CLINICAL STUDY PROTOCOL

Title:	A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Trial to Evaluate the Efficacy and Safety of AQX-1125 (200 mg) in Male Subjects with Chronic Prostatitis/Chronic Pelvic Pain Syndrome
Test Product:	AQX-1125
Protocol Identification:	AQX-1125-205
Sponsor Name, Address, and Telephone Number:	Aquinox Pharmaceuticals (Canada) Inc. Suite 450 – 887 Great Northern Way Vancouver, BC Canada, V5T 4T5 t: 604.629.9223
Compliance Statement:	The trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation and all applicable national and local regulations.
Date/Version of Protocol:	08 March 2018/Version 3.0, Amendment 2
Aquinox Pharmaceuticals (CANADA) Inc. Medical Monitor	Alison E. Heald, MD A E Heald MD — Signature 08 March 2018 — Date:

Confidential Information

PROTOCOL SIGNATURE PAGE

Protocol: AQX-1125-205

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Investigator Statement: I have received and completely reviewed the above-named protocol, including all appendices and amendments. As Investigator, I agree to conduct the trial in accordance with all stipulations of the protocol and in accordance with the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP), all applicable national and local regulations, the Declaration of Helsinki and its amendments.

INVESTIGATOR SIGNATURE AND CONTACT INFORMATION	
Investigator (*signature*)	
Investigator (*please print*)	
Date of Signature	
Investigator's Address	
City, State, Country, Zip Code	
Telephone No.	
Fax No.	
Email	

Signature on this page assures Aquinox that, to the best of the Investigator's knowledge, the affiliated Institutional Review Board (IRB) or Independent Ethics Committee (IEC) operates in accordance with applicable local and national regulations, and that the Investigator understands and agrees to abide by all regulatory obligations and ICH GCP Guidelines while conducting this clinical trial.

Once signed, the original of this form should be detached from the protocol and returned to the Sponsor.

(Please retain a copy for your files)

STUDY CONTACT INFORMATION

Serious Adverse Events and Treatment Emergent Adverse Events of Special Interest

Any SAE, or treatment emergent adverse events of special interest (TEAESI) occurring in a subject while receiving study drug or within 30 days of receiving study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone, fax, or e-mail to the Sponsor (or designee).

Unless otherwise instructed, SAE and TEAESI reports are to be submitted by email or fax to:

CTDS Drug Safety Manager
Email: AquinoxPVG@clinicaltrialdata.com
Fax: 978.486.4055
Telephone: 978.486.4022

Who will forward a copy to:

Medical Monitor:
Alison Heald, MD
Aquinox Medical Monitor
Email: consulting@alisonheald.com
Telephone: 206.465.3912

1 SYNOPSIS

Name of Sponsor/Company: Aquinox Pharmaceuticals (Canada) Inc.

Name of Product: AQX-1125
Name of Active Ingredient: AQX-1125

Title: A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Trial to Evaluate the Efficacy and Safety of AQX-1125 (200 mg) in Male Subjects with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Development Phase: 2

Objectives:

Primary Objective

The primary objective of this study is to evaluate the effect of 12 weeks of treatment with AQX-1125 (200 mg) administered orally once-daily compared to placebo on the change from Baseline (Visit 2) to Week 12 (Visit 4) in maximum daily pelvic pain (mean) in male subjects with non-bacterial chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) using a standardized 11-point Numerical Rating Scale (NRS) pain score recorded daily by an electronic diary (eDiary).

Secondary Objectives

The secondary objectives of this study are to evaluate:

- The effects of 12 weeks of treatment with AQX-1125 (200 mg) administered orally once-daily compared to placebo on the change from Baseline (Visit 2) to Week 12 (Visit 4) for each of the following:
  - National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) pain subscale and all domains total score
  - Male sexual health as measured using the International Index of Erectile Function Questionnaire, Erectile Function Domain (IIEF-EF)
  - Average daily pelvic pain (eDiary), average and maximum pelvic pain (Paper-based NRS, in clinic), using the standardized 11-point NRS
  - 24-hour voiding frequency (eDiary)
- Time course of effects: AQX-1125 (200 mg) compared to placebo on the change from Baseline (Visit 2) at Week 6 (Visit 3), Week 12 (Visit 4), and Week 16 (i.e. 4 weeks after end of treatment) for each of the pain and symptom scale endpoints
- The overall response to treatment for AQX-1125 (200 mg) compared to placebo as measured by the subject's Global Response Assessment (GRA), Patient's Global Impression of Change scale (PGI-C) and Patient's Global Impression of Severity scale (PGI-S) at Week 12 (Visit 4)
- The proportion of subjects with ≥30% and ≥50% improvement in maximum daily pelvic pain (mean) using the standardized 11-point NRS recorded by the eDiary and the NIH-CPSI pain subscale compared to placebo, at Weeks 6 (Visit 3) and 12 (Visit 4)
- Responder analysis: response to treatment defined by any of the following:
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with no change in the amount or strength of concomitant analgesic medications
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with a decrease in the amount or strength of concomitant analgesic medications
- Discontinuation of study medication due to treatment failure (% meeting treatment failure criteria and time to event)

Safety Objectives

The safety objectives of this study are to evaluate:

- Safety and tolerability of AQX-1125 (200 mg) compared to placebo during the 12-week treatment period
- Ocular safety based upon assessment of lenticular opacification using Lens Opacification Classification System (LOCS) III, best corrected visual acuity (BCVA) using the Logarithm of the Minimum Angle of Resolution (LogMAR) chart, intraocular pressure (IOP), corneal staining, and slit lamp examination

Name of Sponsor/Company: Aquinox Pharmaceuticals (Canada) Inc.

Name of Product: AQX-1125

Name of Active Ingredient: AQX-1125

Methodology:

In this double-blind, placebo-controlled study, approximately 100 male subjects diagnosed with CP/CPPS will be randomized to either AQX-1125 (200 mg) or placebo in a 1:1 ratio across approximately 30 centers in North America. The study will consist of a screening period of up to 3 weeks, a 12-week treatment period followed by a 4-week Off-Treatment Safety Follow-up period, and an Ophthalmic Safety Follow-up Visit 6 months post last dose, for a total study duration of about 41 weeks. There will also be a follow-up telephone call 3 months after the last dose.

