Protocols in his office, by pager, or at home. If neither Dr. Shaw nor Dr. Lesser can be reached, the Research Base clinical nurse, or Research Base PIO or PAL operator should contact Gina Enevold, GNP, Research Base Administrator, either in her office, by pager, or at home.
- Step 2: Once contact has been made; the patient's physician or health care professional should explain the reason for the request to unblind the treatment arm that the patient is on. If the Research Base representative feels that the toxicity (AE/SAE) is possibly, probably or definitely related to the study drug, then the next step will be followed.
- Step 3: The responsible Research Base representative will call the pharmacist @ Biologics, Inc.(phone: 1-800-850-4306). There is an "on-call" service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The Biologics, Inc. pharmacist may contact the patients' physician and/or health care professional directly with the unblinding information. Written documentations of the unblinding process will be sent to the Research Base Principal Investigator /Protocol Information Office by Biologics, Inc.
- Step 4: In the event that the patient's treatment is unblinded, that patient will be taken off study with no further study follow-up. Appropriate procedures for grading toxicities, assigning causality, and reporting severe adverse events (if applicable), should be followed for each protocol for all Phase III Clinical Trials. The event will be reviewed by the CCCWFU Clinical Research Oversight Committee. All Research Base Clinical Trials will be reviewed by the Wake Forest University CCOP Research Base Data Safety and Monitoring Board.

Unblinding Study Participants at Study Completion

Study Participants may be unblinded if all patient specific data for the requesting site are completed and submitted to the Research Base Data Management Center.

Site members can obtain unblinding information by sending an email request to the CCCWFU CCOP Administrator or Data Management Supervisor with a list of PID #s.

After confirming with the Data Management Center that specific data for individual patients at a single site have been received and are complete, Biologics, Inc will be notified. An email from Biologics, Inc containing the unblinding information will be sent directly to the requesting site.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

At each participating site, medical charts will be screened to determine potential eligibility by physicians (including residents or fellows, if applicable), research nurses, or clinical research associates. Patients identified as potentially eligible will then be asked to consider participating in the study. Patients meeting initial eligibility criteria and who agree to participate in the study will sign an informed consent and undergo a baseline history and physical exam, laboratory tests, quality of life tests, and other research related evaluations per protocol. Patients will be instructed in the self-administration of the ArginMax (and PDE-5 inhibitors if taking this medication too).

7.2 Baseline Testing/Pre-study Evaluation

7.2.1 Patients will be given ArginMax or placebo based on the appropriate dose level. All patients will take the assigned medications twice daily. Medication diaries will be provided. All patients will take the same number of pills daily. Patients will be randomized to Placebo 6 capsules twice daily or ArginMax 3 capsules twice daily + Placebo 3 capsules twice daily or ArginMax 6 capsules twice daily.

For patients taking PDE-5 inhibitors sildenafil (Viagra[®], Pfizer Pharmaceuticals), tadalafil (Cialis[®], Lilly ICOS, LLC), and vardenafil (Levitra[®], Bayer Healthcare / Schering Plough Corp.) in addition to ArginMax: this medication will be prescribed based on the manufacturer recommended guidelines and at the discretion of the treating physician.

7.2.2 Patients will be asked to fill out the IIEF (Appendix 8) and the EPIC-26 (Appendix 10) at baseline.

7.2.3 Patients will be asked symptom questions from the study toxicity assessment form at baseline.

7.3 Evaluations at 4 Weeks and 8 Weeks

7.3.1 The SEP (Appendix 9) diary will be collected from the patient at 4 and 8 weeks of treatment (ArginMax or placebo). Patients will answer questions in the SEP after every sexual attempt, indicating whether sexual attempt was successful or not.

7.3.2 Two more questions (Global Efficacy Questions [GEQ] (Appendix 11)) will be added at 4 and 8 weeks to which patients could respond either positively or negatively: "Has the treatment you have been taking improved your erections?" and "Has the treatment you have been taking led to successful intercourse?" Patients will be asked to fill out the IIEF (Appendix 8) and the EPIC-26 (Appendix 10) at 4 and 8 weeks as well.

7.3.3 Potential side effects and risks are described in Section 6.2. Adverse event reporting is described in Section 10.

7.3.4 Patients will be called by the study nurse/coordinator during Weeks 4 and 8 to evaluate compliance, assess adverse events and to update concomitant medication list. Study coordinators will work with patients to solve any difficulties the patients may be having with taking the daily study pills and completing any of the study paperwork requirements.

