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

Randomized Clinical Trial (RCT) # 2

A Randomized, Placebo-Controlled Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pregabalin for the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

VERSION 3.0- Includes Protocol Amendments #1 & 2
August 16, 2006

Sponsored By:

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

Chronic Prostatitis Clinical Research Network-2 (CPCRN-2)
Randomized Clinical Trial #2 (RCT #2)

A Randomized, Placebo-Controlled Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pregabalin for the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

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 #2(PREGABALIN TRIAL) PROTOCOL AMENDMENT

Introduction:

The Chronic Prostatitis Collaborative Research Network 2 (CPCRN-2) Clinical Trial Protocol #2 entitled: "A Randomized, Placebo-Controlled Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pregabalin for the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)"- Version 1.0 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 is being amended as of the effective date *December 12, 2005.* Please refer to the Version 2.0 protocol table of contents for the location of changes listed below.

Summary of Protocol Amendment #1

This protocol amendment includes: 1) those FDA recommendations that have been discussed and approved by the CPCRN-2 Executive and Steering Committees (#1-5 below). Pfizer, Inc (the manufacturer of pregabalin) was also consulted on these issues; 2) a change in trial procedure (#6 below); and 3) a change in the References (#7 below). The goals of this protocol amendment are:

1) To include the risks associated with male-mediated teratogenicity and to recommend condom use for the duration of drug treatment and for three months post-treatment if the individual engages in sexual intercourse with a woman of child-bearing potential. However, condom usage is not a requirement for entry in the trial (i.e. not an Inclusion Criteria). *Please see protocol section 8.3.1- Risks of pregabalin*

2) To include a baseline platelet count so that individuals with a low blood platelet count (less than 100,000/mm^3) are excluded from entry in the trial. Additionally, those individuals with a history of thrombocytopenia or a bleeding diathesis are also excluded. These precautions are being taken because in clinical studies, decreases in platelet counts were observed more frequently with pregabalin than with placebo. *Please see protocol sections 5.3- Laboratory Procedures, 6.2- Exclusion Criteria (#3 and #8), 8.3- Risks of pregabalin, 9.2- Screening Visit, and 9.3- Screening /Randomization Visit.*

3) To exclude individuals with New York Heart Association Class III or IV congestive heart failure. This precaution is being taken because weight gain and swelling are common side effects associated with pregabalin, and may be a serious problem for people with heart problems. The long-term cardiovascular effects of pregabalin-associated weight gain are unknown. Please see protocol sections *6.2- Exclusion Criteria (#7) and 8.3- Risks of pregabalin.*

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4) To exclude individuals taking thiazolidinedione antidiabetic agents (i.e. rosiglitazone and pioglitazone) because these drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure. Please see protocol sections *6.2- Exclusion Criteria (#6) and 8.3- Risks of pregabalin*.

5) To exclude individuals with a history of alcohol abuse given the potential abuse liability of pregabalin. Pregabalin is classified as a Schedule V Controlled Substance. Please see protocol sections *6.2- Exclusion Criteria (#10) and 8.3- Risks of pregabalin*.

6) To replace having to send the NIH-CPSI and Symptom Assessment questionnaires (including the GRA question) to the patient prior to the Telephone Contacts in both Phases I and II of this trial. Instead of having the patient complete and send back, the questionnaires will be administered to the patient over the telephone. Please see protocol sections *9.4 Telephone Contacts* and *9.7 Phase II Continuation*.

7) To replace previous SAS references (*Protocol Section 13.0 #35-42*) with one citation for the most recent version of the statistical software package (Version 8.0).

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

RANDOMIZED CLINICAL TRIAL (RCT) #2

A Randomized, Placebo-Controlled Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pregabalin for the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

SUMMARY OF PROTOCOL AMENDMENT #2

The second edition of this protocol is being amended as of the effective date *August 16th, 2006.* Please refer to the Version 3.0 protocol table of contents for the location of changes listed below.

3.2 Study Design

The following text has been revised:

Each of the eleven (11) sites will randomize approximately 29 participants at a rate of two (2) participants per month. Recruitment will be conducted over a period of fifteen (15) months. A formal pre-planned interim analysis will be conducted when 159 participants have been randomized and have completed the 6 week primary endpoint visit.

Revised text reads:

Recruitment will be conducted over a period of fifteen (15) months, at a rate of approximately two (2) participants per month for each of the ten (10) sites, with the total expected randomized per site of 32 participants. A formal pre-planned interim analysis will be conducted when 106 participants have been randomized and have completed the 6 week primary endpoint visit.

4.0 Study Organizations

University of Sciences Malaysia has been removed as a participating sub-site.
University of Washington/Harborview has been removed as a participating site.

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5.3 Laboratory Procedures

Additional text reads:

A platelet count of obtained up to four (4) weeks prior to screening visit #1 will be acceptable as satisfying screening visit requirements.

6.2 Exclusion Criteria

The following exclusion criterion has been revised:

1. Participant has evidence of facultative Gram negative or enterococcus with a value of ≥ 1000 CFU/ml in mid-stream urine (VB2).

Revised, additional text in bold:

1. *Participant has **continued** evidence of facultative Gram negative or enterococcus with a value of ≥1000 **and ≤ 100,000 CFU/ml** in mid-stream urine (VB2), **as demonstrated by repeat culture obtained no less than seven (7) days post antibiotic treatment.***

6.3 Deferral Criteria

The following deferral criterion has been revised:

1. Participant has had previous gabapentin (Neurontin®) treatment within the past two (2) weeks.

Revised, additional text in bold:

1. *Participant has had previous gabapentin (Neurontin®) or **pregabalin (Lyrica®)** treatment within the past two (2) weeks.*

7.2 Phase II Dosing Schedule

Additional text for clarification reads:

As indicated in Section 3.2 Study Design, the transition in dosing from phase I to phase II occurs regardless of phase I treatment assignment or dose, with the study blind intact. Although this could result in a transition from 600 mg/day active treatment to 150 mg/day active treatment for a participant, such a transition is not expected to be of any clinical relevance.