At Screening Visit 1, each subject will complete a set of questionnaires, and receive (and be trained to use) an eDiary. Subjects will record their average and maximum daily pelvic pain score, at approximately the same time each day (in the evening prior to the last dose of pain medication), as well as their daily use of analgesic pain medications. Baseline ophthalmic assessments, including lenticular opacification assessment using LOCS III, can be completed as a separate visit any time during the screening period (any time before Visit 2).

At Baseline (Visit 2), all subjects will return to the clinic for review of eligibility and to complete the efficacy questionnaires and assessments to establish Baseline values. Average daily pelvic pain scores recorded in the eDiary within the 7 days prior to Baseline (Visit 2) will be part of the study entry criteria. If all entry criteria are met, the subject will be randomized (1:1) to receive a single daily oral dose of 2 tablets for 12 weeks as follows:

- AQX-1125 200 mg dose group: 2 AQX-1125 100 mg tablets; or,
- Placebo group: 2 placebo tablets

All enrolled subjects will record the following in the eDiary (from Screening Visit 1 to Week 16 [Off-Treatment Safety Follow-up Visit]):

- Maximum daily pelvic pain: subjects will assess their maximum pelvic pain for that day on a scale of 0 to 10, with 0 indicating ‘no pelvic pain’ and 10 indicating ‘pelvic pain as bad as you can imagine’
- Average daily pelvic pain. Subjects will assess their average pelvic pain for that day on a scale of 0 to 10, with 0 indicating 'no pelvic pain' and 10 indicating 'pelvic pain as bad as you can imagine'
- Analgesic medication taken each day
- 24-hour voiding frequency: voiding frequency will be measured over a 24-hour period, within a 3-day (72-hours) window before the next scheduled visit (Visit 2, 3, 4 and Off-Treatment Safety Follow-up Visit)

At Week 6 (Visit 3), and Week 12 (Visit 4), and Week 16 (Off-Treatment Safety Follow-up Visit) during the clinic visit, subjects will complete NIH-CPSI, paper-based 11-point NRS (average and maximum pelvic pain experienced over the last 24 hours), GRA, PHQ-9, PGI-C, IIEF, PGI-S, have vital signs assessed and return unused study drug (Week 6 and 12). Any adverse events (AEs) are to be recorded.

Subject compliance with the eDiary will be monitored by trained study site personnel at each study visit.

All subjects completing the 12 weeks of treatment (Visit 4) will be considered completers of treatment. Subjects who withdraw from the study during the treatment period should complete an Early Termination Visit. Subjects who discontinue the double-blind treatment for any reason will be encouraged to continue with all subsequent study-related visits and evaluations, with emphasis on obtaining pelvic pain data, analgesic medication data and voiding frequency data to assess efficacy endpoints. Subjects who complete the study or early terminate during the study will be asked to return for the Safety Follow-up Visit 4 weeks after discontinuing study drug, and the Ophthalmic Safety Follow-up Visit 6 months after the last dose. Subjects will also be contacted via telephone for the follow-up telephone call 3 months after their last dose.

Number of Subjects:

Approximately 100 male subjects at approximately 30 sites in North America.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

For inclusion into the screening period subjects must meet the following criteria:

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Name of Product: AQX-1125
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1. Provide written informed consent and the willingness and ability to comply with all aspects of the study requirements
2. Males, ≥18 and ≤80 years of age at Screening Visit 1
3. Have pain or discomfort in the pelvic region for at least 3 months in the last 6 months, in the absence of a urinary tract infection or other pelvic/urological cause, and have a physician diagnosis of CP/CPPS (NIH Prostatitis Category III)
4. NIH-CPSI of ≥15 on the total score
5. Subjects must agree to use a condom for sexual intercourse from Screening Visit 1 until at least 90 days after the last dose of study drug, unless they have been surgically sterilized (vasectomy) for a minimum of 6 months. True abstinence from sexual intercourse in accordance with the preferred and usual lifestyle of the subject is also acceptable
6. Have an average daily pelvic pain score of ≥4 out of 10 on the 11-point NRS pain scale (mean of the average daily pelvic pain score recorded at each of the 7 days prior to Baseline [Visit 2]). A minimum of 5 daily records within 7 days prior to Baseline (Visit 2) must be recorded
7. Must be capable of voiding independently for 30 days prior to screening (to allow completion of 24-hour voiding diary)

Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for trial:

1. Diagnosis of NIH Prostatitis Categories I (acute prostatitis) or II (chronic bacterial) prostatitis
2. Diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) with symptoms of pain, pressure, or discomfort perceived to be related to the bladder, and associated lower urinary symptoms for >6 weeks in the absence of infection or other identifiable causes
3. Relief of pelvic pain after voiding or have >15 voids per day
4. Post-void residual volume >150 mL
5. Have had an unresolved (positive bacterial urine culture) urinary tract infection within 8 weeks (inclusive) prior to Screening Visit 1 (subjects can rescreen [up to 1 time] once infection clears)
6. History of previous prostate or bladder intervention (i.e. prostate biopsy, cystoscopy, or indwelling urinary catheter) within 1 month of Screening Visit 1, history of microwave therapy, transurethral resection of the prostate, transurethral radiofrequency thermotherapy, transurethral incision of the prostate, transurethral needle ablation, transurethral laser vaporization of the prostate, Urolift®, Rezum, and other urological interventions (e.g., botulinum toxin) within 6 months of Screening Visit 1
7. Unilateral testicular or scrotal pain as the sole symptom of CP/CPPS
8. Ongoing, symptomatic urethral stricture disease
9. Catastrophizing pain score of ≥30 as determined by the Pain Catastrophizing Scale (PCS)
10. Current major depressive disorder (i.e. Patient Health Questionnaire-9 [PHQ-9] score ≥10)
11. Neurologic disease or disorder affecting the bladder, ability to void spontaneously, or directly contributing to urinary symptoms (e.g., multiple sclerosis, autonomic neuropathy)
12. Severe, excruciating pain during rectal exam (i.e. an "inability to perform the exam")
13. History of chronic substance abuse, dependency or abuse of opioids, or other narcotics within the last 2 years
14. Currently receiving, or expect to receive, any of the following prohibited medications or procedures:
    - **Non-steroidal anti-inflammatory drug or other medication (e.g. alpha-blockers) for CP/CPPS,** unless on a stable dose for ≥30 days prior to Screening Visit 1
    - **Long-acting opioids:** within 2 weeks prior to Baseline (Visit 2) or expected to take any long-acting opioids at any time during the study

