CHRONIC PROSTATITIS COLLABORATIVE RESEARCH NETWORK-2 (CPCRN-2)

Proposed Randomized Clinical Trial (RCT) #1

A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients

VERSION 2.0

Effective Date: September 12, 2005

Includes Protocol Amendment #1 and #2

Sponsored By:

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institutes of Health (NIH)
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INVESTIGATOR AGREEMENT PAGE

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Randomized Clinical Trial #1 (RCT #1)

A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients

INVESTIGATOR (S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of subjects.

- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

- I will ensure that the requirements relating to obtaining HIPAA authorization following the federal mandate for disclosure of access to data and associated privacy protection will be met.

- I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.

- I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.

- I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments by providing them with copies of the protocol, any subsequent protocol amendments, and access to all information furnished by the sponsor.

Principal Investigator Signature: _____

Date: _____

Name (Please Print): _____

Institution: _____

Once signed, this original shall be maintained in the Regulatory Binder at the clinical center, with a copy faxed to the Project Manager at the DCC (215-573-6262).

CPCRN-2 RCT #1(ALFUZOSIN TRIAL) PROTOCOL AMENDMENT

Introduction:

The Chronic Prostatitis Collaborative Research Network 2 (CPCRN-2) Clinical Trial Protocol #1 entitled: "A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients"- Version 1.0 – Effective August 16, 2004, was developed by the CPCRN-2, and will be maintained by the Data Coordinating Center (DCC) at the University of Pennsylvania over the course of the study through issuance of protocol amendments and revisions.

The first edition of this protocol (Version 1.0, August 16, 2004) is being amended as of the effective date April 12, 2005. Please refer to the protocol table of contents for the location of changes listed below.

Summary of Protocol Amendment #1

The goals of this amendment are:

1) To update Clinical Site name changes
2) To allow a physical examination completed by the Principal Investigator or his/her designee on a newly diagnosed study participant prior to the participant signing study consent to be utilized as the physical examination currently required at study baseline screening visit 1. This physical examination and associated urine and/or EPS lab results, conducted up to four (4) weeks prior to study baseline screening visit #1, will be acceptable for satisfying screening visit requirements. A focused physical examination is part of the routine standard of care in the initial evaluation of a urology patient and therefore, will reduce participant burden and inconvenience in not having multiple identical procedures performed within a short period of time.
3) To clarify that all sites do not need to use the same brand of dipstick for urinalysis.
4) To clarify sample size adjustments and the frequency of Patient Recruitment reports.

1. STUDY DESIGN AND OBJECTIVES

[Section 2.5 Study Organizations]

- "Cleveland Clinic, Florida" changed to "Cleveland Clinic, Ohio"
- "University of Washington" (Berger site) changed to "University of Washington Medical Center/Harborview Medical Center/UW Medicine" "
- University of Washington-Harborview Medical Center/University of Sciences Malaysia" (Krieger site) changed to "University of Washington/University of Sciences Malaysia"

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2. TRIAL TESTS AND PROCEDURES

- ***Current Protocol Text Reads:***

[Section 7.2 Screening Visit#1 – item #6] *Physical Examination*. Each participant will undergo a focused physical examination. This examination will include an abdominal exam, external genital exam, rectal exam, prostate exam, and perineal exam.

***Change Protocol Text to Read*:**

[Section 7.2 Screening Visit#1 – item #6] *Physical Examination*. Each participant will undergo a focused physical examination at this baseline visit. This examination will include an abdominal exam, external genital exam, rectal exam, prostate exam, and perineal exam. If the participant has received a prior focused physical examination conducted by the Principal Investigator or his/her designee within four (4) weeks of study enrollment, a documented copy of this prior physical examination will be acceptable.

- ***Current Protocol Text Reads:***

[Section 7.2 Screening Visit#1 – item #7] *Urinalysis, Urine, and EPS Specimens for Microscopy and Culture.* Each participant will provide two (2) urine specimens (VB2 and VB3) and an EPS (expressed prostatic secretion) specimen for either analysis or culture.

***Change Protocol Text to Read*:**

[Section 7.2 Screening Visit#1 – item #7] *Urinalysis, Urine, and EPS Specimens for Microscopy and Culture.* Each participant will provide a VB2 specimen, a VB3 and/or EPS (expressed prostatic secretion) specimen for either analysis or culture. If the participant has provided these specimens as part of the focused physical examination conducted by the Principal Investigator or his/her designee within four (4) weeks of study enrollment, a documented copy of these laboratory results will be acceptable.

- ***Current Protocol Text Reads:***

[Section 7.2 Screening Visit#1 – item #7] *Urinalysis, Urine, and EPS Specimens for Microscopy and Culture.* Dipstick urinalysis will be conducted on the midstream urine (VB2) for macroscopic analysis; all centers will be required to use the same brand of dipstick.

The statement “all centers will be required to use the same brand of dipstick” has been removed.

3. STATISTICAL CONSIDERATIONS

- ***Current Protocol Text Reads:***

[Section 10.2 Sample Size Calculations] “This proposed sample size includes adjustments for clustering within clinical sites (5% increase), withdrawal (15% increase), and interim monitoring (5% increase)”

***Change Protocol Text to Read*:**

[Section 10.2 Sample Size Calculations] “This proposed sample size includes adjustments for clustering within clinical sites (20% increase) and interim monitoring (5% increase)”.

- **[Section 10.6 Report Table]**

Frequency of Patient Recruitment/Targets Report changed from “q2 weeks” to “q4 weeks”.

CPCRN-2 RCT #1(Alfuzosin Trial) protocol AMENDMENT #2

Introduction:

The Chronic Prostatitis Collaborative Research Network 2 (CPCRN-2) Clinical Trial Protocol #1 entitled: "A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients"- Version 1.0 – Effective August 16, 2004, was developed by the CPCRN-2, and will be maintained by the Data Coordinating Center (DCC) at the University of Pennsylvania over the course of the study through issuance of protocol amendments and revisions.

The first edition of this protocol (Version 1.0, August 16, 2004) is being amended as of the effective date July 20, 2005. Please refer to the protocol table of contents for the location of changes listed below.

Summary of Protocol Amendment #2

1. Revise entry criteria to remove "chronic" epididymitis from the list of symptoms in Deferral Criteria #4 and to remove Deferral Criteria #6 to reflect a label change allowing the use of erectile dysfunction medications with alpha blockers.
2. Allow prospective participants to return for their Screening Visit #2 when their 2-day urine culture results (required to assess eligibility) are available, rather than wait at least 7 days to return.

1. PARTICIPANT CRITERIA

a. [Section 4.1.3 Deferral Criteria #4] Participant has experienced symptoms of acute or chronic epididymitis within the past three (3) months.

- ***Change Protocol Text to Read*:** Participant has experienced symptoms of acute epididymitis within the past three (3) months.

b. [Section 4.1.3 Deferral Criteria #6] Participant has been taking excluded medications such as Cialis®, Levitra®, and Viagra® in the past one (1) week.

- ***Remove this deferral criteria***

2. TRIAL TESTS AND PROCEDURES

a. [Section 7.1 Procedural Summary- second paragraph] This study is comprised of phases for each participant: i) the screening phase and ii) the treatment and follow-up phase. The screening phase, which assesses a participant's eligibility via inclusion, exclusion, and deferral criteria, will consist of two baseline visits no more than four (4) weeks and no less than one (1) week apart.

- ***Change Protocol Text to Read*:** This study is comprised of phases for each participant: i) the screening phase and ii) the treatment and follow-up phase. The screening phase, which assesses a participant's eligibility via inclusion, exclusion, and deferral criteria, will consist of two baseline visits no more than four (4) weeks and no less than two (2) days apart (when 2-day urine culture results are available).

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b. [Section 7.2 Screening Visit#1 – first sentence] The first screening visit should occur no more than four (4) weeks and no less than one (1) week prior to randomization.

- ***Change Protocol Text to Read*:** The first screening visit should occur no more than four (4) weeks and no less than two (2) days prior (when 2-day urine culture results are available) to randomization.

c. [Section 7.3 Screening Visit#2 – first sentence] Screening Visit #2 should be completed at least one (1) week after, but no more than four (4) weeks after Screening Visit #1.

- ***Change Protocol Text to Read*:** Screening Visit #2 should be completed at least two (2) days after (when 2-day urine culture results are available), but no more than four (4) weeks after Screening Visit #1.

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1 INTRODUCTION

Nonbacterial prostatitis, also referred to as prostatodynia, chronic prostatitis (CP), and chronic pelvic pain syndrome (CPPS),[1] is a diagnosis applied to men experiencing pelvic (perineal, testicular, penile, lower abdominal) pain, with or without voiding symptoms, in the absence of a specific identifiable symptom cause. Despite its high prevalence (5%-16%),[2-4] surprisingly little is certain about the etiology, diagnosis, and effective treatment of this syndrome. The symptoms may or may not be associated with the prostate gland. Standard diagnostic tests and evidence-based treatments are lacking.[5;6] Therapy is usually with antibiotic medications, despite negative culture findings and no randomized clinical trial evidence to support this choice of treatment.[7]

Chronic prostatitis is a significant cause of health care use. The syndrome accounts for about two million office visits per year in the United States,[8] and many patients undergo multiple, diverse diagnostic procedures and treatments.[9] Analysis of National Ambulatory Medical Care Surveys of 1990-1996 revealed that visits associated with a diagnosis of prostatitis were approximately equally divided between urologists' and primary care physicians' offices.[8;10]

Non-bacterial prostatitis or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a condition affecting men, characterized by idiopathic pelvic pain with or without urinary symptoms.[11] Although symptoms of urinary frequency and urgency may be present in some patients with prostatitis, in general, it is the absence of these urologic symptoms that diagnostically differentiates this syndrome from Interstitial Cystitis (IC), which is found in both men and women.[12] Urodynamic and endoscopic abnormalities are found both in IC and CP/CPPS.[13;14] CP/CPPS may be characterized by inflammation in genitourinary (GU) secretions (Type IIIA) or absence of genitourinary inflammation (Type IIIB). Asymptomatic chronic inflammatory prostatitis (Type IV) is detected in some men evaluated for infertility or prostate cancer. The relationship to CP/CPPS (Type III) is unknown. Infection with common GU pathogens is not present in either IIIA or IIIB although infection with organisms not detectable on culture cannot be eliminated.[15] There is little evidence for an infectious etiology. Other possible etiologies are immunologic response,[16] musculoskeletal abnormalities,[17] neuropathic inflammation,[18] and genetic causes.[19]

Findings from a recent CPCRN study revealed no significant treatment effect with ciprofloxacin or tamsulosin hydrochloride.[20] Smaller studies, however, have shown positive treatment effect with the use of prolonged treatment with alpha-adrenergic blocking agents terazosin[9] and alfuzosin[8] in specific populations of patients early in the course of the disorder. Alfuzosin is a more recent alpha-adrenergic blocking agent and may affect both the peripheral and central nervous system response to pain.[10] We believe there is enough evidence to study the treatment of alfuzosin in patients with relatively new onset CP/CPPS.

2 STUDY DESIGN AND OBJECTIVES

2.1 Primary Objectives

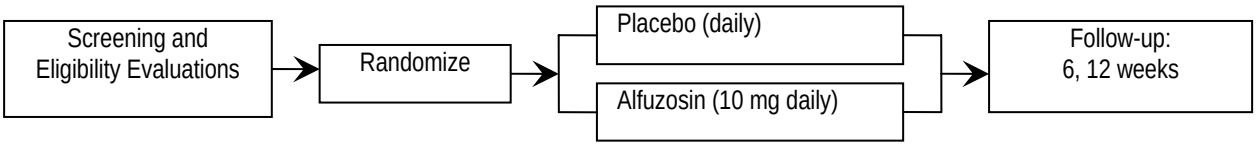
1. To compare 12 weeks of treatment with alfuzosin versus placebo in newly-diagnosed, alpha-blocker naïve CP/CPPS participants with respect to the primary endpoint in the NIH-CPSI.
2. To evaluate the safety and tolerability of 12 weeks of alfuzosin in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.

2.2 Secondary Objectives

1. To characterize newly-diagnosed, alpha-blocker naïve CP/CPPS participants with respect to symptom severity.
2. To assess the incidence of depression and anxiety, and its relationship to symptom severity and response to treatment, in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.
3. To assess domains of male sexual function and its relationship to symptom severity and response to treatment, in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.
4. To assess the impact of patient expectations on symptom severity and response to treatment, in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.