9.2 Screening Visit (Visit #1)

Additional text under *Blood Specimen*:

A documented copy of laboratory results obtained up to four (4) weeks prior to screening visit #1 will be acceptable for these specimens.

9.3 Screening/Randomization Visit (Visit #2)

The following text has been revised:

- *Review VB2 Culture Results*. The research staff will review culture results from the baseline visit to determine participant eligibility. Participants will be excluded from the trial if they have evidence of facultative Gram negative or enterococcus with a value of ≥ 1000 CFU/ml.

Revised, additional text in bold:

- *Review VB2 Culture Results. The research staff will review culture results from the baseline visit to determine participant eligibility. Participants will be excluded from the trial if they have* ***continued*** *evidence of facultative Gram negative or enterococcus with a value of ≥ 1000* ***and ≤ 100,000*** *CFU/ml****, as demonstrated by repeat culture obtained no less than seven (7) days post antibiotic treatment.***

9.6 Dose Taper Phase

Additional text reads:

Participants who were only able to tolerate the 300mg/day dose will taper down for 4 days at 150mg/day. Participants who were only able to tolerate the 150mg/day do not need to taper down.

12.10 Data Safety Monitoring and Interim Analysis

This section has been revised at the request of the UPPCRN Data and Safety Monitoring Board (DSMB) so that the interim analysis of efficacy and safety occurs earlier in the recruitment period. This is to ensure that sufficient time exists between the results of the interim analysis and the end of recruitment such that decisions regarding early closure or protocol amendments can have an appropriate impact on enrollment. The interim analysis will now take place after approximately one third (n=106) of the participants have been enrolled and followed for six weeks. It is expected that this will occur approximately ten (10) months after the initiation of accrual.

Table of Contents:

1.0 Introduction

Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a chronic pain syndrome of unknown etiology. The current NIH definition of CP/CPPS includes genitourinary pain with or without voiding symptoms in the absence of uropathogenic bacteria, as detected by standard microbiological methods, or another identifiable cause such as malignancy.[1] The accepted research definition is that of chronic pelvic pain for at least 3 of the preceding 6 months in the absence of other identifiable causes. Although the etiology and pathogenesis of the symptoms in CP/CPPS are unknown, one proposed mechanism is that of a neurogenic origin. The defining symptom in participants with CPPS is pain. This indicates some neurologic involvement, either locally or centrally.

This idea is supported by data from the NIH sponsored Chronic Prostatitis Cohort study, in which a history of neurologic disease was almost five times more likely in the cases compared to the controls.[2] One of the few biomarkers to correlate with the levels of pain in CP/CPPS is nerve growth factor (NGF).[3] NGF is a neurotrophin that has been found to have a role in the regulation of nociceptive nerves, and as a mediator and amplifier of neurogenic inflammation. NGF regulates the sensitivity of adult sensory neurons to capsaicin, which excites C-mechano heat receptors.[4] Data from animal studies also indicates a possible neurogenic mechanism. Experimental evidence for central remodeling is provided by the finding that chemical irritation of the rat prostate and bladder causes c-fos expression at spinal cord levels L6 and S1 along with plasma extravasation in the skin at the identical L6 and S1 dermatomes, underscoring the overlap of afferent nerve fiber distribution.[5] One of the hallmarks of such remodeling or windup is neurogenic inflammation. In the Wistar rat model of spontaneous prostatitis with age increased nerve fiber density, the sensory neuropeptide calcitonin gene-related peptide and evidence of progressive mast cell degranulation are noted at progressive ages.[6] One of the products released from activated mast cells is nerve growth factor (NGF).[7]

Given this, one way to treat participants with CP/CPPS would be with medications used to treat neuropathic pain. One such medication is the antiseizure medication gabapentin. In this study, we propose to use pregabalin, developed as a follow-up compound to gabapentin. Pregabalin received FDA approval in late 2004 for treatment of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy. One of the advantages of using pregabalin is that its binding affinity to the alpha-2-delta subunit of voltage gated calcium channels is six-fold greater than that of gabapentin.[8] Therefore, a lower pregabalin dose can be used to achieve efficacy, which will result in fewer side effects for the participant.

2.0 Study Agent and Rationale for Use in CP/CPPS

2.1 Pregabalin

Pregabalin is a new medication which has recently been approved for the treatment of post herpetic neuralgia and diabetic neuropathy. Pregabalin is an antiepileptic medication that also has effects on chronic pain. Although structurally related to GABA, it does not act at GABA receptors and does not act in a physiologically similar way to GABA.[9] It binds to the alpha-2-delta subunit of voltage gated calcium channels, selectively attenuating depolarization induced calcium influx into neurons via presynaptic channels, and reduces the release of several excitatory neurotransmitters including glutamate, noradrenaline, and substance P.[10-13]

There are three full published studies of pregabalin for neuropathic pain, two of which looked at its effect on post herpetic neuralgia and one on diabetic peripheral neuropathy. All of these studies used pregabalin in a three times per day (tid) dosing. Dworkin et al[14] used dose of 300 mg per day in three divided doses or 600 mg per day in three doses. The decision on which dose to use was made based on creatinine clearance; participants with a clearance of < 60 ml/min received 100 mg po tid; those with a clearance > 60 ml/min received 200 mg po tid. Sabatowski et al[8] used doses of 150 and 300 mg po in three divided doses in a random fashion. Participants with a creatinine clearance calculated from their serum creatinine of <30 ml/min were excluded from the study. The diabetic neuropathy study[15] compared 300 mg per day as 100 mg po tid vs placebo; no dose escalation was used for this trial. Pregabalin has been used in a twice per day dosing in a study published in abstract only to date.[16] The twice per day study went up to 600 mg per day. Pregabalin is approved for use by the EU for neuropathic pain, including PHN and diabetic neuropathy, at doses of 150-600 mg as either bid or tid dosing. The dose can be titrated up from 150 per day to 300 mg per day after 3-7 days. The dose can then be increased to 600 mg per day if needed after an additional 7 days.[17]