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- **Short-acting opioid or opioid-containing analgesics**: more than 10 doses/month, or more than a single dose > 2 days per week, or any short-acting opioid within 3 days prior to randomization
- **Oral steroid therapy, immunosuppressants / immunomodulators** (including daily phosphodiesterase Type 4 inhibitors) within 30 days prior to Screening Visit 1 and throughout the study
- Have taken any **investigational drug or device** within 90 days prior to Screening Visit 1, or have had previous exposure to AQX-1125

15. Any prior history of pelvic cancer (e.g., colorectal, genitourinary) or treatment (radiation or chemotherapy) thereof
16. Major surgery within 3 months prior to Screening Visit 1
17. Have any other condition/disease which, in the opinion of the Investigator, could compromise subject safety or interfere with the subject's participation in the study or in the evaluation of the study results. In case of any doubt, the Investigator shall consult the medical monitor.
18. Known intolerance to micro-crystalline cellulose (Avicel® PH-102), mannitol or other ingredient of AQX-1125 tablets

Test Product, Dose and Mode of Administration:

Two AQX-1125 (activator of the Src homology 2-containing inositol-5'-phosphatase 1 protein) 100 mg tablets will be administered orally once daily with a glass of water, around the same time of day, for 12 weeks. Tablets should be taken with food or eat a light meal no more than 4 hours prior to consumption.

Reference Therapy, Dose and Duration of Administration:

Matching placebo is identical in appearance to the test product and contains no active ingredient. Two placebo tablets will be administered orally once daily with a glass of water, around the same time of day, for 12 weeks. Tablets should be taken with food or eat a light meal no more than 4 hours prior to consumption.

Duration of Treatment:

Subjects will participate in a 12-week, double-blind treatment phase. After the treatment phase, there will be a 4-week post last dose Safety Follow-up, as well as a 6-month post last dose Ophthalmic Safety Follow-up. There will also be a 3-month post last dose Telephone Call Follow-up.

Variables:

Primary Endpoint

The primary endpoint is the change from Baseline (Visit 2) to Week 12 (Visit 4) in the maximum daily pelvic pain (mean) using a standardized 11-point NRS pain score recorded daily by an eDiary.

Secondary Endpoints

The secondary endpoints are:

- The change from Baseline to Week 12 for each of the following:
  - NIH-CPSI pain subscale and all domains total score
  - Male sexual health as measured using the IIEF-EF
  - Mean of average daily pelvic pain scores (eDiary), average and maximum pelvic pain (Paper-based NRS in clinic)
  - 24-hour voiding frequency (eDiary)
- Time course of effects: AQX-1125 (200 mg once-daily) compared to placebo on the change from Baseline (Visit 2) to Week 6 (Visit 3), Week 12 (Visit 4), and Week 16 (i.e. 4 weeks after end of treatment) for each of the following:
  - Mean of maximum daily pelvic pain score (eDiary)
  - NIH-CPSI pain subscale and all domains total score

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- IIEF-EF
- Mean of average daily pelvic pain scores (eDiary), average and maximum pelvic pain (Paper-based NRS in clinic)
- 24-hour voiding frequency (eDiary)

- Response to treatment compared to placebo as measured by the GRA, PGI-C, and PGI-S at Week 12 (Visit 4)
- A ≥30% and ≥50% improvement in maximum daily pelvic pain (using the 11-point NRS recorded by eDiary and the NIH-CPSI pain subscale) compared to placebo, at Week 6 (Visit 3) and Week 12 (Visit 4)
- Responder analysis: Response to treatment defined by any of the following:
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with no change in the amount or strength of concomitant analgesic medications
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with a decrease in the amount or strength of concomitant analgesic medications
- Discontinuation of study medication due to treatment failure (% meeting treatment failure criteria and time to event)

Safety Endpoints

The safety endpoints are:

- The frequency and severity of AEs will be reported for the treatment phase and will include:
  - Abnormal, clinically significant vital signs, laboratory tests, electrocardiogram (ECG), weight or findings on physical examinations
  - Ophthalmic safety based upon assessment of lenticular opacification using LOCS III, BCVA using the LogMar chart, IOP, corneal staining and slit lamp examination at Baseline, 12 weeks, and 6 months post last dose, and at Early Termination (ET).

Statistical Methods:

This study will investigate the comparative treatment effect of AQX-1125 versus placebo in subjects with CP/CPPS. The statistical analysis will use inferential methods (*P* values) and estimation (point estimates with confidence intervals) to evaluate the effect of AQX-1125 compared to placebo. This study is powered to demonstrate a statistically significant effect of AQX-1125 versus placebo ($P < 0.05$) in the primary endpoint, if the treatment effect is sufficiently large. If a statistically significant result is not obtained but the estimated effect predicts a statistically significant effect in a larger, subsequent study comparing AQX-1125 to placebo, this study will be considered a success.

Sample Size and Power

Sample size was calculated using the 2-sample means statement in the POWER procedure in SAS. A sample size of 45 subjects per treatment group will provide 80% power to detect a 1.2-point difference in the change from Baseline maximum pelvic pain score between AQX-1125 and placebo assuming a between-subject standard deviation of 2.0 and a 2-sided 5% significance level.

Assuming a 10% rate of discontinuation from study drug, the total number of subjects to be randomized is approximately 100. Subjects who discontinue will be included in the primary analysis, resulting in a slight decrease in power if the discontinuing subjects in the placebo group have no additional change after discontinuation of study drug while the discontinuing subjects in the AQX-1125 group have a loss of efficacy after discontinuing study drug.

Analysis

Subject pelvic pain as assessed by the 11-point NRS (eDiary) will be summarized at each week during the study. Analyses in the week prior to the Week 6 Visit, Week 12 Visit and Week 16 Visit (Off-Treatment Safety Follow-Up) will be produced with mean, median, standard deviation, and quartiles for both pelvic pain score and the change from baseline in pelvic pain score, using the mean of the maximum observed value from each of the 7

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days prior to each visit (Baseline, Week 6, Week 12 and Week 16). This will be reported for maximum daily pelvic pain score and similarly for average daily pelvic pain score. The proportion of subjects who respond to treatment at Week 6, Week 12 and at Week 16 will be summarized. Use of concomitant analgesic medication will be summarized with the percentage (%) of subjects taking each class of medication (permitted short-acting opioid-containing analgesics and non-opioid containing analgesics: e.g., acetaminophen) and the daily dose (mean, median, standard deviation, and quartiles, using subjects who took any such medication on at least 1 of the 7 days prior to the Baseline, Week 6, Week 12 or Week 16 Visit).