2.3 Study Design

The proposed randomized clinical trial will utilize a 2-arm randomized clinical trial design as shown below. All participants who meet eligibility criteria at baseline screening will be randomized to either alfuzosin 10 mg daily or an identical looking placebo.



2.4 Study Time Frame

Approximately 270 eligible patients, 135 per treatment arm, will be randomized either to alfuzosin or to its matching placebo, and followed for a period of 12 weeks after randomization. There will be four (4) research clinic visits: Visit 1 (screening), Visit 2 (baseline/randomization), Visit 3 (6-week evaluation) and Visit 4 (12-week primary endpoint evaluation).

It is expected that the limitations of the inclusion criteria (recent onset and alpha-blocker treatment naive) may have an impact on the ability of the participating clinical centers to recruit these study participants. Each of the eleven (11) Clinical Sites (see next section) will randomize approximately 25 participants at the rate of one participant per month. Allowing for an additional twelve (12) weeks of follow-up on all participants, the total time required for accrual and follow-up for this trial is expected to be 28 months.

2.5 Study Organizations

The CPCRN-2 Study Organization consists of eleven (11) clinical centers that will recruit participants for the RCT:

1. Cleveland Clinic, OH 44195
2. Harvard Medical School -Massachusetts General Hospital & Brigham and Women's Hospital, Boston, MA 02114
3. Northwestern University, Chicago, IL 60611
4. Queen's University, Kingston, Ontario, Canada K7L 2V7
5. Stanford University Medical Center, Stanford, CA 94305
6. Temple University, Philadelphia, PA 19140
7. University of California, Los Angeles, CA 90095

8. University of Maryland, Baltimore, MD 21201
9. University of Mississippi, Jackson, MS 39216
10. University of Washington Medical Center/Harborview Medical Center/UW Medicine, Seattle, WA 98195
11. University of Washington, Seattle, WA 98108/ University of Sciences Malaysia

In addition to the Clinical Sites, the group includes a Data Coordinating Center (DCC) located at the University of Pennsylvania School Of Medicine. The DCC will provide data management/computing and biostatistical leadership for the design/conduct of the trial. Additional responsibilities include: 1) the preparation and distribution of the Manual of Procedures (MOP), 2) collaboration with study investigators in the development, testing, and use of all CRFs and study procedures, 3) the development and application of quality assurance procedures including data tracking and validation, query processes, and maintenance of related documentation, and 4) the training of clinical site staff and coordination of site monitoring. The CPCRN-2 Executive Committee oversees all aspects of group research. Finally, the Data and Safety Monitoring Board (DSMB) of the Urological Pelvic Pain Collaborative Research Network (UPPCRN) will review the research protocol and plans for data and safety monitoring. Responsibilities include the periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that could affect study outcome. The DSMB will also monitor developments that may have an impact on the safety of the participants or the ethics of the study, and make recommendations concerning continuation or conclusion of the trial.

2.6 Study Endpoints

2.6.1 Primary Endpoint

The primary endpoint to be used for efficacy evaluation is the response rate, defined as a 4-point decrease from baseline to 12 weeks in the NIH-CPSI Total Score (scale of 0 - 43).[21] The decision to use this 4-point cut-off is based on analysis of the previous CPCRN clinical trial on ciprofloxacin and tamsulosin (unpublished data). The NIH-CPSI total score responsiveness to change, from baseline to 6-weeks, was examined relative to the GRA outcome scale and the two scales were shown to be highly correlative. Among those who reported "moderately improved" or "markedly improved" (n=39) on the GRA, 35 participants (90%) reported a $\geq$ 4-point decrease. Moreover, the proportion of participants meeting the responder criteria of a 4-point change who reported no improvement on the GRA ("false positive") was 15.7%. This false positive rate decreases only trivially with an increasing threshold of a 5-point decline (12.8%) or a 6-point decline (11.6%).

In this trial "responders" will be defined as those subjects demonstrating at least a 4-point drop from baseline to 12 weeks in the NIH-CPSI; the proportion of responders by this definition will be compared between treatment groups. Although such an improvement would be unlikely to be interpreted by most patients as a major improvement in symptoms, it will allow detection of even a subtle improvement in order to not miss any potentially therapeutic response. This is particularly important in a population of men with more recent onset of symptoms and less pre-treatment than the previous CPCRN trial.

Using the 4 point decrease as primary outcome may result in some loss in statistical power, but allows study withdrawals to be considered as non-responders for an intent-to-treat analysis. (The drop out rate for the previous CPCRN trial was approximately 10% over 6-12 weeks).

2.6.2 Secondary Endpoints

A number of secondary outcome measures related to both specific symptoms and overall symptom scores will be used to supplement the analysis based on the primary endpoint. One secondary endpoint will be a participant-reported Global Response Assessment (GRA) of symptom change at twelve (12) weeks relative to baseline or withdrawal; whichever comes first. Additional symptom-related secondary outcome measures include the subscales of the NIH-CPSI (for pain, urinary symptoms, and quality of life), the McGill Pain Questionnaire (a measure of pain intensity), the MOS SF-12 (a measure of health-related quality of life), the Hospital Anxiety and Depression Scale (a measure of depressive symptom severity), the International Index of Erectile Function (a measure of male sexual function), and select questions from the Male Sexual Health Questionnaire (for ejaculatory function and ejaculatory bother). When combined, the primary and secondary endpoints address all of the recommended core outcome domains for chronic pain clinical trials. Laboratory and procedural measures to be assessed at baseline include urine screening and expressed prostatic secretions (EPS) and urine testing.

Additional details of the proposed secondary endpoints are provided below.

- Symptom Assessment Form (SYM): These are individual questions about pain, urgency and abnormal frequency obtained on 0 – 10 Likert scales.
- Global Response Assessment (GRA): The GRA is a single question patient-driven symmetrical outcome scale with seven categories ranging from 1 for "markedly worse" to 4 for "no change" to 7 for "markedly improved". The GRA has been recommended as the primary outcome measure for interstitial cystitis (IC) trials[22] and has been used as the primary outcome measure in two NIDDK sponsored studies in IC. This question will only be asked during follow-up visits.
- McGill Pain Questionnaire (MPQ): The MPQ will be used because it evaluates the quality of pain as well as the intensity of pain, adding a dimension that the NIH-CPSI does not capture. Total pain scores and both subscores of sensory and affective pain will be evaluated.
- Medical Outcomes Study Short Form 12 (SF-12): Both the Physical Composite Score (PCS) and the Mental Composite Score (MCS) will be evaluated
- Hospital Anxiety and Depression Scale (HADS)-This 14-question scale provides scores for the independent measures of anxiety and depression.
- International Index of Erectile Function (IIEF): This 15 question index addresses the relevant domains of male sexual function, including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.
- Male Sexual Health Questionnaire (MSHQ): Only the questions from the Ejaculatory Function (7 questions) and Ejaculatory Bother (1 question) domains will be administered and evaluated.
- Urine (VB2 and VB3), and expressed prostatic secretions (EPS) will be collected. Details are described in a later section of this protocol.
- Adverse Events/Serious Adverse Events: These are described in detail in a later section of this protocol.

3 STUDY INTERVENTIONS AND RATIONALE

3.1 Alfuzosin (Uroxatral®)

Patients who have been treated with alpha-blockers show improvement in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia, and many anecdotal reports suggest that they

do the same for the LUTS, as well as the pain/discomfort, associated with CP/CPPS. Alpha-blockers were among the first potential therapies for CP/CPPS to undergo prospective randomized placebo controlled assessment. Phenoxybenzamine,[23;24] alfuzosin,[25] terazosin,[26;27] and tamsulosin[26] have all showed at least modest benefits compared to placebo therapy (see table below). But these early trials evaluating alpha-blockers for abacterial prostatitis and prostatodynia were hampered by a lack of consensus regarding definition of the condition and the fact that no validated outcome measures were available. Studies to date have also been small and of short duration, often enrolling men with a very long history of CP/CPPS at treatment failures.

Nickel et al.[28] reported on 58 men with CP/CPPS randomized to tamsulosin 0.4 mg or placebo for 6 weeks after a 2-week placebo run-in. After 6 weeks, patients treated with tamsulosin had a statistically significant treatment effect (-3.6; $p = 0.04$) compared to placebo patients. A significant treatment effect was not observed in patients who had mild symptoms (25^{th} percentile – 1.6 points; $p = 0.53$) while those with severe symptoms (75 percentile) had a statistically and clinically significant response compared to placebo (treatment effect was –8.3 points; $p < 0.01$).

Cheah et al.[9] randomized 100 chronic prostatitis patients, of whom 86 completed the study, to either terazosin or placebo for 14 weeks. Patients on terazosin had a 50% reduction in mean symptom score compared to 37% in the placebo treated group ($p=0.001$). Terazosin resulted in modest but significant improvement in all domains of the NIH-CPSI (pain, urinary and quality of life domains).

Mehik et al.[29] randomized 21 CP/CPPS patients to 6 months of alfuzosin treatment and 19 patients to 6 months of placebo therapy. Patients in the alfuzosin group had a significant amelioration of symptoms compared to the placebo therapy group that was evident at 2 months and became even more clinically significant by 6 months. At the end of the 6-month active treatment phase, symptoms in the alfuzosin group returned slowly over the next 6 months.

The National Institutes of Health sponsored a CPCRN study comparing placebo, ciprofloxacin, tamsulosin and ciprofloxacin plus tamsulosin in a randomized controlled clinical trial in men with CP/CPPS.[30] This yet to be published trial was presented at the May 2004 Annual AUA meeting. In a 2 x 2 design, 196 male patients were randomized to treatment arms of tamsulosin (+/- ciprofloxacin) or placebo (+/- ciprofloxacin). No statistically or clinically significant difference was observed between groups. However the patients enrolled in this study, compared to the three randomized trials described above, were very chronic (long duration of symptoms) and heavily pre-treated (including previous alpha-blockers).

Alpha-blockers may benefit patients suffering from chronic prostatitis, but like many other treatments, do not produce spectacular cure rates, especially in chronic patients who have failed many previous therapies. It appears that long-term therapy (over six weeks) in alpha-blocker naïve patients may provide the most benefit in CP/CPPS. Alpha-blockers should be evaluated in prospective randomized placebo controlled trials in men recently diagnosed with CP/CPPS who have not been previously treated with alpha-blockade.

Alpha Blocker	Year	n	Active Response	Placebo Response
Phenoxybenzamine	1981	37	50% improved	8% improved
Phenoxybenzamine	1983	39	Decrease in pain compared to placebo ($p<0.05$)	
Alfuzosin	1992	20	Modest improvement compared to placebo ($p=0.01$)	
Terazosin	1994	24	76% significant improvement	N/A
Terazosin or alfuzosin	1998	163	64% had satisfactory symptom response	N/A
Terazosin or tamsulosin	1999	18	Significant improvement compared to baseline	No significant improvement compared to baseline
Terazosin	2001	69	Symptom score improvement compared to placebo ($p=0.001$)	
Tamsulosin*	2002	58	52% response	33% response
Terazosin*	2003	86	56% response	36% response
Alfuzosin*	2003	40	65% response	24% response

Alfuzosin is a newer alpha-adrenergic blocking agent, which has been developed, tested, and used in Europe extensively for the treatment of benign prostatic hyperplasia (BPH). It is a quinazoline derivative (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride, unlike tamsulosin hydrochloride (FLOMAX®) which is a methoxybenzene sulfonamide. Since it is an alpha-1 selective antagonist, dose titration is not necessary. Treatment-associated blood pressure alterations are small, although vasodilatory related adverse events may occur more frequently with alfuzosin than with placebo, suggesting that participants with symptomatic hypotension should be monitored closely. As with all alpha-blockers, there is the potential for syncope. Little or no incidence of abnormal ejaculation relative to placebo has been reported when participants use alfuzosin,[31;32] differing from those reported using other alpha-blockers.[33;34] In clinical trials in the treatment of BPH, efficacy as measured by improvement in voiding symptoms and peak flow rates has been reported as significant compared to placebo.[33]

3.2 Ethical Considerations and Rationale for Use of a Placebo

All patients will be informed that they may risk temporary discomfort, and all will be fully informed about alternative treatments that may be available to them outside of the RCT. This is a short duration trial, in which placebo control will be used for a 12 week period of time following randomization. Since evidence of effectiveness of existing medical therapies is limited, and there is no established uniformly acceptable treatment for CP/CPPS, it is important that effective clinical treatment choices be made available to patients. Investigation of a potentially effective treatment agent in a short-term placebo controlled study may provide reliable clinical evidence in the treatment of CP/CPPS patients.[35;36]

4 PARTICIPANT CRITERIA

4.1 Study Population

This study will attempt to recruit "newly diagnosed" and "alpha-blocker treatment naïve" CP/CPPS patients, in contrast to the population recruited for the previous CPCRN trial. The patients in the previous trial had longstanding symptoms, and many had failed previous treatment with the study drugs; thus, the study population was likely enriched by patients who were less likely to respond. We chose to first study "newly diagnosed" and "alpha-blocker treatment naïve" patients with CP/CPPS, since it has been hypothesized that this population may be more likely to respond to conservative treatment. This focus is consistent with the goals of the NIDDK Request for

Applications to establish the Chronic Prostatitis Collaborative Research Network (CPCRN) which emphasized the ability of centers to recruit and evaluate treatments for newly diagnosed CP/CPPS patients.