The efficacy appears to follow a dose dependent effect.[17] Double blind study completion rates also appear to be dose dependent, reported at 88% and 79% with 150 mg and 300 mg per day of pregabalin vs 75% placebo[8] and reduced to 65% for the 600 mg dose[14] in the studies on PHN. In the diabetic neuropathy study at dose of 300 mg per day, the completion rate was 86% compared to 89% of placebo participants in this trial.[15] The main side effects seen in clinical studies include dizziness, somnolence, peripheral edema, headache, dry mouth and diarrhea. The side effects of dizziness, somnolence and peripheral edema are also dose related, but with little difference between the 300mg and 600 mg per day in tid dosing.[17]

In trials, the analgesic effects of pregabalin are seen in the first week[8,15] and as early as the second day.[14] The above referenced trials were all for 8 weeks. This included a dose escalation in one trial.[14] This rapid effect onset justifies a proposed trial of six (6) weeks of treatment in order to minimize participant exposure.

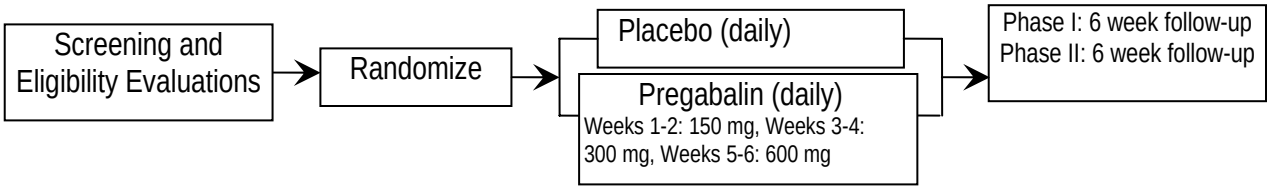
3.0 Study Design and Objectives

3.1 Primary Study Objectives

1. To compare six (6) weeks of treatment with pregabalin versus placebo in CP/CPPS participants with respect to the primary endpoint in the NIH-CPSI
2. To evaluate the safety and tolerability of six (6) weeks of pregabalin in CP/CPPS participants

3.2 Study Design

A schematic of the design of the proposed two-armed double-blind randomized clinical trial is shown below.



Phase I:

All participants who meet eligibility criteria at baseline screening will be randomized to either pregabalin (utilizing a dose escalation of pregabalin from 150 mg to 300 mg and finally to 600 mg daily) or an identical looking placebo. In the dose escalation, if a participant experiences side effects at a particular dose, he will be allowed to drop back to the maximum tolerated dose. Participants will be advised to take the medication three times per day (tid).

The goal is to randomize a total of 318 participants with an allocation ratio of 2:1, treat and follow them for a total of six (6) weeks. Eligibility for the trial and assessment of treatment efficacy will occur over three (3) visits: a screening visit, a baseline/randomization visit and an endpoint evaluation visit after six (6) weeks. There will also be two (2) phone contacts: at the end of week 2 and week 4 to obtain information on adverse events and symptom scores during the drug titration period.

Recruitment will be conducted over a period of fifteen (15) months, at a rate of approximately two (2) participants per month for each of the ten (10) sites, with the total expected randomized per site of 32 participants. A formal pre-planned interim analysis will be conducted when 106 participants have been randomized and have completed the 6 week primary endpoint visit.

Phase II

We are also proposing an optional open-label phase for this trial. The purpose for this extension is to improve recruitment. Participants who understand that they will be eligible to try a new drug at the end of a masked treatment period during which they have a 33.3% chance of receiving a placebo will be more likely to enter such a trial. At the same time, we will be able to obtain some uncontrolled efficacy and safety data on the use of pregabalin in a

longer treatment period. Participants will have the option to enroll after completion of the initial six (6) weeks of treatment. All participants, regardless of what they were previously on in Phase 1, will be offered active therapy and followed for an additional six (6) weeks. Participants will remain blinded to their initial treatment assignment until the end of the open label phase. Participants are not obligated to participate in the open label extension. Those participants who discontinue study participation will be instructed to begin a one (1) week taper from the study drug, before complete discontinuation.

4.0 Study Organizations

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

1. Cleveland Clinic, Cleveland, 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/King-Drew University, Los Angeles, CA 90095
8. University of Maryland, Baltimore, MD 21201
9. University of Mississippi, Jackson, MS 39216
10. University of Washington, Seattle, WA 98108

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.

5.0 Study Endpoints

5.1 Primary Endpoint

The primary endpoint to be used for efficacy evaluation is the response rate, defined as a 6-point decrease from baseline to 6 weeks in the NIH-CPSI Total Score (scale of 0 - 43).[18] The decision to use this 6-point cut-off is based on analysis of the previous CPCRN clinical trial on ciprofloxacin and tamsulosin.[19] 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 have a high correlation. Among those who reported "moderately improved" or "markedly improved" (n=39) on the GRA, 30 participants reported a ≥ 6-point decrease. This translates into 77% sensitivity and 71% specificity.

The responder criteria based on a 6-point decrease in the CPSI Total Score will allow detection of clinically detectable improvement in symptoms, as the goal is to identify treatment agents with solid clinical efficacy.

Using a 6-point decrease rather than the mean score change as primary outcome may result in somewhat less statistical power, but it allows study withdrawals to be considered as non-responders for an intent-to-treat analysis. (The dropout rate for the previous CPCRN trial was approximately 10% over 6-12 weeks).