Other secondary endpoints will be summarized at Baseline, Week 6, Week 12, and Week 16, including observed values at each timepoint and change from Baseline at post-baseline timepoints, with mean, median, standard deviation, and quartiles for continuous data, and counts and percentages for categorical and binary data.

Comparison of AQX-1125 to placebo at Week 12 for the primary efficacy endpoint will use repeated measures analysis of variance to compare change from Baseline in maximum pain score (NRS score) (dependent variable) between treatment arms (AQX-1125 and placebo). Baseline maximum pain score (NRS score) will be included in the model as a covariate. Change from Baseline to Week 6 and Week 12 will be included in the analysis. A *P* value less than or equal to 0.05 for the change from Baseline at Week 12 will be considered statistically significant. All randomized subjects will be included in the primary analysis.

Comparison of AQX-1125 to placebo for proportion of subjects who are responders will be used to further understand the effect of AQX-1125 on pelvic pain. *P* values for the test of equal numbers of responders in each group will be reported, without adjustment for multiplicity, and used descriptively.

Other secondary endpoints will be tested in an analogous procedure, with *P* values used for descriptive purposes rather than for statistical inference.

Safety data will be summarized with no inferential analysis planned. AEs and treatment-emergent AEs (TEAE) will be summarized by System Organ Class (SOC) and Preferred Term (PT) with counts by treatment group. Ophthalmological findings will be listed and summarized.