We have chosen an alpha-adrenergic receptor blocker for the trial because of recent findings suggesting that such agents were efficacious, as compared with placebo, for patients who had not received prior therapy with alpha-blockers and who were treated for 12 weeks. The study will test whether the long-acting subtype-selective alpha-adrenergic receptor blocker alfuzosin is better than placebo in improving symptoms of CP/CPPS in men with minimal previous treatment.

4.1.1 Inclusion Criteria

1. Participant has signed and dated the appropriate Informed Consent document.
2. Participant is male.
3. Participant is ≥ 18 years of age
4. Participant has an overall score on the NIH-CPSI of ≥ 12 out of a potential of 0–43 points at both screening visits.
5. Participant has had symptoms of discomfort or pain in the pelvic region for at least a six-week interval at the time of presentation.
6. Symptoms bothersome enough to prompt a physician visit have been present for two years or less.

4.1.2 Exclusion Criteria

Any participant satisfying one of the following criteria will not be eligible to participate in the CPCRN-2 RCT #1 Study.

1. Participant has evidence of facultative Gram negative or enterococcus with a value of ≥ 1000 CFU/ml in mid-stream urine (VB2).
2. Participant has previously received alfuzosin (Uroxatral®), tamsulosin hydrochloride (Flomax®), doxazosin mesylate (Cardura®), terazosin HCL (Hytrin®), or other alpha-adrenergic receptor blockers for symptoms of CP/CPPS or within the past two years for any other reason.
3. Participant has a history of prostate, penile, testicular, bladder, or urethral cancer or has undergone pelvic radiation, systemic chemotherapy, or intravesical chemotherapy.
4. Participant has a history of moderate or severe hepatic impairment, severe renal sufficiency, severe or unstable cardiovascular (i.e. prolonged QT), respiratory, hematological, endocrinological, neurological or other somatic disorders.
5. Participant has unilateral orchialgia without pelvic symptoms, active urethral stricture, or neurological disease or disorder affecting the bladder.
6. Participant has uninvestigated, significant hematuria.
7. Participant has undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy.
8. Participant has a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol.
9. Participant is currently taking exclusionary medications such as potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, or ritonavir) or erythromycin.

4.1.3 Deferral Criteria

There are several conditions for which a participant will be deferred from entry into the study. Once it is formally ascertained that the condition is not present or has subsided according to the time frame identified, the participant will be reconsidered for entry into the trial. The following list identifies some of the conditions for deferment.

1. Participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml, within the past three (3) months.
2. Participant has had clinical evidence of urethritis, i.e. including urethral discharge or positive culture, within the past three (3) months, diagnostic of the following sexually transmitted diseases (STDs): gonorrhea, chlamydia, mycoplasma, or trichomonas.
3. Participant has had a prostate biopsy in the past three (3) months.
4. Participant has experienced symptoms of acute epididymitis within the past three (3) months.
5. Participant has been diagnosed with or treated for symptomatic genital herpes in the past twelve (12) months.
6. Participant has been taking prescription drugs with 5-alpha reductase activity (i.e. dutaserade or finasteride) in the past twelve (12) months.

5 PARTICIPANT RECRUITMENT AND CONSENT

5.1 Participant Recruitment

Participant recruitment will be conducted through the urology clinic at each of the designated clinical sites. Participants may be self-referred or referred through their physician (either solicited or unsolicited by the urology clinic). Male participants referred to the clinics with symptoms of Interstitial Cystitis who the investigator feels are more appropriately diagnosed as CP/CPPS will be introduced to the CPCRN protocol and asked whether they are interested in participating in the study. Potential study participants who meet the basic study eligibility criteria and are interested in participating will sign the informed consent form approved by the local Institutional Review Board (IRB) prior to beginning study participation. This form will provide consent for both the screening and the follow-up procedures.

5.2 Informed Consent

Interested subjects will be asked to sign the informed consent form approved by the local Institutional Review Board (IRB). This form will provide consent for both the screening and the follow-up procedures. Potential participants may sign written consent to participate prior to screening visit B1.

Each clinical center will prepare an informed consent form following the guidelines of their local Institutional Review Board (IRB), and applicable regulations for Informed Consent. The form will, at a minimum, contain a description of the potential risks, benefits, expense to the subject, and alternative treatment. Prior to signing the informed consent, the Research Coordinator will review the details of the consent form orally with the participant, and answer any questions that the participant has concerning participation in the RCT. The original signed consent form will be kept in the participant study file at the clinical center, while a copy of the signed consent form will be given to the participant.

5.2.1 HIPAA Authorization

Following the newly mandated federal HIPAA regulations, authorizations will be provided to all research participants at the time of presentation of consent which detail all potential risks of disclosure and individuals and organizations who may have access to participant research data.

5.2.2 Patient Confidentiality

Procedures to assure confidentiality will be strictly observed. All data will be 1) kept in confidential locked files; 2) identified by subject number only; and 3) kept separately from identifying information used for subject tracking and follow-up contacts. Identifying information will kept in separate locked files. No identifying information will be disclosed in reports, publications or presentations. As an additional safeguard of confidentiality, the investigators will obtain a Federal Certificate of Confidentiality from the National Institutes of Health (NIH).

5.3 Risks and Benefits to Participants

This is a double-masked, placebo-controlled RCT evaluating the efficacy of alfuzosin (UROXATRAL®) in participants with newly-diagnosed and alpha-blocker naïve CP/CPPS participants. After evaluation of previous study data and physician participant records using these drugs, it is anticipated that there may be a direct benefit to the participants; however, direct benefits are not guaranteed. The information gained from this study may eventually prove beneficial to the treatment and diagnosis of other patients with CP.

5.3.1 Risks of Alfuzosin (Uroxatral®)

Alfuzosin is a synthetic antagonist of the alpha1 adrenergic receptor in humans. Hypersensitivity to alfuzosin can occur resulting in skin rashes, pruritis, urticaria, or angioedema. Participants with a known hypersensitivity to alfuzosin or any component of the drug formulation should be excluded. The principal risk of alpha-adrenergic blockers is a lowering of blood pressure while on the drug. This can result in dizziness, syncope, or postural hypotension. In the U.S studies of alfuzosin, symptomatic postural hypotension occurred in 2 of 473 men receiving 10 mg/day (0.4%) compared to none of 493 men receiving placebo. Participants should be warned of the risk of dizziness, lightheadedness, or syncope when taking alfuzosin. Alfuzosin should not be taken by men with moderate to severe hepatic impairment or co-administered with potent inhibitors of CYP3A4. Cimetidine can increase the level of alfuzosin. Alfuzosin should not be combined with antihypertensive medications. Individuals with congenital QT interval prolongation or patients with symptomatic angina pectoris should be monitored closely. Some tiredness, abdominal pain, dyspepsia, constipation, and nausea have been reported by men taking alfuzosin. Additional adverse events (between 1%-2% of patients receiving alfuzosin) include bronchitis, sinusitis, pharyngitis, tachycardia, and chest pain. In rare cases, alfuzosin has been associated with priapism and impotence.

5.3.2 Risks of Placebo

Placebo is an inactive agent and there are no risks associated with its use.

6 TREATMENT PROCEDURES

Participants meeting all eligibility criteria will be randomized electronically to one of the two treatment arms. Each participant will receive two bottles of tablets, either containing alfuzosin (UROXATRAL®) or its matching placebo. The first bottle will be provided at the time of randomization and contain seven (7) weeks worth of tablets (6 weeks treatment and one additional

week to provide a window of time between visits). The second bottle will be provided at the 6- week visit and contain six (6) weeks of tablets. The study medications will be provided in tamper evident sealed bottles, and will be labeled according to regulatory requirement per Code of Federal Regulations (CFR), Title 21, Part 312.6.

The Research Coordinator will provide explicit instructions to the participant at the time of randomization and dispensing of study drugs. The participant will be instructed that if at any time he should miss a daily dose, he should take the next dose at the usual time. The participant may not "double-up" a dose. The participant will be instructed to save the containers, even if they are empty, and return all study medications at each follow-up visit, to assist the study in compliance monitoring.

6.1 Characteristics of Alfuzosin (UROXATRAL®)

More detailed prescribing information for alfuzosin is included in Appendix C.

6.1.1 Dosing Schedule

The recommended dosage is one 10 mg alfuzosin tablet daily to be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

6.1.2 Drug Manufacturing and Packaging

Alfuzosin (UROXATRAL®) is currently manufactured by Sanofi-Synthelabo (Paris, France). Sanofi-Synthelabo will be providing the alfuzosin tablets for this trial and shipping them directly to the University of Pennsylvania Investigational Drug Service (IDS) for blinded re-packaging and labeling.

6.1.3 Placebo for Alfuzosin

Sanofi-Synthelabo will also be providing the placebo tablets for this trial and shipping them directly to the University of Pennsylvania Investigational Drug Service (IDS) for blinded re-packaging and labeling. The placebo tablets will be packaged and labeled identical to the alfuzosin tablets.

6.2 Concomitant Medications

If patients are receiving drugs that cause vasodilation or hypotension (i.e., antihypertensives, nitrates, etc), additive effect may occur during the treatment with the study medication, which could cause dizziness, and even syncope (i.e., related to hypotension). The patients should be warned of the possible occurrence of such events. The investigator will advise the patient of the possibility of postural hypotension during changing position (which should be done gradually during the first few days of treatment); in case of any events of this type, the patients will be instructed to report them to the investigator immediately. The investigator will decide if any action is necessary i.e. whether to allow the patient to continue the trial or to discontinue the trial treatment.

6.2.1 Exclusionary Medications

Participants will be monitored at each clinic and phone visit as to their use of over the counter and prescription medications. The primary exclusion is prior use of any alpha-adrenergic receptor blocker for symptoms of CP/CPPS or for any other reason. During the course of the study, the participant MAY NOT initiate or otherwise consume any of the following medications:

- Tamsulosin hydrochloride (Flomax®)
- Terazosin HCL (Hytrin®)
- Doxazosin mesylate (Cardura®)

- Potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir)
- Erythromycin

6.2.2 Warnings

Postural hypotension with or without symptoms (i.e. dizziness) may develop within a few hours following administration of alfuzosin. As with other alpha-adrenergic receptor blockers, there is a potential for syncope. Patients should be warned of the possible occurrence of such events when beginning alfuzosin and should avoid situations (ie. driving, operating machinery, or performing hazardous tasks) where injury could result should syncope occur during this period. Care should be taken when afuzosin is administered to patients who have had a hypotensive response to other medications.

6.2.3 Cautions

- The pharmacokinetics of alfuzosin have not been studied in patients with mild hepatic insufficiency.
- Caution should be exercised when alfuzosin is administered in patients with severe renal insufficiency.
- Use of alfuzosin should also be discontinued if symptoms of angina pectoris newly appear or worsen.

6.2.4 Contraindications

Alfuzosin should not be given to patients with moderate or severe hepatic insufficiency because the alfuzosin clearance rate is reduced in these individuals, resulting in a three- to four-fold higher alfuzosin plasma concentration compared to healthy subjects.