5.2 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), and the Sexual Health Inventory for Men (SHIM) (a measure of male sexual function). 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, expressed prostatic secretions (EPS), and blood tests.

Additional details of the proposed secondary endpoints are provided below:

- *Global Response Assessment (GRA)*: The GRA is a single question participant-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[20] 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.

- *Hospital Anxiety and Depression Scale (HADS)*-This 14-question scale provides scores for the independent measures of anxiety and depression.

- *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.

- *Pain Medication Questionnaire (PAIN)*: These are individual questions to assess the impact of pain medications on patients enrolling in the trial.

- S*exual Health Inventory for Men (SHIM)*[21]: This 5-question index is an abbreviated form of the International Index of Erectile Function.[21] The SHIM includes questions about confidence in the ability to achieve an erection, the frequency with which participants are able to achieve and maintain erection sufficient for penetration, difficulty in completing intercourse, and the frequency with which intercourse is satisfactory. Each question is scored on a scale of 1 to 5, with 5 indicating better function. A score of $\geq$22 is considered normal.

- *Symptom Assessment Form (SYM)*: These are individual questions about pain, urgency and abnormal frequency obtained on 0 – 10 Likert scales.

5.3 Laboratory Procedures

- Clinical laboratory methods will be used to 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/or VB3 post-massage urine. 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/or VB3 urine will be collected for quantitative leukocyte evaluation. Alternatively, laboratory results obtained up to four (4) weeks prior to the Screening Visit #1 will be acceptable as satisfying screening visit requirements.

- Baseline creatinine clearance will be calculated from a serum creatinine measurement taken at the first screening visit using the equation ((*140-age) x lean body weight (kg))/(72 x plasma creatinine*). Alternatively, a serum creatinine measurement obtained up to four (4) weeks prior to the Screening Visit #1 will be acceptable as satisfying screening visit requirements. Creatinine clearance is being measured to detect individuals with impaired renal function since pregabalin clearance is reduced in these individuals.

- In order to screen out individuals with a low platelet count (<100,000/mm^3), the number of platelets will be determined from a blood sample provided at Screening Visit #1. A platelet count of obtained up to four (4) weeks prior to screening visit #1 will be acceptable as satisfying screening visit requirements.

6.0 Study population

This study will recruit men who have failed to respond to previous therapies for CP/CPPS (so-called "refractory participants"), including antibiotics. Thus the study protocol has been designed to test a new and novel therapy in a population of men with long-standing symptoms and who have failed previous treatments with standard CP/CPPS drugs.

6.1 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 at least a moderate overall score on the NIH-CPSI (overall score ≥ 15 out of a potential of 0–43 points).
5. Participant must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months.
6. Participant has a non-zero pain domain score on the NIH-CPSI at the time of enrollment.

6.2 Exclusion Criteria

Any participant satisfying any one of the following criteria will NOT be eligible to participate in the proposed randomized clinical trial:

1. Participant has continued evidence of facultative Gram negative or enterococcus with a value of ≥ 1000 and ≤ 100,000 CFU/ml in mid-stream urine (VB2), as demonstrated by repeat culture obtained no less than seven (7) days post antibiotic treatment.
2. Participant has a calculated creatinine clearance of <60 mL/min.
3. Participant has a platelet count <100,000/mm^3.
4. Participant is allergic to antiepileptic/antiseizure medications.
5. Participant has a known allergy or sensitivity to pregabalin (Lyrica®).
6. Participant is taking thiazolidinedione antidiabetic agents (i.e. rosiglitazone and pioglitazone).
7. Participant has New York Heart Association Class III or IV congestive heart failure.
8. Participant has a history of thrombocytopenia, or a bleeding diathesis.
9. Participant has a history of prostate, bladder or urethral cancer.
10. Participant has a history of alcohol abuse.
11. Participant has inflammatory bowel disease (such as Crohn's disease or ulcerative colitis, but not irritable bowel syndrome).
12. Participant has undergone pelvic radiation or systemic chemotherapy.
13. Participant has undergone intravesical chemotherapy.

14. Participant has been treated with intravesical BCG.
15. Participant has unilateral orchalgia without other pelvic symptoms.
16. Participant has an active urethral stricture.
17. Participant has a neurological disease or disorder affecting the bladder.
18. Participant has a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol.

6.3 Deferral Criteria

There are several medical conditions/procedures for which a participant will be deferred from entry into the study. Once it is determined that the condition (or procedure) is not present or has subsided according to the time frame identified, the participant will be re-screened to assess eligibility for the trial. The following list identifies the conditions for deferment.

1. Participant has had previous gabapentin (Neurontin®) or pregabalin (Lyrica®) treatment within the past two (2) weeks.
2. Participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml, within the past three (3) months.
3. Participant has had clinical evidence of urethritis, e.g. 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.
4. Participant has had a prostate biopsy in the past three (3) months.
5. Participant has experienced symptoms of acute epididymitis within the past three (3) months.
6. Participant has been diagnosed with or treated for symptomatic genital herpes in the past twelve (12) months.
7. Participant has started, stopped, or changed dose level of ANY prescription drugs with 5-alpha reductase activity (i.e. dutasteride or finasteride) in the past six (6) months.
8. Participant has started, stopped, or changed dose level of ANY prostatitis-specific medications within the past four (4) weeks.
9. Participant has undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as alcohol ablation or thermal therapy less than one (1) year ago.