7.4 Post-intervention Follow-up Period

There is no study specific follow up period after the 8 week visit. Patients will be followed by their treating oncologist as indicated for their stage of disease and time since definitive therapy.

7.5 Study Parameters Table

Baseline H & P, VS, Height & Weight are to be conducted within 6 months prior to registration.

Evaluation/ Procedure	Baseline	Week 4	Week 8
Informed Consent	X		
H & P	X (A)		
Blood pressure/ Height and Weight	X (A)		
Toxicity Assessment Sheet (TAS)	X	X	X
Concomitant Medications	X	X	X
Medication Diary		X	X
Telephone Contact		X	X
Expanded Prostate Cancer Index Composite Short Form (EPIC-26 (Appendix 10))	X	X	X
International Index of Erectile Function (IIEF (Appendix 8))	X	X	X
Sexual Encounter Profile Questionnaire (SEP (Appendix 9))		X	X
Global Efficacy Questionnaire (GEQ (Appendix 11))		X	X

(A) May be completed by a physician, PA or NP within 6 months prior to registration

7.6 Off Treatment Criteria

Any grade 3 or higher toxicity as defined by the CTCAE Active Version that is possibly, probably, or definitely related to ArginMax will result in discontinuation of ArginMax usage.

Participants may go “off-treatment” and stop taking ArginMax for the following reasons: AE or SAE associated with intolerance of study intervention, inadequate agent supply, noncompliance, use of unacceptable concomitant medications, development of a medical contraindication, medically necessary unblinding of study agent (see section 6.9), or participant refuses to take further study medication .

Patients experiencing less than grade 3 toxicity will be encouraged to remain on study and take as much study intervention as they are able to tolerate.

Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants who discontinue treatment but agree to provide outcome data will not be replaced.

7.7 Off Study Criteria

Participants may go “off-study” for the following reasons: completed the study and any study-required follow-up, lost to follow-up or medically necessary unblinding of study agent (see section 6.9), withdrawal of consent, death, or other reasons as discussed/approved by study principal investigator. Patients who fail to complete the study will be replaced. However, all data collected for those who drop out will be used in the analyses to decrease bias and increase the probability of selecting the ‘best’ regimen.

8. PROTOCOL SPECIFIC TRAINING REQUIREMENTS – N/A

9. SPECIMEN MANAGEMENT – N/A

10. REPORTING ADVERSE EVENTS

DEFINITION: An adverse event (AE) is any untoward medical occurrence in a study participant. An AE does not necessarily have a causal relationship with the treatment or study participant. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6.2.

10.1 Adverse Events

10.1.1 AE Data Elements:

- AE reported date
- CTCAE v4.03
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study agent
- Outcome of the event
- Comments

10.1.2 Severity of AEs

- 10.1.2.1 Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.03. as stated on the next page.

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

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.1.3 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

10.1.4 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

10.2 Serious Adverse Events

10.2.1 DEFINITION: ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997 define serious adverse events as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

10.2.2 Reporting Serious Adverse Events

In order to assure complete and timely reporting of adverse events and toxicity, the following general guidelines are to be observed. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supersede the General Guidelines. A

protocol may stipulate that specific grade 4 events attributable to treatment are expected and may not require the standard reporting, however, exceptions to standard reporting must be specified in the text of the protocol.

Adverse Event reporting begins after the patient is registered to the study (or begins the run-in period of the study or begins the wash out period of the study). Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

SAEs (Grade 4 and/or Grade 5) for this protocol should be followed until resolved, especially for those related to the study agent. Documentation should include:

- PID
- Date of SAE
- Description of the event
- Relationship of the SAE to the study intervention
- Severity
- Intervention

1. The protocol Principal Investigator will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require notification within 24 hours of discovery.
3. Any medical event which precipitates hospitalization or prolongation of existing hospitalization must be reported regardless of attribution or whether the adverse event is expected or unexpected.
4. A written report, including all relevant clinical information and all data collection forms due up to and including the date of the event will be sent by mail or FAX to the RB DMC within 10 calendar days unless specified otherwise within the protocol. The material must be labeled:

Attention: Adverse Event Reporting
Research Base Data Management Center
Department of Radiation Oncology
1st Floor Cancer Center
WFUBMC
Medical Center Boulevard
Winston-Salem, NC 27157

5. The Research Base Grant PI, Clinical Research Oversight Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

6. Serious adverse events will be communicated by phone and MedWatch as soon as identified to the CCCWFU Research Base Data Management Center (DMC) at (336) 713-3172. The DMC is responsible for communicating with the FDA, the drug sponsor, WFU IRB, and other regulatory agencies, as well as reporting all SAE's grade 4 or 5 to the Clinical Research Oversight Committee (CROC).
7. Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.
8. When submitting AE, SAE reports and supporting documentation, the study number and the case number (PID #) only must be recorded on the FDA Form 3500 (MedWatch) so that the case may be associated with the appropriate study file.