7 TRIAL TESTS AND PROCEDURES

7.1 Procedural Summary

Prior to the baseline screening, potential participants must have had symptoms of discomfort or pain in the pelvic region for at least a six-week interval at the time of presentation. Every potential study participant will undergo a series of screening procedures that take approximately 2 - 3 weeks to complete. The screening phase entails at least two clinic visits. The data collected and diagnostic procedures completed during this phase are identified in Sections 7.2 and 7.3, in the order in which they will be obtained or undergone. The order of the procedures has been selected to ensure that eligibility criteria checked by non-invasive methods precede those checked by more invasive methods, and to provide a balance of participant comfort and timeliness.

This study is comprised of phases for each participant: i) the screening phase and ii) the treatment and follow-up phase. The screening phase, which assesses a participant's eligibility via inclusion, exclusion, and deferral criteria, will consist of two baseline visits no more than four (4) weeks and no less than two (2) days apart (when 2-day urine culture results are available). Any candidate failing any of the inclusion or exclusion criteria, during either of the screening visits will be considered ineligible for the protocol. Some participants may have their entry into the study deferred to a later time based on the results of the deferral criteria.

7.2 Screening Visit #1 (First Baseline Screening Visit)

The first screening visit should occur no more than four (4) weeks and no less than two (2) days

prior (when 2-day urine culture results are available) to randomization. During this screening visit, the forms and procedures listed below will be completed. If a participant fails to meet any of the study eligibility criteria, based on the data collected during this visit, he would not be required to complete the physical examination, urinalysis, or urine culture for the purposes of the study.

Eligibility Criteria. Each participant will complete a preliminary screening form that checks whether he meets the initial inclusion/exclusion/deferral criteria. These criteria will be verified at the second baseline visit.

Participant Contact Information. Participants will be asked to provide the clinical center with their address, phone (home, work, and cell) number, e-mail address, primary care physician, and the name, telephone number, and address of two other contacts. This information will be stored at the Clinical Center and available only to selected study personnel.

Participant Medical History. Each participant will provide the research staff with general medical history and specific genitourinary medical history. In particular, the participant will be asked to provide information regarding his disease and surgical histories.

Demographic Questionnaire. Each participant will provide the research staff with his demographic information, including date of birth (age), race, ethnicity, marital status, income, and level of education.

Participant Symptom Index. Each participant will provide the research staff with an assessment of his discomfort/pain by completing the NIH-CPSI and also complete the three questions about pain, urgency, and frequency on the SYM form.

Physical Examination. Each participant will undergo a focused physical examination at this baseline visit. This examination will include an abdominal exam, external genital exam, rectal exam, prostate exam, and perineal exam. If the participant has received a prior focused physical examination conducted by the Principal Investigator or his/her designee within four (4) weeks of study enrollment, a documented copy of this prior physical examination will be acceptable.

Urinalysis, Urine, and EPS Specimens for Microscopy and Culture. Each participant will provide a VB2 specimen, a VB3 and/or EPS (expressed prostatic secretion) specimen for either analysis or culture. If the participant has provided these specimens as part of the focused physical examination conducted by the Principal Investigator or his/her designee within four (4) weeks of study enrollment, a documented copy of these laboratory results will be acceptable. The urine specimens will be collected via a modified "four-glass test" (FGT) described in Meares and Stamey[37]. This FGT will be attempted one time only at Screening Visit #1 (at baseline).

Dipstick urinalysis will be conducted on the midstream urine (VB2) for macroscopic analysis. The VB2 specimen will also be cultured for 2 days to determine whether there is evidence of bacterial infection (UTI status). A positive culture will be defined as 1000 CFU/ml of urine and be the basis for participant exclusion in the trial. Both EPS and the post-EPS urine (VB3) will be collected and a microscopic urinalysis completed to quantify white blood cells. None of these samples will be banked under this protocol.

Next Visit Preparation.

- Appointment scheduling. An appointment will be made for Screening Visit #2, to occur no sooner than one (1) week and no later than four (4) weeks after Screening Visit #1.

- Concomitant medications. Each participant will receive instructions from the RC to bring to Screening Visit #2 all/or a list of all the over-the-counter and prescribed medications that he is currently taking.

7.3 Screening Visit #2 (Second Baseline Screening Visit) and Randomization

Screening Visit #2 should be completed at least two (2) days after (when 2-day urine culture results are available), but no more than four (4) weeks after Screening Visit #1. Participants who still meet all eligibility criteria at this visit will complete the questionnaires described below, and will continue on to randomization. During this visit, the patient will have an opportunity to ask questions and express concerns related to the study.

Eligibility Checklist. An eligibility checklist confirming that the participant still meets all eligibility criteria will be completed by the RC prior to randomization.

Concomitant Medications. The research staff will record the medications currently being taken by the participant. Participants will be asked to recall their medications if they fail to bring them to the second screening visit.

Adverse Events/Serious Adverse Events. The research staff will record any adverse events that have newly occurred, changed, or have been resolved.

Urinalysis, Urine, and EPS Specimens for Microscopy and Culture. The research staff will review culture results from the baseline visit to determine participant eligibility.

Symptom Questionnaires. Each participant will complete the following symptom questionnaires at this visit and all subsequent follow-up visits:

1. NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)
2. Symptom Assessment Form (SYM)
3. MOS SF-12 Health Status Questionnaire (SF-12)
4. McGill Pain Questionnaire (MPQ)
5. Hospital Anxiety and Depression Scale (HADS)
6. International Index of Erectile Function **(**IIEF**)**
7. Male Sexual Health Questionnaire (MSHQ)

Randomization will also take place during this visit. All eligibility criteria will be reviewed with the patient, as well as checked against their symptom questionnaires, and medication use from the previous visit. In particular, the symptom scores at each of the 2 baseline screening visits will be compared with the minimum cut points required. If the patient is eligible for the study, the patient eligibility checklist will be entered into the computer database by the research coordinator and computer randomization will be performed. At the time of randomization, the participant will be provided with tamper-evident bottles of the study medication (or its matching placebo) and thorough instructions of the dosing schedule. Details of the participant instructions will be provided in the Manual of Procedures (MOP).

7.4 Post-Treatment Follow-Up Visits

The participant will be required to return for two additional clinic visits, at week six (6) and at week twelve (12) post-randomization and treatment start.

7.4.1 Week Six (6) Clinic Visit

Concomitant Medications. The research staff will record the medications currently being taken by the participant. Participants will be asked to recall their medications if they fail to bring them to the second screening visit.

Adverse Events/Serious Adverse Events. The research staff will record any adverse events that have newly occurred, changed, or have been resolved.

Symptom Questionnaires. As described in Section 7.3, the participant will be required to complete a number of different questionnaires, with the addition of the single question GRA, which is only completed during the week six (6) and week twelve (12) post-treatment visits.

7.4.2 Week Twelve (12) Clinic Visit

At week twelve, participants will complete the same forms and questionnaires as the clinic visit at week six, with the addition of the following:

1. Study Stop Form
2. Treatment Stop Form

8 ADVERSE EVENTS AND PARTICIPANT WITHDRAWALS

The Investigator(s) will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, adverse events, or precautions pertinent to the safety of the drug under investigation. Details of adverse events reporting are described below.

8.1 Definitions of Adverse Events (AEs)

An adverse event is any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.[38] The term "adverse event" could include, but not be limited to, any of the following events, which develop or increase in severity during the course of the study:

- Any signs or symptoms whether thought to be related or unrelated to the condition under study
- Any clinically significant laboratory abnormality
- Any abnormality detected during physical examination

The following data will be recorded on the appropriate case report forms (CRFs), regardless of whether they are thought to be associated with the study or the drug under investigation. ("Associated with the use of the drug" means that there is a reasonable possibility that the event may have been caused by the drug.)

- Any event reported by the participant, other than those expected and described in the treatment brochure, will be immediately reported to the treating urologist.
- Signs and symptoms will be graded by the Research Coordinator as mild, moderate, or severe as referenced by Common Toxicity Criteria (CTC) Standard (to be provided with the Manual of Procedures).

Adverse events will be addressed at each participant visit and as reported by the participant, a detailed description of the adverse event will be recorded on the Adverse Event CRF. Adverse Event CRFs will be reviewed regularly by the DCC and reports will be produced on a quarterly basis summarizing the adverse events by clinical center and masked treatment assignment.

All adverse events (clinical signs, laboratory values or other) must be followed until the return to normal or until stabilization of the patient conditions.

8.2 Serious Adverse Events

8.2.1 Definition of Serious Adverse Events (SAEs)

A serious adverse event is defined as any untoward (unwanted) medical occurrence that at **ANY** dose

- Results in death
- Is life-threatening
- Results in a persistent of significant disability/incapacity
- Results in in-patient hospitalization or prolongation of existing hospitalization
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.[39] Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

As a convention for alfuzosin studies, syncope (actual loss of consciousness) is to be considered as a serious adverse event under the category of medically important event.

8.2.2 Reporting Obligations for SAEs and IND Safety Reports

The Clinical Site is responsible for reporting SAEs to the DCC within 24 hours of first knowledge of the event via telephone, followed by a facsimile (which includes both the corresponding Adverse Event Case Report Form and the MedWatch Form). In addition, the site must promptly report all SAEs to their IRB via written/dated notification in accordance to the IRB's reporting requirements. Copies of all such correspondence must be maintained in the clinical site's main study binder.

Upon notification from the clinical site, the DCC will notify the sponsor (NIDDK of SAEs within one (1) working day. Should any SAEs fall into the category of IND Safety Reports (serious, unexpected, and possibly related to drug), the DCC will work with the NIDDK to report the event to the FDA and all investigational sites in accordance to the process and timelines specified in the FDA regulations. DCC will serve as the sponsor's designee by disseminating the IND safety reports to all clinical sites and promptly notifying the Licensed Product Holders. All DSMB members will also be apprised of all SAEs following the timelines above.

8.2.3 Follow-Up of Serious Adverse Events

All serious adverse events must be followed with appropriate medical management until resolved or until progression has been stabilized.

8.3 Potential Adverse Events

8.3.1 Alfuzosin (UROXATRAL®)

The side effects may include a lowering of blood pressure, dizziness, lightheadedness, syncope (fainting), postural hypotension (decrease in blood pressure when you sit or stand), fatigue,

abdominal pain, dyspepsia (heartburn), constipation, nausea, bronchitis (bronchial tube inflammation), sinusitis (nasal infection), pharyngitis (infection or irritation of the pharynx and/or tonsils), and impotence.

The incidence of adverse events has been ascertained from 3 placebo-controlled clinical trials involving 1,608 men in whom daily doses of 10 and 15 mg alfuzosin were evaluated. In these 3 trials, 473 men received UROXATRAL®. In these studies, 4% of patients taking UROXATRAL® 10 mg tablets withdrew from the study due to adverse events, compared with 3% in the placebo group.

The following adverse events have also been reported in post-marketing experience: skin rashes, pruritis, tachycardia (fast heart rate), chest pain, priapism (prolonged and painful erection of the penis).

8.3.2 Placebo

The placebo is an inactive agent and adverse events are not expected.

8.4 Unmasking (Unblinding) of Treatment

At the end of Baseline Screening Visit #2, participants will be randomly assigned to one of the two treatment groups following a randomization schedule generated by the DCC prior to study initiation. Neither the Principal Investigator nor the investigational site personnel will know the treatment group to which any participant is randomized. If there is a serious adverse event which is thought by the clinical site staff to be possibly or probably related to the coded medication, the clinical site staff, when necessary for the safety of the participant, will unmask treatment group assignment upon conferring with the clinical site Principal Investigator. The clinical site staff must report the unmasking to the DCC within one (1) working day, to be followed by submission of a detailed report to the DCC within three (3) working days of the initial DCC contact. The clinical site must also promptly notify their IRB of the unmasking occurrence in accordance to reporting requirements.

In accordance to the ICH *Guideline for Industry Clinical Safety Data Management's* section on expedited reporting: "Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse event is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion." For the purposes of this protocol, if dissemination of this unmasking information from the Sponsor to the Licensed Product Holders is requested, a collaborative discussion regarding the appropriate process will be initiated.

Unmasking of treatment assignment is anticipated to be an uncommon occurrence and is highly discouraged. At the end of the trial, each participant will be asked to which treatment arm s/he thought s/he had been assigned to aid in evaluating the success of the blinding.

8.5 Participant Withdrawals

It is expected that some participants may drop out of the trial due to side effects or lack of efficacy prior to the twelve (12) week endpoint. However, all attempts will be made to get complete data on all participants, including those who cease treatment prior to twelve (12) weeks, in order to conduct the primary intent-to-treat analysis for secondary endpoints. It is expected that a maximum of 15% of participants will withdraw completely from treatment AND follow-up prior to twelve (12) weeks.