7.0 Treatment Procedures

Pregabalin is well tolerated at 300 mg –600 mg per day in clinical trials of post herpetic neuralgia and diabetic peripheral neuropathy.[8,14,15] It does not appear that a dose titration is mandatory. In the referenced trials, one study[14] used a titration, starting at 150 mg po per day in 3 doses for 3 days and then increasing up to 300 mg per day; the other two studies did not dose escalate and started participants off on 300 mg per day from the first day.[8,15]

In an as yet unpublished trial looking at pregabalin in treating fibromyalgia, a dose of 450 mg per day was effective but 300 mg per day was not (R. Dworkin, personal communication, February 8, 2005). Thus, we propose a dose escalation up to 600 mg per day. However, given the increased side effects and high dropout rate (35%) observed at the 600 mg per day dose,[15] we propose to allow participants to drop back to a lower dose if they experience side effects that would otherwise lead them to drop out of the study.

Participants meeting all eligibility criteria will be randomized electronically to one of the two treatment arms. Each participant will receive a kit with three bottles of study medication at Visit #2. Participants who opt to enroll in the open-label phase of the trial will be supplied with a second kit of study medications at Visit # 5. Study medication bottles will be labeled A, B, and C. Bottle A will contain 50 mg pregabalin capsules or matching placebo; bottle B will contain 100 mg pregabalin capsules or matching placebo; and bottle C will contain 200 mg pregabalin capsules or matching placebo. 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. Additional study medication details and instructions will be provided in the Medication Manual.

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.

7.1 Phase I Dosing Schedule

Study medication will be in capsule form. Participants will be on a TID dose schedule as below. More detailed prescribing information will be included in the Medication Manual to be provided by the Investigational Drug Service at the University of Pennsylvania (Penn IDS).

- 150 mg/day (50 mg tid) for two weeks
- 300 mg/day (100 mg tid) for two weeks
- 600 mg/day (200 mg tid) for two weeks

The participant will be instructed to start with the 150 mg/day dose and based on tolerance, increase to the 300mg/day dose two weeks later (i.e. switch from Bottle A to B), then 600mg /day dose for the two weeks after that (i.e. switch from Bottle B to C). At any time the participant cannot tolerate a scheduled increased dose, he may adjust the study medication dose by going back to a previous dose (i.e. switch back to A from B).

7.2 Phase II Dosing Schedule

Study medication will be in capsule form. Participants will be on a TID dose schedule as below.

- 150 mg/day (50 mg tid) for one week
- 300 mg/day (100 mg tid) for one week
- 600 mg/day (200 mg tid) for four weeks

The participant will be instructed to start with the 150 mg/day dose and based on tolerance, increase to the 300mg/day dose one week later (i.e. switch from Bottle A to B), then 600mg /day dose for the four weeks after that (i.e. switch from Bottle B to C). There is a more rapid dose titration in the open label, as compared to in Phase I, because this is how the medication will be used in clinical practice given the quick effect onset. Similar to Phase I, any participant that cannot tolerate a scheduled increased dose, may go back to a previous, lower dose. As indicated in Section 3.2 Study Design, the transition in dosing from phase I to phase II occurs regardless of phase I treatment assignment or dose, with the study blind intact. Although this could result in a transition from 600 mg/day active treatment to 150 mg/day active treatment for a participant, such a transition is not expected to be of any clinical relevance.

7.3 Drug Manufacturing and Packaging

7.3.1 Pregabalin

Pregabalin (Lyrica®) is currently manufactured by Pfizer, Inc. Pfizer will be providing the pregabalin capsules for this trial and shipping them directly to the Investigational Drug Service at the University of Pennsylvania (Penn IDS) for blinded re-packaging and labeling.

7.3.2 Placebo for Pregabalin

Pfizer, Inc. will also be providing the placebo capsules for this trial and shipping them directly to the Penn IDS for blinded re-packaging and labeling. The placebo capsules will be packaged and labeled identical to the pregabalin capsules.

7.4 Concomitant Medications

7.4.1 Drug Interactions:

Pregabalin is not metabolized by the liver, does not affect the cytochrome P450 system nor is bound to plasma protein and therefore does not have drug-drug interactions from these mechanisms.[9] No evidence of pharmacokinetic drug-drug interactions has been observed or reported. However, pregabalin appears to potentiate or be additive in the impairment of cognitive and gross motor function caused by oxycodone, ethanol, and lorazepam[22]. Similarly, concomitant use of the thiazolidinedione class of antidiabetic drugs could be additive in leading to weight gain and fluid retention.

7.4.2 Exclusionary medical condition:

Renal excretion is the primary route of pregabalin elimination; 98% of the administered dose is eliminated as unchanged drug in the urine.[17] Therefore, significant impairment of renal function could lead to higher pregabalin blood levels.[23]

8.0 Participant Recruitment and Consent

8.1 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.

8.2 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 1.

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.

8.2.1 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.

8.2.2 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.

8.3 Risks and Benefits to Participants

This is a double-masked, placebo-controlled RCT evaluating the efficacy of pregabalin in CP/CPPS patients. It is not guaranteed that participants in this trial will receive any direct

benefit. The information gained from this study may eventually prove beneficial to the treatment and diagnosis of other patients with CP/CPPS.

8.3.1 Risks of pregabalin

Common Side Effects: Dizziness, somnolence and peripheral edema (mainly of the lower limb) of mild-to-moderate intensity are the most frequently observed adverse events, and appear to be dose-dependent. The incidences of dizziness were 12% and 28% with pregabalin 150 mg/day and 300mg/day (vs.15% with placebo),[8] and 28% with pregabalin 600 mg/day (vs. 12% with placebo).[14] The incidences of somnolence were 15% and 24% with pregabalin 150 mg/day and 300mg/day (vs.7% with placebo),[8] and 25% with pregabalin 600 mg/day (vs. 7% with placebo).[14] The incidences of peripheral edema were 3% and 13% with pregabalin 150 mg/day and 300mg/day (vs. 0% with placebo),[8] and 19% with pregabalin 600 mg/day (vs. 2% with placebo).[17] Other common events include dry mouth, asthenia, amblyopia, thinking abnormal, and weight gain.[22]