Date of the Synopsis: 08 March 2018

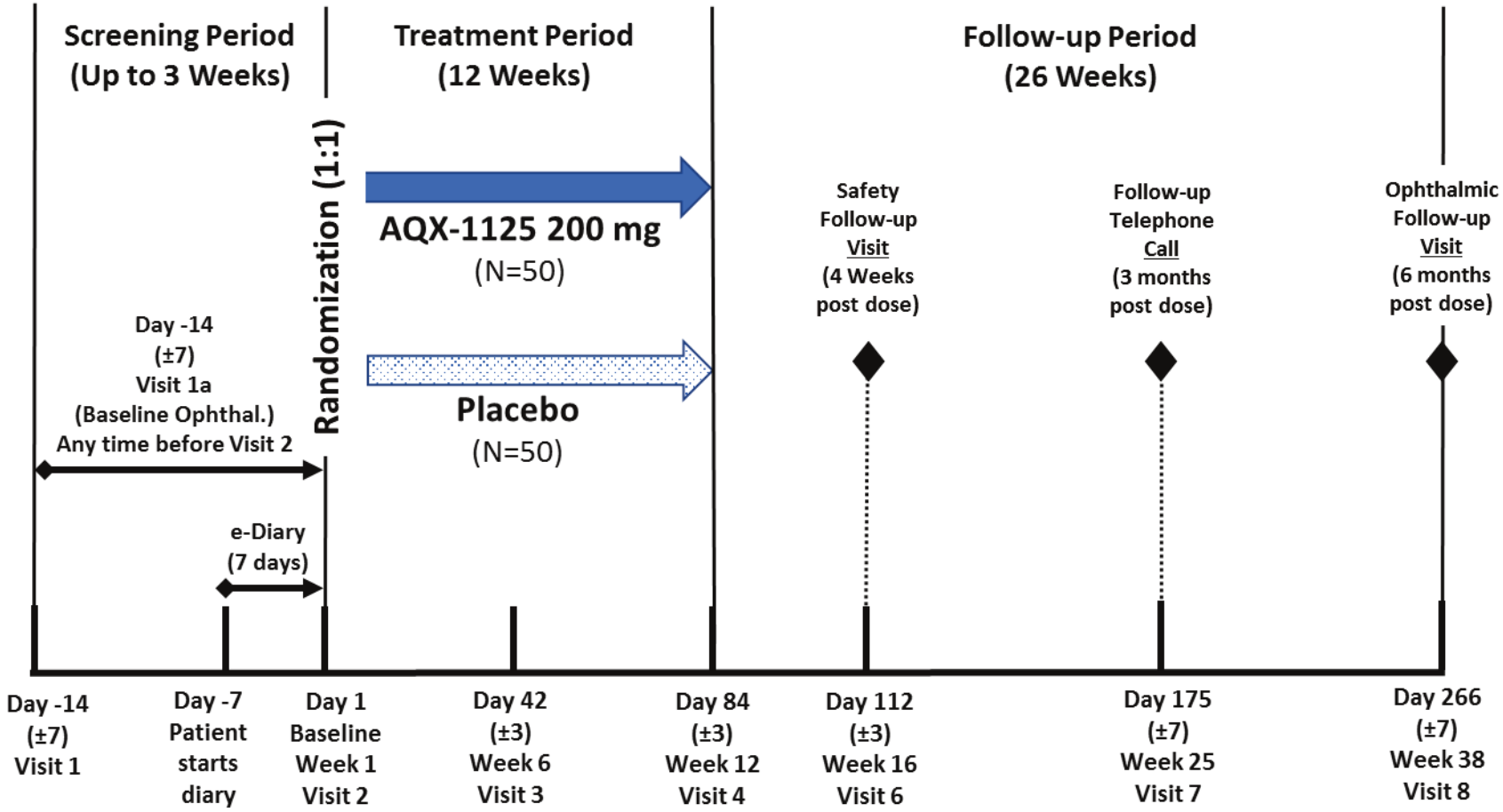

Figure 1. AQX-1125-205 study design flowchart

Table 1. AQX-1125-205 Schedule of Events

Event	Screening Period[a]		Baseline	Treatment Period			Safety Follow-up		
Assessment	Visit 1	Baseline Opthal. Visit 1a	Visit 2	Visit 3	Visit 4	ET[j]	Off-Treatment	Telephone call[k]	Ophthalmic[k]
Week			1	6	12	NA	16	25	38
Day (± window)	-14 (±7)	Before Visit 2	1	42 (±3)	84 (±3)	NA	112 (±3)	175 (±7)	266 (±7)
Informed consent	✓								
Inclusion/Exclusion criteria	✓		✓						
Randomization			✓						
Demographics[b]	✓								
Medical/Surgical history	✓								
Physical examination	✓		✓		✓	✓	✓[m]		
UPOINT classification	✓								
NIH-CPSI[c]	✓		✓	✓	✓	✓	✓		
Paper-based 11-point NRS[c,d]	✓		✓	✓	✓	✓	✓		
PCS[c]	✓								
PHQ-9[c]	✓		✓	✓[n]	✓[n]	✓[n]	✓[n]		
GRA[c]				✓	✓	✓	✓		
PGI-C[c]				✓	✓	✓	✓		
IIEF, PGI-S[c]			✓	✓	✓	✓	✓		
Ophthalmic assessments[e]		✓			✓	✓	✓[m]		✓
12-lead supine ECG[f]	✓				✓	✓	✓[m]		
Vital signs (HR, BP, temperature)	✓		✓	✓	✓	✓	✓		
Height	✓								
Weight	✓				✓	✓	✓		
Clinical chemistry,[g] hematology, urinalysis	✓		✓		✓	✓	✓[m]		
Urine: bacterial culture & sensitivity, leukocyte esterase test	✓								
24-hour voiding frequency[h]			✓	✓	✓	✓	✓		
AE collection	✓		✓	✓	✓	✓	✓	✓[l]	✓[l]
Concomitant medications	✓		✓	✓	✓	✓	✓		
Study drug dispensing[i]			✓	✓					

Event	Screening Period[a]		Baseline	Treatment Period			Safety Follow-up		
Assessment	Visit 1	Baseline Opthal. Visit 1a	Visit 2	Visit 3	Visit 4	ET[j]	Off-Treatment	Telephone call[k]	Ophthalmic[k]
Week			1	6	12	NA	16	25	38
Day (± window)	-14 (±7)	Before Visit 2	1	42 (±3)	84 (±3)	NA	112 (±3)	175 (±7)	266 (±7)
Study drug compliance check				✓	✓	✓			
Study drug accountability				✓	✓	✓			
eDiary Issue/Train/Review/Collect	I/T		R	R	R	R	R/C		

Abbreviations: AE=adverse event; BCVA=best corrected visual acuity; BP=blood pressure; C=collect; ECG=electrocardiogram; eDiary=electronic diary; ET=Early Termination; GRA=Global Response Assessment; HR=heart rate; I=issue; IIEF =International Index of Erectile Function; IOP=intraocular pressure; LOCS= Lens Opacity Classification System; LogMAR=Logarithm of the Minimum Angle of Resolution; NA=not applicable; NIH-CPSI=National Institute of Health Chronic Prostatitis Syndrome Index; NRS=Numerical Rating Scale; PCS=Pain Catastrophizing Scale; PGI-C=Patient's Global Impression of Change scale; PGI-S=Patient's Global Impression of Severity scale; PHQ-9=Patient Health Questionnaire; R=review; T=train; UPOINT=Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles.

[a] Minimum screening period is 7 days, which includes the baseline ophthalmic assessment at Visit 1a.

[b] Demographics include age, birth year, sex, race and ethnicity.

[c] Questionnaires must be completed prior to other assessments.

[d] Paper-based 11-point NRS will be administered in-clinic during the study visit to assess the average and maximum daily pelvic pain.

[e] Ophthalmic assessments include BCVA using the LogMAR chart (i.e. after manifest refraction), IOP (preferably measured by Goldmann tonometry, before and after dilation with mydriatic agent) corneal staining, slit lamp examination, and lenticular opacification using LOCS III. Baseline ophthalmology assessment can be completed as a separate visit any time during the screening period (any time before Visit 2). Background incidence of cataracts in subjects noted prior to dosing should be recorded as medical history. Ophthalmic assessments at all post-Baseline Visits should occur within the specified Visit windows.

[f] Subjects will be resting supine for at least 5 minutes before the ECG recording.

[g] Clinical chemistry does not need to be fasting.

[h] Voiding frequency will be measured over a 24-hour period, within a 3-day (72 hours) window before the scheduled visits.

[i] The first dose of study drug at Baseline (Visit 2) will be administered in the clinic. At subsequent Visits, subjects are to refrain from taking study drug at home on the morning of the clinic visit day and should be dosed in the clinic.

[j] If a subject withdraws from the study, all assessments for the ET Visit should be conducted.

[k] Subjects who withdraw from the study anytime during the study will have a follow-up period of 6 months, consisting of an Off-Treatment Safety Follow-up Visit (4 weeks post last dose), telephone call follow-up (3 months post last dose) and ophthalmic assessment (6 months post last dose).

[l] Subjects will be asked for updates on new and ongoing (after the 28 days follow-up) ocular AEs only.

[m] Repeat at Off-Treatment Safety Follow-up is only needed if there are outstanding safety concerns from Week 12.

[n] Score will not be recorded in the database, assessment will be performed for patient safety/monitoring purposes only clinically significant findings will be reported as adverse events.

NOTE: Unscheduled visits may be conducted at any time during the study and may include the same assessments as Week 12.

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3 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AD	Atopic dermatitis
AE	Adverse event
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
BCVA	Best Corrected Visual Acuity
BCRP	Breast cancer resistance protein
BP	Blood pressure
C	Collect
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CP/CPPS	Chronic Prostatitis/Chronic Pelvic Pain Syndrome
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRF	Case Report Form
DL	Lactation days
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic diary
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GGT	Gamma glutamyl transpeptidase
GRA	Global Response Assessment
HR	Heart rate
I	Issue
IB	Investigator's Brochure
IC/BPS	Interstitial cystitis / bladder pain syndrome
ICF	Informed Consent Form
ICH	International Council on Harmonisation, formerly called the International Conference on Harmonisation
IEC	Independent Ethics Committee
IIEF	International Index of Erectile Function Questionnaire
IIEF-EF	International Index of Erectile Function Questionnaire, Erectile Function Domain
IND	Investigational New Drug
IOP	Intraocular pressure