Under certain circumstances, a study participant may have his treatment terminated prior to the twelve (12) week clinic visit. These circumstances include: unacceptable concomitant medications/treatments, unacceptable adverse events as determined by the Principal Investigator (PI), participant dissatisfaction with treatment, or participant disinterest in continued study participation. In addition, any participant who acquires a serious or life-threatening medical condition while participating in the study may have the study treatment terminated early at the discretion of the PI. A participant may also undergo early study termination because of a change of residence outside the driving distance of the CPCRN-2 network.

9 ADMINISTRATIVE RESPONSIBILITIES

9.1 General Considerations and the Manual of Operating Procedures (MOP)

The DCC has developed written standard operating procedures (SOPs) to ensure that all aspects of the randomized clinical trial are conducted in a standard and uniform manner. These procedures will be organized into a Manual of Procedures (MOP), which will comply with the protocol, GCP, and applicable regulatory requirements. All study-associated personnel will be trained in study conduct and procedures prior to the start of the trial. A data and safety monitoring plan and data-monitoring schedule will be developed to assess protocol adherence. This plan will be presented to the DSMB for approval for implementation.

9.2 Institutional Review Board

It is the responsibility of the Principal Investigator at each site to provide the appropriate Institutional Review Board (IRB) with all pertinent material, including a copy of the informed consent. Approval of the protocol and the informed consent form must be obtained and forwarded to the sponsor prior to screening or enrolling any subjects. The Investigator also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes, notification of adverse reactions, and termination of the study according to the appropriate IRB requirements.

9.2.1 Investigator Assurances

Prior to initiating the study, the Principal Investigator at each study site will sign a protocol signature page, providing assurances that the study be performed according to the standards stipulated therein. The original signed copy of this document will be maintained in the site's regulatory binder and a copy will be sent to the DCC.

9.3 Laboratory Accreditation

The Principal Investigator must maintain documentation of adequate licensure or accreditation for all clinical laboratory facilities used for study sample analysis. In addition, the clinical laboratory's normal values for test results must be forwarded to the DCC prior to study initiation and annually thereafter. This documentation should cover the entire period the protocol is active.

9.4 Sponsor Monitoring/On-site Monitoring

The progress of the study may be monitored by an experienced site-monitoring firm, subject to sponsor funding availability, for compliance with applicable government regulations and protocol. These individuals will have access to all records necessary to ensure integrity of the data and the regulatory documents at the clinical sites.

9.5 Compliance with Agencies

The sponsor will ensure that this study is performed in compliance with applicable regulations associated with the Food and Drug Administration (FDA), the International Conference on Harmonization (ICH),[40] and the Declaration of Helsinki. The sponsors will also keep a 1572 (Statement of Investigator), and current CVs of all Principal Investigators and Research Coordinators on file.

9.6 Record Retention

The DCC must maintain all trial records for a period in accordance with their internal Standard Operating Procedures (SOP) and applicable regulations. The Clinical Site must retain source records, including original Patient Consent Forms, until either the sponsor or DCC notifies them in writing.

9.7 Direct Access to Source Documents

Investigators will maintain, on-site, in an orderly fashion, for a period of no less than seven (7) years, and make available to the sponsor or the sponsor's representative, the following documents: the signed study protocol, amendments, informed consent documents, investigator brochure, approval letters from the IRB, drug accountability forms, CRFs, all primary source documentation, and all letters of correspondence.

9.8 Data Management and Quality Assurance

The Data Coordinating Center (DCC) will coordinate all study activities pertaining to:

- Design, development, production, testing and distribution of case report forms (CRFs) over the internet to the client workstations at each clinical center
- Collection, entry, verification, validation and query resolution of data
- Quality Assurance monitoring and reporting

Data management issues, especially those concerning data quality and integrity in multi-center trials, as discussed extensively in Meinert[41] DeMets[42]Neaton[43] Bailey[44], and McFadden[45], will be addressed within the Manual of Procedures (MOP) and emphasized during the Research Coordinator (RC) training prior to protocol initiation.

The DCC will develop and maintain a computerized Data Management System (DMS) for this Protocol that will be deployed over the WORLD WIDE WEB using standard Web Browser tools on client workstations within each of the Clinical Centers. Case report forms (CRFs) will be available to be printed locally at the clinical centers from Portable Document Files (PDF). Originals of these forms will be retained by the Clinical Sites. Double data entry will be performed at the Clinical Centers, utilizing the DMS tools available on the clients' workstations. There will be a manual back-up system for implementing randomization of participants, in the event the DMS system is not functional at the moment that a new randomization is required.

Validation checks will be performed at the centralized database to verify data accuracy and identify missing, unclear, illogical, or problematic responses. Queries will be generated to resolve discrepancies. Confidentiality will be strictly adhered to by assigning a unique participant identifier that will not identify the subject by name. The Manual of Procedures will define these processes in detail.

10 STATISTICAL CONSIDERATIONS

10.1 Summary of Study Design

The proposed study design is a two-arm, double blind, randomized clinical trial (RCT) to evaluate the effect of alfuzosin as compared to placebo. The primary analysis on which sample size requirements are based is the comparison of response rates defined based on the decrease in the NIH-CPSI total score as described in Section 2.5. The proportion of "responders" in each treatment arm will be compared, in an intent-to-treat analysis, to evaluate the overall safety and efficacy of alfuzosin as compared to placebo. Approximately 270 eligible patients, 135 per treatment arm, will be randomized and followed for a period of twelve (12) weeks after randomization.

An overview of the design considerations and statistical analysis plan, including sample size and power considerations, is provided in the following sections. Additional details will be provided in the study Data Analysis and Monitoring Plan (DAMP), provided prior to study initiation.

10.2 Sample Size Calculations

The primary analysis on which sample size requirements are based is the comparison of response rates defined based on the change in the NIH-CPSI total score. For this comparison, we desire adequate numbers of participants to detect a difference in response rates between 40% and 60% (difference of 20%). The estimated response rate of 40% for the placebo group is based on previous CP/CPPS studies, although it is recognized that currently there is limited information on response rates among newly diagnosed and alpha-blocker naïve CP/CPPS participants. Assuming 80% power to detect the specified difference between groups at a two-sided $\alpha = 0.05$ level of significance using Fisher's exact test, a total of 270 participants (135 per arm) are required. This proposed sample size includes adjustments for clustering within clinical sites (20% increase) and interim monitoring (5% increase). Total required sample sizes for alternative response rate differences are shown in the table below.

Response Rate			Sample Size Per Arm		Total Sample Size	Per Center over 2 Years	
Placebo	Alfuzosin	Difference	Unadjusted	Adjusted		Total	Per Month
20%	35%	15%	151	191	382	35	1.5
30%	45%	15%	175	175	350	32	1.3
40%	55%	15%	186	235	470	43	1.8
50%	65%	15%	182	230	460	42	1.8
20%	40%	20%	91	115	230	21	0.9
30%	50%	20%	103	130	260	24	1.0
40%	**60%**	**20%**	**107**	**135**	**270**	**25**	**1.0**
50%	70%	20%	103	130	260	24	1.0
20%	45%	25%	62	78	156	15	0.6
30%	55%	25%	68	86	172	16	0.7
40%	65%	25%	69	87	174	16	0.7
50%	75%	25%	66	84	168	16	0.7

10.3 Randomization and Stratification

To ensure balance across treatment groups within each Clinical Site, a stratified randomization will be used. Within each of the eleven strata defined by Clinical Site, subjects will be randomly allocated in equal proportions to the two treatment arms using a permuted block randomization

procedure with variable block sizes of 4, 6, and 8. The variable block size will assure that neither participants nor their physicians will know the participant's location in the block.

We have chosen not to stratify the randomization scheme by any other variable than Clinical Site. This variable was chosen to control for factors unique to each clinic site, such as the characteristics of that site's patient population. While there clearly are other variables that will be observed and recorded before randomization, and which could be used for stratification, including patient's medical history or severity of symptoms, researchers are divided over the wisdom of stratification at the time of randomization on factors other than study site. Most importantly, stratification by multiple variables would likely result in small numbers per group and a fairly large chance of departure from the desired allocation ratio. Additionally, the usefulness of stratification is a function of how well the variable is related to the outcome measure.[41] There are no data to suggest that any of the potential stratification variables for this trial would be associated with achieving response in this study. Finally, since we are proposing a study with 135 participants per group, stratification on variables other than study site should not be necessary to assure that the two arms of the study will have approximately equal representation of the major potentially confounding variables.[46] However, a careful analysis will be carried out at the end of the trial to ensure that this is the case. Analysis procedures primarily involving regression methods will be used to adjust for any baseline group differences as discussed further below.[41]

In order to maintain blinding, both the active drug and placebo will have an identical appearance. The treatment assignment code, corresponding to each treatment identifier number, will be known only to the person serving as the Data Coordinating Center Quality Assurance Director, until the completion of treatment and data collection on all participants. This information may also be known to the dispensing pharmacists at each institution, or a related centralized dispensing group. The study participants, and all other members of the investigative team, will remain blinded to the treatment assignment, including the investigators, the biostatisticians, the study nurses, and referring physicians. At the end of a patient's study phase, the subjects and the treating physicians will be asked to guess their treatment groups, and provide the basis for their judgments for analysis later, to determine whether the blinding has been broken. However, except in the case of emergency unmasking (Section 8.4), the treatment codes will not be identified until the DSMB has approved unblinding in preparation for the public dissemination of results.

10.4 Intent-to-Treat Analyses and Missing Data

An intent-to-treat analysis, for which all participants randomized are included, will be used for the primary comparison of treatments. All attempts will be made to keep missing data to a minimum. Participants who discontinue treatment during the trial, particularly in the case of an adverse event, will not be considered withdrawals from study unless they withdraw consent for further follow-up. These participants will be encouraged to continue on study in order to provide complete follow-up information. However, it is expected that up to 15% of the randomized participants may withdraw prior to the final assessment of response at twelve (12) weeks. These participants will be considered treatment failures and included in the denominator for evaluation of response rates defined for the primary endpoint.

The characteristics at time of randomization for those participants without complete follow-up will be examined; however, there will be limited statistical power to detect any but major differences between these participants and those with complete follow-up. In addition, in order to assess the potential biases introduced by differential withdrawal among treatment arms, a comparison of withdrawal rates and/or time to withdrawal will be included as an ancillary analysis to the primary

endpoint comparison. Additional details of the evaluations of withdrawals are provided in the section regarding longitudinal data analysis below.

In general, missing data will not be imputed. The possible exception is validated symptom scales for which methods of imputing missing items have been previously developed. For example, the following procedure will be used to calculate the NIH-CPSI Pain Score in the event there are missing responses. If no more than two binary items are missing from the NIH-CPSI questions 1a-1d, 2a, 2b, and no other pain items are missing, the NIH-CPSI Pain Score will be imputed as follows: sum of all non-missing items * 21/(21-# missing items). If only question #3 is missing then the NIH-CPSI pain score will be imputed as follows: sum of all non-missing items*(21/16). Every effort will be made to use statistical methods that are robust to missingness, and the number of subjects included with each analysis will be given with the results.

10.5 Statistical Analyses

In addition to the analyses described subsequently, descriptive statistics will be used during the course of the project as part of data management procedures for monitoring data quality. A brief overview of some of the statistical methods that may be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections. It is recognized that these methods may be revised, and additional ones considered, as the details of the specific analyses are developed. Details of the statistical analysis will be outlined in the Data Analysis and Monitoring Plan (DAMP).

10.5.1 Descriptive Analyses

Standard descriptive statistics will be used to describe participants' baseline characteristics and study outcome measures at each of the 6 and 12 week visits, both overall and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, race/ethnicity, other demographic characteristics, pain intensity and pain-related disability ratings, urinary urgency and frequency, depressive symptom severity, general health-related quality of life summary scores, and laboratory and procedural measures. Summary statistics such as means, standard deviations, medians, and ranges will be produced for all measured variables. Frequencies will be computed for all categorical and ordinal variables. Graphical methods including stem-and-leaf diagrams and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations if warranted. The balance of baseline measures across the treatment groups will be compared using appropriate 2-sample tests including Wilcoxon rank-sum tests and Fisher's exact tests.