Weight Gain and Peripheral Edema: Pregabalin treatment caused weight gain. Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown. There is also limited data on congestive heart failure patients with New York Association Class III or IV cardiac status. Pregabalin treatment also caused edema, primarily described as peripheral edema. Concomitant use of pregabalin and drugs that can cause additional weight gain and/or fluid retention, such as the thiazolidinedione class of antidiabetic drugs, could have an additive effect and possibly exacerbate or lead to heart failure, especially in patients with preexisting cardiac conditions. [22]

Platelet Count: In clinical studies, decreases in platelet counts were observed more frequently with pregabalin than with placebo; however these changes were not associated with events that could indicate changes in platelet or overall hemostatic function.[22]

Renal: Pregabalin is associated with an elevation in creatinine kinase levels in some patients. Review of individual patient cases does not suggest a clinically important risk of renal dysfunction associated with these elevations. Pregabalin had no apparent effect on liver and renal function.[22]

Reproductive Toxicity: In pre-clinical studies in rats, pregabalin administration resulted in decreased sperm motility and decreased fertility at exposures ≥27x the mean human exposure at the maximum recommended clinical dose of 600 mg/day and were reversible. In a human clinical study, no effects on sperm numbers and function were observed. Pregabalin was not teratogenic in mice, rabbits or female rats over an exposure range 31 to 77x the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In embryo-fetal studies in rabbits and female rats, pregablin induced fetal toxicity at ≥39x the mean human exposure. However, since these effects have not been systematically evaluated in clinical studies, participants will be cautioned about these reproductive risks and precautions will be taken to reduce the risk of male-mediated teratogenicity. It will be recommended to participants that they use condoms, if engaging in sexual intercourse with a woman of child-bearing potential, for the duration of drug treatment and for three months post-treatment.

Abuse Potential: Pregabalin is labeled as a Schedule V controlled substance and may cause some individuals to feel "high". The potential abuse liability of pregabalin has been

thoroughly evaluated. Data from clinical programs (in over 10,000 individuals) and postmarketing exposure (in approximately 15,000 individuals) provide evidence that pregabalin is unlikely to be abused.[22] An antidepressant-like discontinuation syndrome may occur in some individuals, but a gradual discontinuation, as with a drug taper off can help to alleviate this.

8.3.2 Risks of placebo

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

9.0 Trial Tests and Procedures

9.1 Procedural Summary

This study is comprised of two phases for each participant: i) the screening phase and ii) the treatment and follow-up phase. A visit schedule can be found in Appendix A. 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 fewer than two (2) days apart, when laboratory results from the 2-day urine culture 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. The treatment/follow-up phase will consist of one visit. There will also be two telephone contacts. A detailed Forms and Visit Schedule can be found in Appendix A.

9.2 Screening Visit (Visit #1)

During this first clinic 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*. The research staff will check whether the participant 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.

- *Blood Specimen:* Each participant will provide a blood specimen for a serum creatinine measurement (which will be used in calculating a baseline creatinine clearance level) and for a platelet count. A documented copy of laboratory results obtained up to four (4) weeks prior to screening visit #1 will be acceptable for these specimens.

9.3 Screening/Randomization Visit (Visit #2)

This second screening visit should be completed at least two (2) days after, but no more than four (4) weeks after 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 clinic visit, the participant 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 "pre-existing conditions," as defined in the Manual of Procedures (MOP).

- *Review VB2 Culture Results*. The research staff will review culture results from the baseline visit to determine participant eligibility. Participants will be excluded from the trial if they have continued evidence of facultative Gram negative or enterococcus with a value of $\geq$ 1000 and $\leq$ 100,000 CFU/ml, as demonstrated by repeat culture obtained no less than seven (7) days post antibiotic treatment.

- *Review Creatinine Clearance Measurement*. The research staff will review lab results from the baseline visit to determine participant eligibility. Participants will be excluded from the trial if they have a calculated creatinine clearance value of <60 mL/min.

- *Review Platelet Count*. The research staff will review lab results from the baseline visit to determine participant eligibility. Participants will be excluded from the trial if they have a platelet count of <100,000/mm^3.

- *Symptom Questionnaries.* Each participant will complete the following symptom questionnaires at this visit and at the next Clinic visit:

  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. Sexual Health Inventory for Men (SHIM)
  7. Pain medication Questionnaire (PAIN)

Randomization will also take place during this visit. All eligibility criteria will be reviewed with the participant, as well as checked against their symptom questionnaires, and medication use from the previous visit. In particular, the symptom scores at each of the two baseline screening visits will be compared with the minimum cut points required. If the participant is eligible for the study, the participant 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 study medication (or its matching placebo) and thorough instructions of the dosing/titration schedule.

9.4 Telephone contacts

Telephone Contact #1 (Visit #3)- The research coordinator will contact the participant after completion of the 150mg dose in order to determine adverse effects of medication and to monitor tolerance. The research coordinator will also administer the NIH-CPSI and SYM questionnaires (including the GRA question) over the phone.

Telephone Contact #2 (Visit #4)- The research coordinator will contact the participant after completion of the 300mg dose in order to determine adverse effects of medication and to monitor tolerance. The research coordinator will also administer the NIH-CPSI and SYM questionnaires (including the GRA question) over the phone.

9.5 Treatment Visit (Visit #5)

The participant will be required to return for a third clinic visit six weeks after treatment start. The primary efficacy measure is the CPSI.

- *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 been resolved.

- *Symptom Questionnaires*. As in the Screening/Randomization Visit (Visit #2), the participant will be required to complete a number of different questionnaires, with the addition of the single question GRA.

Unused study medications will be returned and the RC will do a pill count and assess drug compliance. The *Study Stop Form* and *Treatment Stop Form* will also be completed at this visit for those participants not continuing on to Phase II.