10.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the MedWatch form in the appropriate format. Follow-up information should be sent to the RB Data Management Center as soon as available.

SAEs (Grade 4 and/or Grade 5) for this protocol should be followed until resolved, especially for those related to the study agent. Documentation should include:

- PID
- Date of SAE
- Description of the event
- Relationship of the SAE to the study intervention
- Severity
- Intervention

Table A: Reporting requirements for Adverse Events (AEs) and Serious Adverse Events (SAEs) for this protocol occurring within 30 days of study completion must be reported via MedWatch

	MILD				MODERATE				SEVERE			
	1		1		2		2		3		3	
	Unexpected		Expected		Unexpected		Expected		Unexpected		Expected	
	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required
Possible Probable Definite	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required

	LIFE-THREATENING/DISABLING				DEATH			
	4		4		5		5	
	Unexpected		Expected		Unexpected		Expected	
	*With Hospitalization	*Without Hospitalization	*With Hospitalization	*Without Hospitalization	*With Hospitalization	*Without Hospitalization	*With Hospitalization	*Without Hospitalization
Unrelated Unlikely	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days
Possible Probable Definite	24-hour; 5 calendar days	24-hour; 5 calendar days	24-hour; 5 calendar days	24-hour; 5 calendar days	24-hour; 5 calendar days	24-hour; 5 calendar days	24-hour; 5 calendar days	24-hour; 5 calendar days

* See Section 10.2.1 for SAE Definition

11. STUDY MONITORING

11.1 Data Management Schedule

The Eligibility checklist/Registration Form should be completed on-line prior to placing the patient on study. Data forms will be submitted to the CCCWFU CCOP Research Base. See Section 10.2.2 for mailing address, or fax to (336) 713-6476 according to the timetable below:

Form	Submission Schedule
H&P, TAS, Concomitant meds, Flow sheet, IIEF (Appendix 8), EPIC-26 (Appendix 10)	Baseline
TAS, Concomitant meds; Flow Sheet, Telephone contact, Med Diary, IIEF (Appendix 8), EPIC-26 (Appendix 10) SEP (Appendix 9) Diary; GEQ (Appendix 11)	Week 4
TAS, Concomitant meds; Flow Sheet, Telephone contact, Med Diary, IIEF (Appendix 8), EPIC-26 (Appendix 10) SEP (Appendix 9) Diary; GEQ (Appendix 11)	Week 8

11.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

11.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, and physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and

- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

11.4 Data and Safety Monitoring Board

The CCCWFU CCOP Research Base Data Safety Monitoring Board meets every six months to review all Research Base Phase II and III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the statistician. Areas of review may include the following: Date study Opened; Study Objectives; Patient Accrual; Patient Status and Retention; Study Status; Last Contact Status; Patient Compliance; Number of Biopsies/Labs as needed; Patient Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to Drug, Arm assigned; Summary of Primary and Secondary Measures.

11.5 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, and NCI/DCP requirements unless the standard at the site is more stringent.

Record retention should be 2 years after the study is discontinued (21 CFR 312.62).

11.6 CDUS Reporting

The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

The primary objective of this randomized dose selection trial is to determine the 'best' dose of ArginMax, when given with or without PDE-5 inhibitors, for use in a subsequent Phase III trial. The 'best' dose will be defined as the one that results in the greatest improvement in erectile function after 8 weeks of therapy for male prostate cancer survivors as quantified by changes in the erectile function domain of the IIEF (Appendix 8).

Secondary objectives include an assessment of toxicity as well as obtaining estimates of accrual, retention, adherence, variability, and treatment efficacy for use in the design of a subsequent Phase III clinical trial and to assess quality of life and sexual function based on other questionnaires (namely the Sexual Encounter Profile Patient Diary and the Global Efficacy Questions).