10.5.2 Analysis of Primary Outcome

The primary endpoint to be used for efficacy evaluation is response rates determined based on the change from baseline in the NIH-CPSI total score (scale of 0-43). Responders" will be defined as those subjects demonstrating at least a 4-point decrease from baseline to 12 weeks in the NIH-CPSI; the proportion of responders by this definition will be compared between treatment groups. This method of using response rates as the primary outcome, although it may yield some loss in statistical power, allows study withdrawals to be considered as non-responders for an intent-to-treat analysis. The primary analysis comparing response rates between treatment arms will make use of the exact conditional test (ECT) version of Mantel-Haenszel methods to adjust for within-center clustering and any other observed clinical heterogeneity, as implemented within the Proc-StatXact software system[47]. Logistic regression and generalized estimating equation (GEE) methods will be carried out to evaluate whether observed differences, if any, are attributable to imbalances in prognostic factors such as baseline symptom severity[47]. Standard regression diagnostics will be used to assess model

adequacy, and to examine potential outlying or influential data points. Since there is only one interim assessment between baseline and the twelve-week primary endpoint visit, there will be insufficient information to calculate time to response due to interval censoring. However, profiles of the changes over time will be evaluated via the longitudinal data analyses described below.

10.5.3 Secondary Analyses

A number of secondary analyses will be conducted, both to evaluate the secondary symptom-related outcomes and to supplement the primary endpoint comparison. Secondary outcomes are listed in Section 2.5 and include the GRA, subscores of the NIH-CPSI, the MOS SF-12, the MPQ, the HADS, the IIEF, and the MSHQ.

For example, one type of response will be based on the participant GRA of change as measured at twelve (12) weeks or withdrawal, whichever comes first. One method of analysis will be to classify participants who indicate that they are "moderately or "markedly" improved as intervention responders. The analysis of this binary outcome will be identical to that described for the primary endpoint above. Additional analysis examining the correlation between a 6-point decrease and/or a 25% mean change in the NIH-CPSI could also be conducted, if needed to provide additional measures of responsiveness.

For the various measures evaluated repeatedly over time, changes over time will be compared among treatment groups using methods for longitudinal data analysis[48]. These methods will include random effects regression models for continuous outcomes and GEE methods for categorical and ordinal outcomes such as the GRA[48]. Both within- and between-participant variability in these outcomes will be carefully assessed to provide pilot data for future clinical trials. When applicable, additional analyses of the symptom outcomes may include evaluation of secondary response rates defined by specific changes in symptoms (i.e. 50% drop in symptom score). For measures obtained only at baseline and one follow-up time point, change from baseline will be compared among groups using analysis of variance (ANOVA) and regression methods. Withdrawal rates will be compared between arms using standard methods. Also, modeling the informative of dropout patterns may be conducted to address whether or not the extent of adherence at 12 weeks is associated with the level of treatment response.

10.6 Data Safety Monitoring and Interim Analysis

The study will be monitored routinely for issues of data quality, study conduct (including recruitment and follow-up rates), data quality, toxicity, and adverse events. Adverse event data will be summarized by body system, derived from the Common Toxicity Criteria (CTC) code entered into the database. All adverse events, regardless of their presumed relationship to the study treatment, will be included. Toxicity will be assessed per subject (a) overall and (b) within each body system grouping. Each participant will be counted only once in each body system. In the case of multiple events occurring in the same body system for a given participant, the highest grade of severity experience by that participant will be used. Estimates of toxicity rates, both overall and within treatment group, will be produced. These analyses will be presented to the DSMB.

Due to the restrictive nature of the inclusion criteria, slow accrual is expected. Thus we propose to perform one interim analysis comparing treatment safety and efficacy between groups sixteen (16) months after the initiation of accrual, when approximately one half (n=135) of the participants have been accrued and followed for 12 weeks. The results of these analyses will be presented to the DSMB. The purpose of this interim analysis will be to determine whether or not there is sufficient evidence of a difference between treatments in response rates such that the trial should be discontinued prior to reaching the target accrual goal. To avoid inflating the overall Type I error rate

for the primary analysis of efficacy, an O'Brien-Fleming boundary[49] will be used to calculate the nominal significance level to which the interim p-value is compared. Only an "upper" boundary, which allows for closure in the case of evidence of a treatment difference, will be used at this interim analysis. Assuming looking at 12 week data on 135 participants, corresponding to an information time of 50%, the boundary significance level to which the observed p-value will be compared is 0.0031. Therefore, if the p-value is less than 0.0031 for the test of comparing response rates, the trial will be terminated due to significant treatment differences. However, any final decision to terminate the trial early will have to be approved by the DSMB. As mentioned, sample sizes have been adjusted to account for a very slight loss of statistical power due to the interim monitoring. Study closure will generally not be considered based on the secondary endpoints.

The statisticians who conduct the interim analysis will not know the actual treatment assignments. The DCC Quality Assurance Director will provide these to the Chairperson of the DSMB in a sealed envelope. This envelope may be opened if deemed necessary by the DSMB.

The table below outlines the proposed reporting schedule that will be used for this study. The abbreviations are as follows: CDM denotes clinical data management staff at the Data Coordinating Center (DCC); SC denotes the CPCRN Steering Committee, including all clinical site investigators, the DCC, and NIDDK representatives; and IRB indicates the local Institutional Review Boards for the Clinical Sites and DCC. The reports indicated as occurring every 3 to 4 months are generated to correspond to meetings of the Steering Committee.

Type of Report	**Prepared By:**	**Provided To:**	**Frequency:**
Serious Adverse Events (SAEs)	Sites, DCC	SC, DSMB, IRBs	Immediately
Patient Recruitment/Targets	CDM, Biostat	SC	q 4 weeks
Data Quality, Timeliness	CDM	SC, DSMB	q 3-4 mos
Demographics (combined)	CDM	SC, DSMB	q 3-4 mos
Adverse Events (combined)	Biostat	SC, DSMB	q 3-4 mos
Interim Analysis: Safety only	Biostat	DSMB	q 6 mos
Interim Analysis: Safety and Efficacy	Biostat	DSMB	50% accrual, follow-up
Final analysis: Safety and Efficacy	Biostat	DSMB	100% accrual, follow-up

10.6.1 Final Analysis

The final analysis of the data will take place after the completion of accrual, follow-up, and data collection and validation on all subjects. Details of the plans for final analysis will be outlined in the Data Analysis and Monitoring Plan (DAMP), reviewed by the DSMB prior to study initiation. For the final analysis, the boundary significance level to which the observed p-value will be compared is 0.049.

10.6.2 Statistical Computing

The appropriate ASCII and SAS data files will be extracted from the Oracle database for use in statistical analysis. Primary analyses, including graphical methods, will be implemented using various commercially available statistical packages including SAS [50-57] and S-plus.[58] The Proc StatXact for SAS Users software[59] will be used to compute the exact tests of discrete measures between groups. All software is currently available through the networked computing environment within the DCC.

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APPENDIX A: FORMS AND VISIT SCHEDULE

Form Name	-1 to -4 Weeks (Screening) Visit 1 (B1 Clinic)	0 Weeks (Randomization) Visit 2 (B2 Clinic)	6 Weeks (Follow-up) Visit 3 (Clinic)	12 Weeks (Follow-up) Visit 4 (Clinic)
Prescreening/Screening/Baseline				
Pre-Screening Summary (PRESCR)				
Informed Consent (Administrative)	X			
Medical History (MEDHX)	X			
Eligibility Checklist (ELIG)	X	X		
NIH-Chronic Prostatitis Symptom Index (CPSI)	X	X	X	X
Randomization (RAND)		X		
Procedures and Labs				
Adverse Events/Serious Adverse Events (AE)		X	X	X
Demographics (DEMO)	X			
Dispensing Log (DISP)		X	X	
Drug Compliance (DCOMP)			X	X
EPS and Urine Testing (EUT)	X			
Physical Exam (EXAM)	X			
Urine Screening (URINE)	X			
Symptom Questionnaires				
Symptom Assessment (SYM)	X	X	X (GRA)	X (GRA)
Health Status Questionnaire® (SF-12)		X	X	X
The McGill Pain Questionnaire® (MPQ)		X	X	X
Hospital Anxiety and Depression Scale© (HADS)		X	X	X
The International Index of Erectile Function® (IIEF)		X	X	X
The Male Sexual Health Questionnaire (MSHQ)		X	X	X
PRN Forms				
Study Stop Point (SSTOP)	PRN	PRN	PRN	X
Treatment Stop Point (TSTOP)	PRN	PRN	PRN	X
Unmasking Record (UNMASK)	PRN	PRN	PRN	PRN
Administrative Forms				
Clinical Center Staff "Signature and Delegation of Responsibilities" Log (STAFFLOG)	X	PRN	PRN	PRN
Concomitant Medication (CMED)	X	X	X	X
Participant ID Assignment Log (PTLOG)	X			
Participant Contact Information (PTCONT)	X			
Participant Transfer (TRANS)	PRN	PRN	PRN	PRN
Study Drug Tracking Log (TRACK)		X	X	
Visit Checklist	X	X	X	X

APPENDIX B: PROPOSED INFORMED CONSENT FORM

P.I. Name and Department
Telephone Numbers(s)
Co-P.I. Name(s)
Day Telephone Number(s)
24-Hour Emergency Number
IRB # of protocol

PROPOSED PARTICIPANT INFORMED CONSENT FORM

Chronic Prostatitis Clinical Research Network-2 (CPCRN-2) RCT#1 PROTOCOL

A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients

You are being asked to participate in a research study because you have been newly diagnosed with Chronic Prostatitis and have been informed that you may be eligible for the investigational study known as: "A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients." Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in the study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. If you decide to participate in the study, you will be asked to sign and date this form.

The CPCRN-2 has been established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to identify and study treatments for people with symptoms of CP/CPPS. It is hoped that such a research study will eventually lead to improvement in the treatment of CP/CPPS. This research study is being conducted at a number of medical centers including: Cleveland Clinic Florida; Harvard Medical School- Massachusetts General Hospital & Brigham & Women's Hospital; Northwestern University Feinberg School of Medicine; Queen's University; Stanford University Medical Center; Temple University; David Geffen School of Medicine at UCLA; University of Maryland; University of Mississippi Medical Center; University of Washington; and University of Washington- Harborview Medical Center/University of Sciences Malaysia.

What is the purpose of the study?

The purpose of this study is to investigate the efficacy and safety/tolerability of alfuzosin (trade name: Uroxatral®), a prescription medicine that is called an "alpha blocker". Uroxatral® has been approved by the United States Food and Drug Administration (FDA) to relieve the signs and symptoms of benign prostatic hyperplasia (BPH) or non-cancerous enlargement of the prostate.

Uroxatral® works by relaxing the muscle surrounding the prostate, bladder neck, and prostatic urethra. Uroxatral® (and other similar alpha blocker drugs) have been used to treat CP/CPPS. This study will attempt to determine if Uroxatral®is effective in providing relief for CP/CPPS.

Who is being invited to participate in this study?

You will be invited to participate in this study if you are male, ≥ 18 years of age, have experienced symptoms of discomfort or pain in the pelvic region for at least a six (6) week interval, and have had symptoms bothersome enough in the past two years to prompt a doctor's visit. Approximately 270 participants with newly clinically diagnosed CP/CPPS will be involved in this study. If you choose to participate, your involvement in the study will last at least 12 weeks.

What will I be asked to do if I participate in this study?

If you choose to participate in this study, and after you have signed and dated the consent form, the clinical research coordinator will evaluate your eligibility for the study. As part of the study you will be asked to complete the following:

1. ***Participate in Screening Visit 1***

The Screening Visit will be an in-person visit where we will get your informed consent and provide you with more information about the study. You will be required to complete a medical history and a physical examination. The physical examination will include an abdominal examination, external genital exam, rectal exam, prostate exam, and perineal exam (area around the scrotum and anus). Urinalysis and a urine culture (examining a urine sample to detect the presence of blood, infection and other processes and doing a white blood cell count), as well as EPS (expressed prostatic secretion) specimen testing, which involves a rectal exam, will also be conducted. You will also be asked to complete questionnaires to assess your pain/discomfort, urinary symptoms and a Quality of Life (QOL) index.