At this visit, sites that choose to will have the option of asking whether the participant is willing to provide a second urine and EPS specimen, provided that this additional procedure is specified in the site's informed consent.

9.6 Dose Taper Phase

The participant electing not to continue into Phase II will be provided with "taper down" instructions, beginning at week seven (7). The taper down will be completed in one week, with participants on 300 mg/day for the first three (3) days and then 150 mg/day for the remaining four (4) days. Participants who were only able to tolerate the 300mg/day dose will taper down for 4 days at 150mg/day. Participants who were only able to tolerate the 150mg/day do not need to taper down. The participant will be contacted by telephone at the end of week seven (7) to confirm completion of study drug taper (Visit #6). The Research coordinator will also continue to record the participant's concomitant medication use as well as monitor any adverse events that have newly occurred, changed, or been resolved. The NIH-CPSI will also be completed.

9.7 Phase II Study Continuation

At Visit #5, participants will be given the option of discontinuing study participation, or continuing on to the open-label phase of the study (Phase II) for an additional six (6) weeks. Those participants having a Serious Adverse Event in Phase I of the study will be ineligible for Phase II participation.

As in Phase I, there will be two telephone contacts (Visits # 7 and #8) after completion of the 150mg/day dose (1 week duration) and the 300 mg/day dose (1 week duration). Again, the research coordinator will administer the NIH-CPSI and SYM questionnaires (including the GRA question) over the phone.

At the end of the six (6) week Phase II treatment period, participants will return to the clinic for one last visit (Visit #9).

- *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 in the Screening/Randomization Visit (Visit #2), the participant will be required to complete a number of different questionnaires, with the addition of the single question GRA.

Study close-out will take place and include a pill count on returned study medications, drug compliance assessment, and completion of the *Study Stop* and *Treatment Stop* forms for all participants. Similar to the procedure in Phase I of the study, participants will be provided with drug taper instructions and contacted by telephone at the end of the week to confirm completion of the taper (Visit #10).

10.0 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 pre-existing conditions and adverse events reporting are described below.

Definition of Pre-existing Condition

A pre-existing condition is any chronic or acute sign, symptom, illness, or condition that the participant has at the time of entering the clinical trial; with the exception of those associated with the disease under study.

Definition 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.[24] 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.

10.1 Serious Adverse Events

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.[25] 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.

10.2 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.

10.3 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.

10.4 Unmasking (Unblinding) of Treatment

At the end of 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.

10.5 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 six (6) week endpoint. However, all attempts will be made to get complete data on all participants, including those who cease treatment prior to six (6) 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 six (6) weeks.

Under certain circumstances, a study participant may have his treatment terminated prior to the six (6) 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.

11.0 Administrative Responsibilities

11.1 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.

11.2 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.

11.3 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.

11.4 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.

11.5 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.

11.6 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),[26] 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.

11.7 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.

11.8 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.

11.9 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[27] DeMets[28]Neaton[29] Bailey[30], and McFadden[31], 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.

12.0 Statistical Considerations

12.1 Summary of Study Design

The proposed study design is a two-arm, double blind, randomized clinical trial (RCT) to evaluate the efficacy and safety of pregabalin, as compared to matching placebo. The primary endpoint on which sample size requirements are based is the comparison of response rates, with responder being defined in terms of a decrease in the NIH-CPSI total score as described in Section 2.6. The proportion of "responders" in each treatment arm will be compared, in an intent-to-treat analysis, to evaluate the overall efficacy of the active therapy as compared to placebo. Approximately 318 eligible participants, 212 in the active treatment arm versus 106 in the placebo arm, will be randomized and followed for a period of six (6) weeks after randomization for the primary, and all secondary endpoints analyses.

An open-label phase for this trial (Phase II) will be offered to all participants after completion of the initial six (6) weeks of treatment, with the exception of those having a Serious Adverse Event while on study treatment in Phase I. Participants on active therapy or placebo will be offered active therapy and followed for an additional six (6) weeks. Participants will remain blinded to their initial treatment assignment until the end of the open label phase. The Phase II study is for the purpose of evaluating long term treatment effect. The GRA, NIH-CPSI will be re-examined again at the end of the Phase II.

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.

12.2 Sample Size Calculations

The primary analysis on which sample size requirements are based is the comparison of response rates, with responder being defined as 6 or more points of decline in the NIH-CPSI total score from baseline to primary endpoint. For this comparison, we desire adequate numbers of participants to detect a response rate of at least 60% in the active treatment arm versus 40% in placebo (difference of 20%). The estimated response rate of 40% for the placebo group is based on a previous CP/CPPS study (unpublished data). Assuming 90% power to detect the specified difference between the active treatment and placebo arms at a two-sided $\alpha = 0.05$ level of significance, a total of 318 participants are required. With the allocation ration to be 2:1, 212 participants will be randomized to the active treatment arm, and 106 to the placebo arm. This proposed sample size is adjusted for one planned interim analysis to be conducted when one half of the participants complete primary endpoint of Phase I. It also includes 10% inflation to account for clinical center variation in response rates.

Response Rate			Total Sample Size		Sample Size Per Arm	Per Center over 15-month	
Placebo	Pregabalin	Difference	Unadjusted	Adjusted	(Pregabalin/Placebo)	Total	Per Month
40%	55%	15%	516	570	380/190	52	3.5
40%	60%	20%	287	318	212/106	29	2
40%	65%	25%	181	201	134/67	18	1.2

12.3 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 3, 6 and 9. 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 participant population. While there clearly are other variables that will be observed and recorded before randomization, and which could be used for stratification, including participant'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.[27] 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. 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.

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 study nurses, and referring physicians. The biostatisticians will only be provided with the treatment assignment for placebo by the DCC Quality Assurance Director. At the end of a participant'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, the treatment codes will not be identified until the DSMB has approved unblinding in preparation for the public dissemination of results.