Abbreviation	Definition
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
LAR	Late asthmatic response
LDH	Lactate dehydrogenase
LogMAR	Logarithm of the Minimum Angle of Resolution
LOCS	Lens Opacification Classification System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NA	Not applicable
NIH-CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
NOAEL	No observed adverse effect level
NRS	Numerical Rating Scale
PCS	Pain Catastrophizing Scale
PGI-C	Patient's Global Impression of Change scale
PGI-S	Patient's Global Impression of Severity scale
P-gp	Permeability glycoprotein
PHQ-9	Patient Health Questionnaire-9
PP	Per Protocol
PT	Preferred term
QA	Quality Assurance
SAE	Serious adverse event
SAP	Statistical analysis plan
SHIP1	Src homology 2-containing inositol-5'-phosphatase 1
SOC	System Organ Class
SUSAR	Suspected Unexpected Adverse Reactions
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment emergent adverse event
TEAESI	Treatment emergent adverse event of special interest
T_{max}	Time to reach maximum concentration
UPOINT	Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles
US	United States

4 INTRODUCTION

Aquinox Pharmaceuticals (Canada) Inc. (Aquinox) is evaluating AQX-1125, an oral, small-molecule, anti-inflammatory agent for the treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) and other inflammatory diseases.

4.1 Background of Disease

Chronic nonbacterial prostatitis (also known as chronic pelvic pain syndrome, CP/CPPS) is a common male genitourinary condition that causes pain and inflammation in the prostate, pelvis, and the lower urinary tract (Harvard Perspectives on Prostate Disease, 2017; Roddick et al., 2017). The predominant symptom of CP/CPPS is pain in the suprapubic area, perineum and penis but can also occur in the testes, lower back or groin. Pain on ejaculation is one of the most prominent and bothersome symptoms in many patients. Voiding symptoms such as urgency, frequency and poor interrupted urinary flow are common along with sexual dysfunction (Nickel, 2017).

Of the 3 categories of symptomatic prostatitis defined by the National Institutes of Health (NIH), CP/CPPS (Type III) is the most common, accounting for about 90% of all cases. No known etiology has been established, and without a defined causative agent, treatment may be guided largely by a doctor's clinical experience and instincts rather than hard evidence. Although not life-threatening, a diagnosis of CP/CPPS holds the potential for a reduced quality of life (Harvard Perspectives on Prostate Disease, 2017).

The goal of treatment is to improve symptoms. Although antibiotics may be prescribed, little benefit may result as the condition may be chronic and not caused by an active infection. Other common treatments include medications to relax the muscles around the prostate and bladder neck (α-adrenergic blockers), muscle relaxants or tricyclic antidepressants, and prescription pain medication or non-steroidal anti-inflammatory drugs to reduce pain and swelling. Alternative and natural remedies that may reduce ongoing pain include warm baths; acupuncture; pelvic floor physical therapy; relaxation exercises; massage therapy; dietary management; and biofeedback (Roddick et al., 2017).

4.2 Rationale for Use of the Product

AQX-1125 is being developed as a novel, small molecule for the treatment of inflammatory diseases. AQX-1125 represents a new pharmaceutical class of compounds that activate the Src homology 2-containing inositol-5'-phosphatase 1 (SHIP1) protein, a modulator of phosphoinositide signaling for diverse processes including cell growth, activation, and immune/inflammatory regulation (Stenton et al., 2013).

One of the functions of SHIP1 is the metabolism of phosphatidylinositol 3,4,5-triphosphate, PI(3,4,5)P3, a key signaling molecule involved in the regulation of a variety of signal transduction pathways. Based on the clinical and nonclinical data, it is proposed that activation of SHIP1 can modulate the inflammatory process by limiting immune cell activation, proinflammatory mediator production and cell migration in multiple immune cell types and may therefore provide a therapeutic benefit in the treatment of CP/CPPS and other inflammatory diseases.

The in vivo anti-inflammatory activity of AQX-1125 has been demonstrated in nonclinical models of inflammatory pain including a carrageenan-induced model of chronic prostatitis/chronic pelvic pain and an acute model of cyclophosphamide-induced bladder cystitis. In vitro, AQX-1125 can reduce mast cell degranulation, immune cell chemotaxis and pro-inflammatory mediator release. Taken together, these data support the potential effectiveness of AQX-1125 in treating conditions involving pain and inflammation.

4.2.1 Nonclinical Studies

The key findings from the nonclinical studies were:

- AQX-1125 exhibited dose-dependent pharmacologic effects in vitro, including activation of recombinant human SHIP1 and reduction of phosphorylated protein-serine/threonine kinase activated by phosphatidylinositol 3,4,5-triphosphate, PI(3,4,5)P3 (Akt) at serine 473 (pAkt [S473]) in phosphoinositide-3-kinase -activated human T-cells. Functionally, AQX-1125 inhibited chemotaxis in human leukocyte subsets.
- In safety pharmacology studies, AQX-1125 produced a non-statistically significant transient decrease in arousal and locomotor activity in the rat central nervous system study. AQX-1125 inhibited the human Ether-a-go-go-Related Gene potassium current at a half maximal inhibitory concentration of 188.9 µM or 60,731 ng/mL, which is approximately 28-fold higher than the human exposure reported at the highest clinical dose to date of 542 mg. Finally, there were no biologically significant cardiovascular effects in dogs or respiratory effects in rats.
- In vitro assays indicated that permeability glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are involved in the active transport of AQX-1125, but AQX-1125 is not an inhibitor of P-gp, BCRP, or any other common drug transporters evaluated at clinically relevant concentrations.
- AQX-1125 was readily bioavailable and rapidly absorbed with a mean terminal elimination half-life ($t_{1/2}$) of approximately 6 hours in the rat and 9 hours in the dog. Exposures were generally dose-proportional or greater than dose proportional in the rat, and dose-proportional or less than dose-proportional in the dog, depending on the duration of dosing. Accumulation ratios showed higher exposures following multiple days of dosing compared with single doses.
- In vitro binding to plasma proteins from mouse, rats, dogs, rabbits, monkeys, and humans ranged from 26 to 52%, and protein binding to human serum albumin was 38%. In the mouse, the highest concentrations of AQX-1125 (excluding the excretory organs) were observed in the lung, thyroid, and adrenal glands, and the lowest concentration was observed in the brain. Following intravenous (IV) administration of [^{14}C]- AQX-1125 in the albino rat, the highest concentrations (excluding the excretory organs) were in the choroid plexus, seminal vesicles, pancreas, stomach gastric mucosa, and pituitary gland, and the lowest concentration was observed in the brain. Following oral administration of [^{14}C]-AQX-1125 in partially pigmented rats, the highest concentrations (excluding the excretory organs) were observed in the uveal tract, pituitary gland, pancreas, harderian gland, ex-orbital lachrymal gland and stomach mucosa and the lowest concentration was observed in the brain, spinal cord and ocular lens. AQX-1125 accumulated in the testes upon repeated dosing in the rat. In addition, AQX-1125 distributed to the ocular tissues in the rat (lens and aqueous humour) and the dog (lens, cornea and aqueous humour)

following repeated daily dosing. Estimated ocular lens half-life of AQX-1125 is approximately 20 days in the rat and 7 to 9 days in the dog.