2. ***Participate in Baseline Visit 2***

If you qualify for the study and are interested in participating after the Screening Visit, you will be scheduled for the Baseline Visit. The completion of this visit defines enrollment in the study. During this visit, the research coordinator will review and confirm whether you are still eligible for the study. As in the Screening Visit 1, you will be asked to complete questionnaires to assess your pain/discomfort, urinary symptoms and a Quality of Life (QOL) index. Additional questionnaires about your depression/anxiety status and sexual function will also be administered at this time. All of these questionnaires will need to be completed at each subsequent Follow-up visit. You will then be randomly assigned to one of two treatment groups, half treated with medication and half treated with placebo. The medication you will receive will be randomized, that is by chance, like a flip of a coin. Neither your physician nor you will know to which treatment group you will be assigned. However, information regarding which treatment you are receiving will be made available to your physician in case of an emergency. The medication for weeks 1-6 will be given to you at this visit. One group will receive oral placebo (like a sugar pill); the other group will receive oral Uroxatral®.

3. ***Take the study medication***

You need to take one tablet from the bottle of study medication once a day. The research staff will provide you with specific instructions on how to take the study medication. You will take study medications daily for twelve (12) weeks. Medication for weeks 1-6 will be provided at the Baseline Visit 2. Medication for weeks 7-12 will be provided at the six-week follow-up visit.

4. ***Participate in Two Follow-up Clinic Visits***

You will be required to participate in two (2) follow-up clinic visits at six (6) and (12) weeks after medication start. As described previously, you will be asked to fill out a number of questionnaires.

What benefits will I receive from the study?

You may receive no direct benefit from participating in this study. The purpose of this study is to determine the effectiveness of Uroxatral® to improve the symptoms of CP/CPPS. Even though you may receive Uroxatral® or a placebo, there is no assurance that you will receive any benefit from participating in this study. It is possible that your symptoms may even worsen while participating in this study. At the present time, we cannot say for certain that your participation will be of certain benefit.

What are the risks of participating in the study?

The side effects may include a lowering of blood pressure, dizziness, lightheadedness, syncope (fainting), postural hypotension (decrease in blood pressure when you sit or stand), fatigue, asthenia (lack or loss of strength, any weakness), abdominal pain, dyspepsia (heartburn), constipation, nausea, bronchitis (bronchial tube inflammation), sinusitis (nasal infection), pharyngitis (infection or irritation of the pharynx and/or tonsils), and impotence.

The following adverse events have also been reported in post-marketing experience: skin rashes, pruritis, tachycardia (fast heart rate), chest pain, priapism (prolonged and painful erection of the penis).

What else do I need to know?

Alternatives: The alternative is not to participate in the study. Should you choose not to participate, you will receive the usual standard of medical care for your CP/CPPS.

Voluntary Participation and Withdrawal/Early Trial Termination: Your participation in this study is voluntary. You are free to withdraw from the study at any time. If you decline to participate or choose to withdraw, you will still receive the same health care you would have otherwise received. This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the FDA without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the FDA has decided to stop the study.

Confidentiality: You understand that every attempt will be made by the investigator to maintain all information collected in this study strictly confidential, except as required by law. You will be given a unique participant identification number. This number will be used to record your study information. You will never be tracked through the study by name, medical record number or any other personal identifier. A log of the participant names, participant ID numbers, and personal

information (such as home address, telephone number, and emergency contact information) will be maintained in a locked area at the clinical site.

The University of Pennsylvania serves as the Data Coordinating Center (DCC) for this research study which means that the study information from all research centers, after being stripped of your identifying information, will be stored in secure electronic files at the University of Pennsylvania. All study data will be sent to the DCC by secured internet connection. Only authorized members of the research study will have permission to see this data. You further understand that authorized representatives of the Sponsor, the NIDDK, the NIH, *(insert your institution's name)*, as well as the FDA will have access to and may copy, both your medical records and records from your participation in this study. This access is necessary to insure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this research, you will not be identified by name.

To help us protect your privacy, a Certificate of Confidentiality from the National Institutes of Health will be obtained. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. No voluntary disclosure of information that would identify you as a participant in this research study will be made, without your written consent.

Collection of Specimens: Your urine and EPS specimen samples will be collected for culture and analysis, as mentioned in the Screening Visit 1 section of this informed consent. These samples will be stripped of your name and any other identifying information. They will be connected to your study results only by your unique participant identification number. These specimens will not be stored.

Financial Costs and Compensation: You will not have to pay to be in this study. All procedures and tests will be covered by the study. You will receive no money for enrolling in this study. Uroxatral®, the study medication, will be provided free of charge during your participation. [*This section should be customized per site. Parking/transportation reimbursement, if provided, should be itemized*.]

Medical Treatment or Compensation for Injury: You understand that in the event of any physical injury resulting from the research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the [*Insert your Institution's name*]. If you have an illness or injury during this research study that is not directly related to your participation in this study, you and/or your insurance provider or group will be responsible for the cost of the medical care of that illness or injury. [*Clinical sites should customize this section in accordance to their own institution's policies.*]

New Information: During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

Contact Persons for Study: If at any time you have questions, concerns, or comments about this study or a research-related injury, you should contact [*Insert Principal Investigator's name*] at [*Insert telephone number*].

Institutional Review Boards/Subject Rights: The University of Pennsylvania [*Change to your Institution's name*] has a committee called the Institutional Review Board (IRB). It is their responsibility to make sure that the research being conducted is safe and that people in the study are informed about risks and benefits of the research project. If you would like more information or have questions about your rights as a research subject, you can contact the Office of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614. [*Change this to appropriate information for your clinical site's IRB*]

PARTICIPANT'S STATEMENT:

I have read the above information about the Uroxatral® Study. I have been given an opportunity to ask questions about it and to discuss it with [*Insert Principal Investigator's name or authorized personnel*]. All of my questions/concerns have been answered to my satisfaction. I understand that I need to contact the [*Insert your Institution's name and telephone number*], if I move or change my telephone number. My signature below indicates my voluntary participation in this research program and that no procedures associated with this study have been performed on me prior to my signing this consent.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that I may refuse to participate or withdrawal from the study at any time without consequence to my present or future care at the [*Insert your Institution's name*].

DOCUMENTATION OF CONSENT

The original and one copy of this consent form will be kept in a research folder and a second copy of this Consent Form will be given to me to keep.

SIGNATURES

I have read and received a copy of this consent form. I understand that my signature below means that I voluntarily agree to participate in this study.

_____	_____	_____
Printed Name	Signature of Participant	Date

Complete <u>ONLY</u> if patient is unable to sign:

_____	_____	_____
Printed Name	Signature of Legally Authorized Representative (Note relationship with participant)	Date

Completed <u>ONLY</u> if patient or their legal representative is unable to read this consent form and an impartial witness is present for the entire discussion:

_____	_____	_____
Printed Name	Signature of Witness	Date

I certify that I have discussed the study purpose, potential benefits, and risks with the below named participant and/or his/her authorized representative, using language that is understandable and appropriate. I have answered any questions that have been raised and have witnessed the signature of this subject. I have explained the information contained in this document to the subject on the date stated on this consent form.

_____	_____	_____
Printed Name	Signature of Person Obtaining Consent	Date

APPENDIX C: ADDITIONAL DETAILS OF STUDY AGENT

DESCRIPTION

UROXATRAL® (alfuzosin HCl extended-release tablets) works by selective activity at the alpha$_1$-receptors in the lower urinary tract. It relaxes the muscle surrounding the prostate, bladder neck, and prostatic urethra to control a broad range of symptoms, including frequent or urgent need to urinate during the day and night, hesitancy in urination, and reduced urinary flow. UROXATRAL® was developed and marketed as a treatment for benign prostatic hyperplasia (BPH) or non-cancerous enlargement of the prostate.

Each UROXATRAL® tablet contains 10 mg alfuzosin hydrochloride as the active ingredient. Alfuzosin hydrochloride is a white to off-white crystalline powder that melts at approximately 240°C. It is freely soluble in water, sparingly soluble in alcohol, and practically insoluble in dichloromethane.

Alfuzosin hydrochloride is (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2- furancarboxamide hydrochloride. The empirical formula of alfuzosin hydrochloride is $C_{19}H_{27}N_5O_4$•HCl. The molecular weight of alfuzosin hydrochloride is 425.9. The tablet also contains the following inactive ingredients: colloidal silicon dioxide (NF), ethylcellulose (NF), hydrogenated castor oil (NF), hydroxypropyl methylcellulose (USP), magnesium stearate (NF), mannitol (USP), microcrystalline cellulose (NF), povidone (USP), and yellow ferric oxide (NF).

CLINICAL PHARMACOLOGY

The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The static component is related to the prostate size. Prostate size alone does not correlate with symptom severity. The dynamic component is a function of the smooth muscle tone in the prostate and its capsule, the bladder neck, and the bladder base as well as the prostatic urethra. The smooth muscle tone is regulated by alpha$_1$-adrenergic receptors. At least three discrete alpha$_1$-adrenergic receptors have been identified: alpha$_{1A}$, alpha$_{1B}$, and alpha$_{1D}$; their distribution differs between human organs and tissue. UROXATRAL® is a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra.

Pharmacokinetics:

The pharmacokinetics of UROXATRAL® have been evaluated in adult healthy male volunteers after single and/or multiple administration with daily doses ranging from 7.5 mg to 30 mg, and in patients with BPH at doses from 7.5 mg to 15 mg.

Absorption: The absolute bioavailability of UROXATRAL® 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg UROXATRAL® under fed conditions, the time to maximum concentration is 8 hours. C_{max} and AUC_{0-24} are 13.6 (SD = 5.6) ng/mL and 194 (SD = 75) ng·h/mL, respectively. UROXATRAL® exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached with the second dose of UROXATRAL®

administration. Steady-state alfuzosin plasma concentrations are 1.2- to 1.6- fold higher than those observed after a single administration.

Effect of Food: The extent of absorption is 50% lower under fasting conditions. Therefore, UROXATRAL® should be taken immediately following a meal.

Distribution: The volume of distribution following intravenous administration in healthy male middle-aged volunteers was 3.2 L/kg. Results of *in vitro* studies indicate that alfuzosin is moderately bound to human plasma proteins (82% to 90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).

Metabolism: Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Excretion and Elimination: Following oral administration of ^{14}C-labeled alfuzosin solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in feces and 24% in urine. Following oral administration of UROXATRAL® 10 mg tablets, the apparent elimination half-life is 10 hours.

Special Populations:

Elderly: In a pharmacokinetic assessment during phase 3 clinical studies in patients with BPH, there was no relationship between peak plasma concentrations of alfuzosin and age. However, trough levels were positively correlated with age. The concentrations in subjects $\geq$75 years of age were approximately 35% greater than in those below 65 years of age.

Renal Dysfunction: The pharmacokinetic profiles of UROXATRAL® 10 mg tablets in subjects with normal renal function (CL_{CR}>80 mL/min), mild impairment (CL_{CR} 60 to 80 mL/min), moderate impairment (CL_{CR} 30 to 59 mL/min), and severe impairment (CL_{CR} <30 mL/min) were compared. These clearances were calculated by the Cockcroft-Gault formula. Relative to subjects with normal renal function, the mean C_{max} and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment.

Hepatic Insufficiency: In patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), the plasma apparent clearance (CL/F) was reduced to approximately one-third to one-fourth that observed in healthy subjects. This reduction in clearance results in three to four-fold higher plasma concentrations of alfuzosin in these patients compared to healthy subjects. Therefore, UROXATRAL® is contraindicated in patients with moderate to severe hepatic impairment. The pharmacokinetics of UROXATRAL® have not been studied in patients with mild hepatic insufficiency.

Drug-Drug Interactions:

CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin. Therefore, UROXATRAL® should not be co-administered with potent (i.e., ketoconazole,

itraconazole, or ritonavir) CYP3A4 inhibitors. The moderate CYP3A4 inhibitor *Diltiazem* is an antihypertensive medication and the combination of UROXATRAL® and antihypertensive medications has the potential to cause hypotension in some patients.

Warfarin: Multiple dose administration of an immediate release tablet formulation of alfuzosin 5 mg twice daily for six days to six healthy male volunteers did not affect the pharmacological response to a single 25 mg oral dose of warfarin.

Digoxin: Repeated co-administration of UROXATRAL® 10 mg tablets and digoxin 0.25 mg/day for 7 days did not influence the steady-state pharmacokinetics of either drug.