12.4 Intent-to-Treat Analyses and Missing Data

An intent-to-treat analysis, including all randomized participants, 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 six (6)

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.

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.

12.5 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).

12.6 Descriptive Analyses

Standard descriptive statistics will be used to describe participants' baseline characteristics and study outcome measures at 6 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.

12.7 Analysis of Primary Outcome

The primary endpoint to be used for efficacy evaluation is response rates determined by a decline from baseline in the NIH-CPSI total score (scale of 0-43). "Responders" will be defined as those subjects demonstrating at least a 6-point decrease from baseline to 6 weeks in the NIH-CPSI; the proportion of responders by this definition will be compared between the active treatment and placebo group. 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.[32] 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.[33] 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 six-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.

12.8 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 3.3 and include the Global Response Assessment (GRA), subscores of the NIH-CPSI, the Medical Outcomes Study short Form 12 (MOS SF-12), the McGill Pain Questionnaire (MPQ), the Hospital Anxiety and Depression Scale (HADS), the Sexual Health Inventory for Men (SHIM).

For example, one type of response will be based on the participant GRA of change as measured at six (6) 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.[33] These methods will include random effects regression models for continuous outcomes and GEE methods for categorical and ordinal outcomes such as the GRA.[33] 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 6 weeks is associated with the level of treatment response.

12.9 Analyses for the Phase II

The participants enrolled in the open label phase of this study may not represent a random sample of the initial randomized participants; therefore only exploratory analyses will be conducted. The response rates will be compared between those who were originally randomized to receive pregabalin, and those who are receiving pregabalin for the first time. The summary statistics will be provided for the changes in the secondary outcomes from week 6 to week 12.

12.10 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. One interim analysis will be performed approximately ten (10) months after the initiation of accrual, when approximately one third (n=106) of the participants will have been accrued and followed for six (6) weeks. The results of these analyses will be presented to the DSMB. The purpose of this interim analysis will be to compare the efficacy and safety of the active treatment relative to placebo. Both the primary endpoint and selected secondary efficacy endpoints, as well as safety, will be evaluated at the interim analysis. However, decisions regarding early closure (see below) will be based on the primary efficacy endpoint and generally not be considered based on the secondary endpoints.

To preserve the overall Type I error rate for the primary analysis of efficacy, group sequential boundary methods using the Lan and DeMets analog to O'Brien-Fleming boundaries[34] will be used to calculate the nominal significance levels to which the interim p-value is compared. Both upper (for differences in efficacy) and lower (for futility) boundaries will be used. Assuming 6 week data on 106 participants, corresponding to an information time of approximately 33%, the efficacy boundary significance level to which the observed p-value will be compared is 0.0002, and the futility boundary significance level is 0.993. A conditional power analysis may also be conducted at that time to provide additional information regarding early closure for futility. The final decision to terminate the trial early will be made 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. 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
Participant 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, Efficacy and futility	Biostat	DSMB	33% accrual, follow-up for 6 weeks after randomization
Final analysis: Safety and Efficacy	Biostat	DSMB	100% accrual, follow-up for 6 &12 weeks after randomization

12.11 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 0.05.

12.12 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[35]and S-plus.[36] The Proc StatXact for SAS Users software[32] 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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14.0 Appendix A: Forms and Visit Schedule

Form Name	Phase I						Phase II			
	-1 to -4 Weeks (Screening)	0 Weeks (Random-ization)	2 Weeks (Follow-up)	4 Weeks (Follow-up)	6 Weeks (Follow-up)	7 Weeks (Follow-up)	7 Weeks (Follow-up)	8 Weeks (Follow-up)	12 Weeks (Follow-up)	13 Weeks (Follow-up)
	Visit 1 (B1 Clinic)	Visit 2 (B2 Clinic)	Visit 3 (Phone)	Visit 4 (Phone)	Visit 5 (Clinic)	Visit 6 (Phone)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Clinic)	Visit 10 (Phone)
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	X	X	X	X	X	X
Randomization (RAND)		X								
Procedures and Labs										
Adverse Events/Serious Adverse Events (AE)		X	X	X	X	X	X	X	X	X
Concomitant Medications (CMED)		X	X	X	X	X	X	X	X	X
Clinical Lab Results (LABS)	X									
Demographics (DEMO)	X									
Dispensing Log (DISP)		X			X				X	
Drug Compliance (DCOMP)			X	X	X		X	X	X	
EPS and Urine Testing (EUT)	X				X					
Physical Exam (EXAM)	X									
Standard Telephone and Clinic Contact Summary (STCONT)			X	X	X	X	X	X	X	X
Urine Screening (URINE)	X									
Symptom Questionnaires										
Symptom Assessment (SYM)	X	X	X (GRA)	X (GRA)	X (GRA)	X (GRA)	X (GRA)	X (GRA)	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 Sexual Health Inventory for Men® (SHIM)		X			X				X	
Participant Expectations Questionnaire (EXP)		X			X					
Pain Medication Questionnaire (PAIN)		X			X					
PRN Forms										
Phase I Close Out (PHASEI) **Required only when not going onto Phase II					X**					
Study Stop Point (SSTOP)	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	X	
Treatment Stop Point (TSTOP)	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	X	
Unmasking Record (UNMASK)	PRN	PRN	PRN	PRN	PRN	PRN				
Administrative Forms										
Clinical Center Staff "Signature and Delegation of Responsibilities" Log (STAFFLOG)	X	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	
Participant Daily Medication Diary (PTDIARY)	X	X	X	X	X	X	X	X	X	
Participant ID Assignment Log (PTLOG)	X									
Participant Contact Information (PTCONT)	X									
Participant Transfer (TRANS)	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	
Study Drug Tracking Log (TRACK)		X	X	X	X	X	X	X	X	
Visit Checklist	X	X	X	X	X	X	X	X	X	