- There was no significant in vitro metabolism of AQX-1125 with liver microsomes of animals and humans. In the rat, 5 metabolites (R1-R5) were identified in the plasma, urine and feces. In the dog, 4 additional metabolites (D1-D4) were identified in the plasma, urine and feces. AQX-1125 inhibited CYP3A4/5 at the expected intestinal luminal concentrations for a 200 mg dose and induced in vitro CYP3A4 mRNA expression in human hepatocytes.
- In rats, [^{14}C]-AQX-1125 was excreted in the feces (~60%) and urine (~30%) following oral administration and about equally into the urine and feces following IV administration. In dogs [^{14}C]-AQX-1125 was excreted equally into the urine and feces following oral administration. Mass balance recovery in all studies was ≥90%.
- The maximum tolerated dose in single dose toxicity studies was 500 mg/kg in the mouse and 1000 mg/kg in each of the rat and dog species.
- A series of repeat dose toxicity studies in the rat have been conducted for durations of 7 days up to 26 weeks. In the 26-week rat study, the no observed adverse effect level (NOAEL) was 30 mg/kg/day, based on the findings in females of bilateral posterior cortical cataracts and microscopic lens swelling/cataracts, persistent estrous characterized by the interrelated effects to the reproductive tract and mammary glands, and findings in males of reduced caudal epididymal sperm density and counts and epididymal epithelial microvesicular vacuolation at 100 mg/kg/day. At the NOAEL, the mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration–time curve from time 0 to 24 h (AUC_{0-24}) values were 1110 ng/mL and 7100 ng•hr/mL, respectively, in males and 1580 ng/mL and 9940 ng•hr/mL, respectively, in females.
- A series of repeat dose toxicity studies in the dog have been conducted for durations of 10 days up to 39 weeks. In the 39-week dog study, daily administration of AQX-1125 at dose levels of 10, 30, and 50 mg/kg/day resulted in no adverse findings. At the NOAEL of 50 mg/kg/day, the mean C_{max} and AUC_{0-24} values were 6160 ng/mL and 59,300 ng•hr/mL, respectively, in males and 6820 ng/mL and 69,300 ng•hr/mL, respectively, in females.
- No mutagenic potential was observed for AQX-1125 in the bacterial mutation, chromosome aberration, or rat micronucleus tests.
- AQX-1125 had no effect on rat male or female fertility or on early embryonic development at doses up to the highest dose tested of 300 mg/kg/day.
- AQX-1125 was teratogenic in rats, but not in rabbits. The rat embryo-fetal development NOAEL was 30 mg/kg/day (C_{max} 439 ng/mL; AUC_{0-24} 4,710 ng•hr/mL) based on teratogenic effects (external, soft tissue and skeletal malformations and variations and delays in skeletal ossifications) observed at doses ≥100 mg/kg/day. In rabbits, AQX-1125 was not teratogenic at the highest dose tested of 80 mg/kg/day (C_{max} 16,000 ng/mL; AUC_{0-24} 78,700 ng•hr/mL).
- AQX-1125 caused reduced pup viability at doses ≥75 mg/kg/day including increases in dams with no live born pups (150 mg/kg/day), pups dying within the first 4 days after birth and stillborn pups. The deaths occurring in the late stage of gestation/shortly after parturition was suggestive of stress and/or physiological changes associated with the late stage of pregnancy. At 75 mg/kg/day, the F0 dams had body weight loss in lactation days

(DL) 1 to 4 and reduced food consumption throughout the lactation period (DL 1 to 14). Based on these results, the maternal NOAEL, developmental NOAEL and NOAEL for growth and reproduction in the F1 generation in male and female rats was 30 mg/kg/day (C_{max} 469 ng/mL and AUC_{0-24} 4,520 ng•hr/mL).

- AQX-1125 was distributed from maternal circulation to fetal circulation in pregnant rats with fetal plasma levels approximately equal to maternal plasma levels.
- No effects on blood, spleen, bone marrow, or lymph nodes were observed in the mouse. In a mouse *Streptococcus pneumoniae* host-resistance model, AQX-1125 did not change the magnitude of post-infection *Streptococcus pneumoniae* Type 14 titers in the lung or the rate of bacterial clearance from the lung, when compared to the vehicle control group.

Refer to the AQX-1125 Investigator's Brochure (IB) for additional details.

4.2.2 Clinical Experience

A total of 7 clinical studies of AQX-1125 have been completed. Three were studies in healthy normal volunteers (AQX-1125-100, AQX-1125-101, and AQX-1125-102), in which safety, tolerability, pharmacokinetics, food effects, cellular and biochemical changes in sputum, and bioequivalence of AQX-1125 immediate release tablets and capsules were assessed. Single-ascending doses of AQX-1125 ranged from 17 mg to 542 mg. Multiple-ascending doses ranged from 100 mg to 542 mg.

One study each was conducted in subjects with mild atopic asthma (AQX-1125-200), interstitial cystitis/bladder pain syndrome (IC/BPS, AQX-1125-201), chronic obstructive pulmonary disease (COPD, AQX-1125-202), and atopic dermatitis (AD, AQX-1125-204).

4.2.2.1 Healthy Volunteer Studies

Following administration of a single oral dose by capsule (single ascending dose), AQX-1125 was rapidly absorbed with a median time to reach maximum concentration (T_{max}) ranging from 1.0 to 1.5 hours post dose. Plasma drug concentration subsequently declined slowly in a log-linear fashion with a $t_{1/2}$ ranging from 19.5 to 22.4 hours. Mean $t_{1/2}$ was independent of dose. From 17 mg to 542 mg, plasma exposure increased in a dose proportional manner ($AUC_{0-\infty}$) or a slightly higher than dose proportional manner (C_{max}).