A randomized, parallel design will be used to assess the effect of ArginMax on sexual function as quantified by the erectile function domain score of the IIEF. Patients will be stratified by age and PDE-5 inhibitors use and randomized with equal probability to receive various doses of ArginMax. Patient evaluations will occur at baseline and 4 and 8 weeks following randomization. The 8 week evaluation will be used to address the primary objective of the study.

12.2 Sample Size/Accrual Rate

The sample size for this trial will be based on statistical selection theory criterion as described by Simon et al.⁶⁵ For a selection trial, one simply chooses the regimen that results in the 'best' response. While Simon used this idea in the context of choosing the regimen with the best tumor response, the idea is applicable to outcomes with other distributions (in addition to the binomial). In our trial, response is erectile function, which we will assume is normally distributed, so the 'best' regimen will be the one with the highest mean erectile function score. The sample size is chosen to ensure a high probability of selecting the best treatment, given that it is better than all the others by some amount D . We base our preliminary variance estimate for the erectile function score on data provided by Incrocci et al (2006), who used a cross-over design to assess the effect of tadalafil on mean sexual function. In that study, the mean \pm SD erectile function score was 8.4 ± 3.1 at baseline ($n=60$), 9.5 ± 5.9 following a placebo ($n=30$), and 17.7 ± 9.9 following tadalafil ($n=30$). So, with no treatment, a weighted estimate of the mean \pm SD erectile function score is 8.9 ± 4.23 . For those patients who will be taking PDE-5 inhibitors, the mean \pm SD erectile function score should be similar to that of the participants who received tadalafil in the Incrocci study (i.e., 17.7 ± 9.9), although the mean may be smaller since these will be men who feel they are still experiencing problems. Since it is not clear how many of the patients in this study will be taking PDE-5 inhibitors, we will assume they all are for purposes of sample size estimation since that is the most conservative assumption (since standard deviation is greatest in that group, assuming those on PDE-5 inhibitors will be similar to those receiving tadalafil in the Incrocci study).

Incorcci et al (2006) found that tadalafil improved the erectile function domain score by 8.2 units compared the placebo group (9.5 vs 17.7). We do not expect that ArginMax will have this large of an effect. We consider an increase of 4 units due to ArginMax would be clinically meaningful as it would correspond to a unit increase in 2/3 of the individual items comprising the erectile function domain. We used simulations to determine the sample size needed in each group to ensure that the probability of selecting the best regimen was 90% given that the best regimen was 4 units greater than all the others. As suggested by Simon et al, we assume the two lesser regimens have no effect on sexual function. For the simulations, we assume that the erectile function score is normally distributed with a standard deviation of 9.9. We further assume that the means of erectile function in the groups receiving the placebo and the lower ArginMax dose are equal and 4 units smaller than the mean in group receiving the highest dose (e.g., 17.7, 17.7, and 21.7, although the actual means do not matter). We randomly select n independent observations from the

Normal distribution with those means and standard deviations, calculate the mean erectile function scores for each group, and select the group with the greatest observed mean. This is repeated 500,000 times. The probability that the 'best' regimen was chosen is calculated as the proportion of times (of the 500,000 repetitions) that the group with the true higher mean was selected. The sample size in each group (n) is increased until that probability exceeds 90%. Assuming that we simply choose the regimen with the greatest post-treatment mean, we would need a sample size of 31 participants per regimen to ensure that we select the 'best' regimen with 90% probability. That same sample size would be needed if we selected the regimen with the greatest change from baseline, assuming the pre/post correlation for erectile function was 0.5. We will actually use a repeated measures analysis of covariance, adjusting for the baseline erectile function scores, and define the 'best' regimen as the one which has the greatest least squares eight week post-treatment mean, adjusted for the baseline score (alternatively this can be thought of as the regimen with the greatest improvement in erectile function from baseline, adjusted for the baseline score). The sample size depends on the pre/post correlation for the erectile function score, and it decreases as the correlation increases. Incrocci et al (2001) found that the pre/post correlations for all the items of the IIEF were between .35 and .58, so we will conservatively assume a pre/post correlation for the erectile function score of 0.35. The adjusted standard deviation would be 9.27 and we find that 27 patients per group would be needed to ensure that the best regimen would be chosen with 90% probability using an ANCOVA model (simulation as above using a SD of 9.27 and ignoring the extra repeated measure at 4 weeks as that would only increase the probability). In addition to selecting the 'best' regimen, we will only pursue a subsequent phase III trial if there is some evidence of effect. Thus we will require that the least squares mean in the 'best' regimen is at least 2 units higher than the least squares mean for the placebo group. Again using simulations based on a simple analysis of covariance model (simulation as above ignoring the extra repeated measure at 4 weeks but also comparing the observed means), we find that 35 patients per group provides 94% probability of selecting the 'best' regimen and 80% probability that the 'best' regimen will be chosen and the mean in that group be at least 2 units greater than the mean in the placebo arm. Assuming a 25% dropout, we will accrue a total of 140 participants to this study (35x3/.75).