Cimetidine: Repeated administration of 1 g/day cimetidine increased both alfuzosin C_{max} and AUC values by 20%.

Atenolol: Single administration of 100 mg atenolol with a single dose of 2.5 mg of an immediate release alfuzosin tablet in eight healthy young male volunteers increased alfuzosin C_{max} and AUC values by 28% and 21%, respectively. Alfuzosin increased atenolol C_{max} and AUC values by 26% and 14%, respectively. In this study, the combination of alfuzosin with atenolol caused significant reductions in mean blood pressure and in mean heart rate.

Hydrochlorothiazide: Single administration of 25 mg hydrochlorothiazide did not modify the pharmacokinetic parameters of alfuzosin. There was no evidence of pharmacodynamic interaction between alfuzosin and hydrochlorothiazide in the 8 patients in this study.

Clinical Studies:

Three randomized placebo-controlled, double-blind, parallel-arm, 12-week studies were conducted with the 10 mg daily dose of alfuzosin. In these three studies, 1,608 patients were randomized and 473 patients received UROXATRAL® 10 mg daily. The primary efficacy assessments used in these studies included: 1) The International Prostate Symptom Score (IPSS, or AUA Symptom Score), and 2) peak urinary flow rate. The peak flow rate was measured just prior to the next dose in study 2 and on average at 16 hours post-dosing in studies 1 and 3.

There was a statistically significant reduction from baseline to last assessment (Week 12) in the IPSS versus placebo in all three studies, indicating a reduction in symptom severity. Peak urinary flow rate was increased statistically significantly from baseline to last assessment (Week 12) versus placebo in studies 1 and 2. Mean total IPSS decreased at the first scheduled observation at Day 28 and mean peak flow rate increased starting at the first scheduled observation at Day 14 in studies 2 and 3 and Day 28 in study 1.

INDICATIONS AND USAGE

UROXATRAL® is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. UROXATRAL® is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

UROXATRAL® should not be used in patients with moderate or severe hepatic insufficiency, (Childs-Pugh categories B and C) since alfuzosin blood levels are increased in these patients.

UROXATRAL® should also not be co-administered with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir, since alfuzosin blood levels are increased.

UROXATRAL® is contraindicated in patients known to be hypersensitive to alfuzosin hydrochloride or any component of UROXATRAL®tablets.

WARNINGS

Postural hypotension with or without symptoms (i.e., dizziness) may develop within a few hours following administration of UROXATRAL® As with other alpha-blockers, there is a potential for syncope. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result should syncope
occur. Care should be taken when UROXATRAL® is administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

GENERAL PRECAUTIONS

Prostatic Carcinoma: Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting therapy with UROXATRAL® to rule out the presence of carcinoma of the prostate.

Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between UROXATRAL® and other alpha-blockers have not been determined. However, interactions may be expected, and UROXATRAL® should NOT be used in combination with other alpha-blockers.

Coronary Insufficiency: If symptoms of angina pectoris should newly appear or worsen, UROXATRAL® should be discontinued.

Hepatic Insufficiency: UROXATRAL® should not be given to patients with moderate or severe hepatic insufficiency. The pharmacokinetics of UROXATRAL® have not been studied in patients with mild hepatic insufficiency.

Renal Insufficiency: Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal insufficiency. In phase 3 studies, the safety profile of patients with mild (n=172) or moderate (n=56) renal impairment was similar to the patients with normal renal function in those studies. Safety data are available in only a limited number of patients (n=6) with creatinine clearance below 30 mL/min; therefore, caution should be exercised when UROXATRAL® is administered in patients with severe renal insufficiency.

Patients with Congenital or Acquired QT Prolongation: In a study of QT effect in 45 healthy males, the QT effect appeared less with alfuzosin 10 mg than with 40 mg, and the effect of alfuzosin 40 mg did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe UROXATRAL® for patients with

a known history of QT prolongation or patients who are taking medications known to prolong QT, although there has been no signal of Torsades de Pointe in the extensive post-marketing experience with alfuzosin outside the United States. There are no known PK/PD studies of the effects of other alpha blockers on cardiac repolarization.

INFORMATION FOR PATIENTS

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning UROXATRAL®, and they should be cautioned about driving, operating machinery, or performing hazardous tasks during this period.

UROXATRAL® should be taken with food and with the same meal each day.

Patients should be advised not to crush or chew UROXATRAL® tablets.

Laboratory Tests
No laboratory test interactions with UROXATRAL® tablets are known.

Geriatric Use
Of the total number of subjects in clinical studies of UROXATRAL®, 48% were 65 years of age and over, whereas 11% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
There was no evidence of a drug-related increase in the incidence of tumors in mice following dietary administration of 100 mg/kg/day alfuzosin for 98 weeks (13 and 15 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively. The highest dose tested in female mice may not have constituted a maximally tolerated dose. Likewise, there was no evidence of a drug-related increase in the incidence of tumors in rats following dietary administration of 100 mg/kg/day alfuzosin for 104 weeks (53 and 37 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively.

Alfuzosin showed no evidence of mutagenic effect in the Ames and mouse lymphoma assays, and was free of any clastogenic effects in the Chinese hamster ovary cell and in vivo mouse micronucleus assays. Alfuzosin treatment did not induce DNA repair in a human cell line.

There was no evidence of reproductive organ toxicity when male rats were given alfuzosin at daily oral (gavage) doses of up to 250 mg/kg/day for 26 weeks, which corresponds to levels of exposure several hundred times that in humans. No impairment of fertility was observed following oral (gavage) administration to male rats at doses of up to 125 mg/kg/day for 70 days. Estrous cycling was inhibited in rats and dogs at doses of 25 mg/kg and 20 mg/kg, respectively, corresponding to levels of systemic exposure (based on AUC of unbound drug) 12- and 18-fold higher, respectively, than in humans, although this did not result in impaired fertility in rats.

ADVERSE REACTIONS

The incidence of adverse events has been ascertained from 3 placebo-controlled clinical trials involving 1,608 men in whom daily doses of 10 and 15 mg alfuzosin were evaluated. In these 3

trials, 473 men received UROXATRAL®. In these studies, 4% of patients taking UROXATRAL® 10 mg tablets withdrew from the study due to adverse events, compared with 3% in the placebo group.

Table 1 summarizes the treatment-emergent adverse events that occurred in ≥2% of patients receiving UROXATRAL®, and at an incidence numerically higher than that of the placebo group. In general, the adverse events seen in long-term use were similar in type and frequency to the events described below for the 3-month trials.

Table 1 — Treatment-Emergent Adverse Events Occurring in ≥2% of UROXATRAL®-Treated Patients and More Frequently than with Placebo in 3-Month Placebo-Controlled Clinical Studies

Adverse Event	Placebo (n=678)	UROXATRAL (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Upper respiratory tract infection	4 (0.6%)	14 (3.0%)
Headache	12 (1.8%)	14 (3.0%)
Fatigue	12 (1.8%)	13 (2.7%)

The following adverse events, reported by between 1% and 2% of patients receiving UROXATRAL® and occurring more frequently than with placebo, are listed alphabetically by body system and by decreasing frequency within body system:
Body as a whole: pain
Gastrointestinal system: abdominal pain, dyspepsia, constipation, nausea
Reproductive system: impotence
Respiratory system: bronchitis, sinusitis, pharyngitis

The following adverse events have also been reported in postmarketing experience: rash, tachycardia, chest pain, priapism.

Signs and Symptoms of Orthostasis in Clinical Studies: The adverse events related to orthostasis that occurred in the double-blind phase 3 studies with alfuzosin 10 mg are summarized in Table 2. Approximately 20% to 30% of patients in these studies were taking antihypertensive medication.

Table 2 — Number (%) of Patients with Symptoms Possibly Associated with Orthostasis in 3-Month Placebo-Controlled Clinical Studies

Symptoms	Placebo (n=678)	UROXATRAL (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Hypotension or postural hypotension	0	2 (0.4%)
Syncope	0	1 (0.2%)

Multiple testing for blood pressure changes or orthostatic hypotension was conducted in the three controlled studies at each scheduled clinic visit (Days 14, 28, 56, and 84). Patients with a decrease in systolic blood pressure of ≥20 mm Hg after 2 minutes standing following being supine were excluded from the three trials. These tests were considered positive for blood pressure decrease if (1) supine systolic blood pressure was ≤ 90 mm Hg, with a decrease ≥20 mm Hg versus baseline, and/or (2) supine diastolic blood pressure was ≤ 50 mm Hg, with a decrease ≥15 mm Hg versus baseline. The tests were considered positive for orthostatic hypotension if there was a decrease in systolic blood pressure of ≥20 mm Hg upon standing from the supine position during the orthostatic tests. According to these definitions, decreased systolic blood pressure was observed in none of the 674 placebo patients and 1 (0.2%) of the 469 UROXATRAL® patients. Decreased diastolic blood pressure was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the UROXATRAL® patients. A positive orthostatic test was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the UROXATRAL® patients.

A subset of 35 UROXATRAL® treated patients in study 1 had blood pressure measurements 12 to 16 hours after first dose administration to assess the potential to produce orthostatic hypotension. None of these patients showed a positive test for systolic, diastolic or orthostatic blood pressure change.

OVERDOSAGE

If overdose of UROXATRAL® leads to hypotension, it is important that blood pressure and normalization of heart rate be restored by keeping the patient in the supine position. If this measure is inadequate, then the administration of intravenous fluids should be considered. If necessary, vasopressors should then be used, and the renal function should be monitored and supported as needed. Alfuzosin is 82% to 90% protein-bound; therefore, dialysis may not be of benefit.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 10 mg UROXATRAL® tablet daily to be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

HOW SUPPLIED

UROXATRAL® 10 mg is available as a round, three-layer tablet imprinted with “X10”: one white layer containing the active substance between two inactive yellow layers. The resulting three-layered matrix facilitates a controlled release over the dosage interval. The tablets are supplied in bottles containing either 30 or 100 tablets. It is also supplied as a hospital unit dose (blister packs containing 10 cards of 10 tablets each).

References:

1. Uroxatral prescribing information from the Sanofi-Synthelabo website: http://www.sanofi-synthelabous.com/products/pi_uroxatral/pi_uroxatral.html
2. McKeage K, and Plosker GL. Alfuzosin: A review of the therapeutic use of the prolonged-release formulation given once daily in the management of benign prostatic hyperplasia. Drugs. 2002; 62 (4): 633-653.

APPENDIX D: LABORATORY METHODS

Clinical laboratory methods are used to exclude urethritis/cystitis, detect infection by uropathogens, and quantify prostatic inflammation. During the first screening/baseline visit, participants will provide a VB2, followed by prostate massage, collection of expressed prostatic secretion (EPS), and VB3 post-massage urine.

The patient will be examined per physician preference, but it is suggested that the dorsal lithotomy position be utilized to provide better physical examination of the prostate and surround pelvic musculature to determine points of painful sensitivity. Prior to assuming this position, the patient voids <10mls into a sterile cup prior to examination (VB1 or urethral washout specimen) and leaves the bladder half-full to provide a post-massage specimen. The prostate is examined and massaged in the traditional manner to obtain expressed prostatic secretion (EPS). It is convenient to utilize a glass pipette to collect the drops of EPS at the meatus through capillary action. Small capped cuvette style centrifuge receptacles are convenient for depositing the small EPS volumes and for processing or future storing. The patient then provides a post-massage urethral washout specimen (VB3) for culture (<10 mls).

The VB2 urine will be tested with a urine dipstick to detect nitrite, blood, leukocytes, and protein/ketones. The VB2 specimen will also be submitted for a 2-day bacteriological culture. The EPS and VB3 urine will be collected for quantitative leukocyte evaluation. This evaluation is performed by using an autopipette and mixing 80 microliters of EPS with 20 microliters of safranin red and crystal violet stain (Sternheimer Malbin Stain). Good mixing of the specimen with dye is performed using the pipette. The sample is then placed on a cytometer and counted as number of white cells per microliter (mm^3). If there are excessive numbers of leukocytes prohibiting accurate counting, the sample can be diluted 1:2 with normal saline. Only whole white cells with an identifiable nucleus should be counted. Viable cells typically take up the crystal violet in the nucleus. For purposes of standardization, all intact leukocytes—dead or alive--should be counted. Fragments of leukocytes should be ignored. Counts are multiplied by 10 and by the dilution (1.25) to determine the number of cells per microliter. Normal subjects typically have <1000 cells/microliter.