12.3 Randomization and Stratification

We will stratify patients based on age and PDE5 inhibitor usage. In terms of age, based on early data as outlined above for L-arginine supplementation, age has been a cut-point showing both a positive and negative effect in older populations. Given that prostate cancer survivors who received radiotherapy are in general an older population, we will look at males age 65 years old and above vs males below the age of 65 years old. In terms of PDE5 inhibitor, we are unable to provide a PDE-5 inhibitor free of charge to the patients on this trial. Patients will therefore be stratified according to current PDE-5 inhibitors usage. The advantage of this approach is that all patients interested in an intervention will be eligible for enrollment and we will not be losing any specific patient group based on financial means. Within each stratum, patients will be randomized to one of the three treatment groups with equal probability using random permuted block randomization. Analyses will not be done separately by strata.

12.4 Primary Endpoint(s)

The primary outcome measure for this study is the erectile function (EF) score obtained from the IIEF. This outcome (as well as the secondary quality of life and sexual function measures) will be assessed at baseline and 4 and 8 weeks following randomization. Descriptive statistics (means, standard deviations, frequencies, etc.) will be presented for each of these outcome measures at baseline and at each follow-up point stratified by treatment arm. A repeated measures model for longitudinal data will then be used to assess the difference in post-randomization measures between treatment groups assuming equal variance at each time. For this analysis, baseline EF will be a covariate, time, strata, and treatment will be fixed class variables, and the actual outcome measures at 4 and 8 weeks will be the dependent repeated measures. Least squares means for the individual treatment groups as well as the treatment differences, along with 95% confidence intervals, will be estimated at each time and for the average of the two times based on the fitted model. The group with the largest LS means at 8 weeks will be defined as the 'best' regimen. Subsequent RM ANCOVA models will be used that include additional covariates such as age, BMI, PS, time varying PDE-5 inhibitors use, etc. These additional covariates will be included to correct for chance imbalances in important prognostic variables and account for that part of the variability in the outcome measures that is due to the covariates, thus improving the precision of the treatment effect. Regression diagnostics and residual plots will be used to find appropriate transformations for the variables in the model to ensure that the models satisfy the 1) linearity, 2) homogeneity of variances, and 3) normality assumptions. A separate model, suggested by Fitzmaurice et al, which uses the baseline EF as a repeated measure and forces the groups to have equal means at baseline will also be assessed. This model has the advantage that it includes even those participants who only have a baseline measure of EF.

12.5 Secondary Endpoint(s)

The secondary endpoints for this study include;

- 1) Toxicity – (see Section 6.2.)
- 2) Accrual
- 3) Retention
- 4) Adherence
- 5) Quality of life and sexual function

Accrual will be estimated as the number of patients accrued divided by the number of months of accrual. An exact 95% confidence interval for the monthly accrual rate will be calculated based on the Poisson distribution.

Retention will be primarily defined as the proportion of patients who provide 8-week data. That is, participants who discontinue the study drug but remain in the study and complete the outcome assessments will be counted in the numerator for calculating retention. (Their adherence will be low, however.) Retention estimates will be calculated overall and by treatment arm. A Fisher exact test will be used to assess the difference in retention between the three arms. In addition, since participants drop out at varying times throughout the study, Kaplan-Meier methods will be used to estimate the time to drop-out, and a logrank test will be used to assess the difference in these distributions between treatment arms.

Adherence will be calculated 1) as the number of pills taken divided by the ideal number of pills that could have been taken while on study; and 2) as the number of pills taken divided by the number of pills that could be taken if the participant completed the study. We will calculate and report the mean adherence across all individuals as well as the proportion of patients who were 75% adherent (using both definitions of adherence). Neither definition of adherence is perfect. The first gives a measure of the adherence while the patient is engaged in the study. The second gives a measure of the amount of ideal drug taken overall and penalizes those who drop out. ANCOVA will be used to assess the difference in mean adherence between the three arms and a chi-square test will be used to compare the proportion of patients who were at least 75% compliant in the three arms.

In addition to the primary endpoint of the trial, the erectile function score, other subscale scores will be calculated from the International Index of Erectile Function (IIEF).⁵⁶ These include the orgasmic function (OF) domain: questions 9 and 10; sexual desire (SD) domain: questions 11 and 12; intercourse satisfaction (IS) domain: questions 6 to 8; and the overall satisfaction (OS) domain: questions 13 and 14. In addition to the IIEF, the Expanded Prostate Cancer Index Composite (EPIC-26 (Appendix 10)) will be used to assess the quality of life of prostate cancer survivors.⁵⁷⁻⁵⁹ Additionally, patients will keep a Sexual Encounter Profile (SEP) with entries to be made after each sexual attempt. The SEP (Appendix 9) consists of 5 questions related to erectile quality and overall satisfaction. Descriptive statistics (means, standard deviations, frequencies, etc.) will be presented for each of these outcome measures at baseline and at each follow-up point stratified by treatment arm. For the outcomes that can be treated continuously, repeated measures analysis of covariance will be used to obtain estimates of the treatment differences, variances, and correlations over time for use in designing a subsequent phase III trial. For outcomes that are dichotomous or need to be dichotomized, repeated measures logistic regression will be used to assess treatment differences. Strata will be included in both the linear and logistic models. In addition, separate models will include PDE-5 inhibitors use as a time varying covariate as it is expected to have a major effect and it may not be the case that participants use (or do not use) PDE-5 inhibitors consistently throughout the study (as would be reflected in the strata).

12.6 Reporting and Exclusions

Adherence, as defined in 12.4, is one of the outcomes that will be monitored in this study. The primary analyses estimating treatment efficacy will include all randomized patients, regardless of adherence. Drop-outs are a more difficult problem, one that is more satisfactorily handled proactively rather than retrospectively. We will make a concerted effort to minimize the number of drop-outs, beginning with the patients that are accrued. If a patient seems unwilling to participate or indicates that he may not be able to be compliant, we will not press him to participate. In addition, patients who refuse treatment at some point during the course of therapy will be encouraged to stay in the study and provide outcome data. Despite the best of efforts, some data will be missing due to missed visits, deaths, or patients refusing further participation. The primary analyses are based on maximum likelihood methods and assume patients are missing at random, that is the missingness can depend on covariates and observed outcomes but not the missing outcomes. This assumption that the missingness does not depend on the missing data cannot be tested completely since the data needed to test the assumption is missing. Exploratory analyses using multiple imputations will assess the impact of various assumptions regarding the missingness on the estimates of treatment effect.

12.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of ArginMax or placebo. Fisher exact tests will be used to assess differences in toxicity between the three treatment arms.

12.8 Evaluation of Response

All participants included in the study will have their outcomes assessed at baseline and at 4 and 8 weeks following randomization. Efforts will be made to collect these data even if patients refuse further treatment. Data should only be missing for those who expire or withdraw consent. As noted above, all randomized participants will be included in the primary analyses of treatment efficacy on the outcomes described above. The preliminary estimates of treatment effect and the estimates of variability that will be used in the design of a subsequent comparative trial will be based on the analyses of all the randomized patients. Secondary analyses will be performed on the participants who completed the study with good (75% or higher) adherence, perhaps providing us with an upper bound estimate of treatment efficacy should all patients remain in the study and be adherent. This estimate is likely biased, however, and will be interpreted with caution. The reasons for excluding participants from any analysis will be clearly reported.

12.9 Interim Analysis

No interim analysis is planned for this pilot study. However, all Research Base studies are monitored by the CCCWFU DSMB twice yearly for accrual, retention, adherence, data quality, and safety. This will also include an analysis of minority recruitment, retention, and adherence to ensure adequate minority representation among patients accrued to the study (see Section 4.3). Descriptive reports for the DSMB review will consist of summary statistics (means, standard deviations, proportions, etc.) for patient characteristics and outcome measures by treatment arm, actual versus projected accrual, participation by the various sites, and quality control information (retention, adherence, missing data, etc.). Tables, graphs, and charts will be used to illustrate the data when appropriate.

Additionally, any untoward adverse events or other unusual results will be reported to the IRB and to the CCCWFU Clinical Research Oversight Committee for further action. Note that all grade 3+ toxicities are also reviewed by the Wake Forest University Comprehensive Cancer Center's Clinical Research Oversight Committee, which meets monthly.

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