Following repeated once daily dosing for up to 10 days (100 mg to 542 mg), steady state trough plasma concentrations (mean concentration 24 hours post dose) of AQX-1125 were reached at ~5 to 7 days. AQX-1125 was rapidly absorbed with median T_{max} reached by 1.0 to 2.0 hours. Plasma drug concentration subsequently declined slowly in a log-linear fashion with a $t_{1/2}$ ranging from 19.3 to 21.1 hours. From 100 mg to 542 mg, plasma exposure parameters increased in, or near, a dose proportional manner and mean $t_{1/2}$ was independent of dose. Plasma AUC_{0-24} values increased at steady state compared to single dose, indicating plasma accumulation upon repeated dosing indicating concentrations ~50% higher than following a single dose.

The effect of food on the plasma pharmacokinetics of AQX-1125 was to increase in the median T_{max} from 1 to 4 hours. The absorption of a single 200 mg dose of AQX-1125 was not altered by food.

There were no deaths, serious AEs (SAEs), laboratory treatment emergent adverse events (TEAEs), or subject discontinuations due to TEAEs reported during these studies.

4.2.2.2 Asthma Study

One study was conducted in subjects with mild atopic asthma (AQX-1125-200), in which the late asthmatic response (LAR) to inhaled allergen challenge was assessed. AQX-1125 dosing was 450 mg. Steroid-naïve male and female asthmatics were assessed for LAR following inhaled allergen challenge. A significant, 20% improvement in the $AUC_{4\text{-}10}$ of LAR was demonstrated with 450 mg AQX-1125 as compared with placebo (P=0.027). There were no deaths, SAEs, or subject discontinuations due to TEAEs in this study.

4.2.2.3 Interstitial Cystitis/Bladder Pain Syndrome, Chronic Obstructive Pulmonary Disease, and Atopic Dermatitis Studies

Once daily oral dosing with 200 mg AQX-1125 has been studied in 3 Phase 2 trials: for 6 weeks in subjects with IC/BPS, and 12 weeks in subjects with COPD or AD.

In the Phase 2 IC/BPS study, oral AQX-1125 200 mg once daily for 6 weeks reduced maximum pelvic pain, voiding frequency and other urinary symptoms (as measured by the O'Leary-Sant Interstitial Cystitis Symptom and Problem Questionnaire and the Bladder Pain/Interstitial Cystitis Symptom Score) in 69 women with moderate to severe IC/BPS. More programs for this indication are planned in the future.

AQX-1125 did not have a treatment effect on recurrent exacerbations in subjects with COPD following a recent exacerbation or on AD signs and symptoms in subjects with mild to moderate AD in Phase 2 clinical trials. Therefore, there are currently no plans to develop AQX-1125 for COPD or AD.

Across all the Phase 2 studies, the percentage of AQX-1125 subjects who experienced any TEAE (56% overall) was similar to the percentage in placebo (55% overall), and in the 6 week Leadership study of IC/BPS patients, was lower in AQX-1125 (60%) than placebo (78%).

AEs of interest include Gastrointestinal (GI) Disorders, since the main type of AE in Phase 1 safety studies were mild non-serious GI Disorders, which occurred at greater than 2-fold incidence following treatment with 450 mg to 542 mg AQX-1125 compared to placebo. In the Phase 2 studies, with a once daily 200 mg dose of AQX-1125 over 6 or 12 weeks, the incidence of GI Disorders was 21% in AQX-1125 subjects compared with 16% of placebo subjects. As with the Phase 1 studies in healthy subjects, the GI Disorders were generally mild and tolerable.

Eye Disorders are another AE category of interest based on the findings of nonclinical studies. In these Phase 2 clinical studies, the overall incidence of Eye Disorders was lower in AQX-1125 subjects (7%) compared with placebo subjects (10%).

The frequency of SAEs was lower in subjects treated with AQX-1125 (5%) as compared with placebo (7%), including 1 death in each group (0.4% each). These types of events were observed only in subjects with COPD, who had severe underlying disease, and were not related to the study treatments.

Study treatment discontinuations due to TEAEs occurred in 6% of subjects treated with AQX-1125 and 5% of placebo subjects, most of which were considered unrelated to the study treatment. There were more discontinuations due to TEAEs in the 12-week studies of subjects with COPD and AD than in the 6-week study of IC/BPS. This is related to the relatively poor health of the COPD subjects studied, but the longer duration of treatment and follow-up could also be a factor.

Table 2. AQX-1125 Safety across Phase 2 Trials (at Least 6 Weeks of Dosing)

	6 weeks of dosing IC/BPS[a]		12 weeks of dosing COPD[b] + AD[c]		Overall (all Phase 2 combined)	
	Placebo N=32	AQX- 1125 N=37	Placebo N=228	AQX-1125 N=226	Placebo N=260	AQX-1125 N=263
Any TEAE, n (%)	25 (78)	22[d] (60)	118 (52)	126 (56)	143 (55)	148 (56)
GI Disorders[e]	11 (34)	11 (30)	31 (14)	43 (19)	42 (16)	54 (21)
Eye Disorders[f]	3 (9)	2 (5)	22 (10)	16 (7)	25 (10)	18 (7)
SAEs, n (%)	0 (0)	0 (0)	18 (8)	12 (5)	18 (7)	12 (5)
Death	0 (0)	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
TEAEs leading to discontinuation, n (%)	1 (3)	2 (5)	11 (5)	13 (6)	12 (5)	15 (6)

Abbreviations: AD=atopic dermatitis; COPD=chronic obstructive pulmonary disease; GI=gastrointestinal; IC/BPS=interstitial cystitis/bladder pain syndrome; SAE=serious adverse event; TEAE=treatment emergent adverse event

[a] LEADERSHIP Study (AQX-1125-201) in IC/BPS
[b] FLAGSHIP Study (AQX-1125-202) in COPD
[c] KINSHIP Study (AQX-1125-204) in AD
[d] TEAEs shown are those reported from the start of dosing through to the end of the Week 10 follow-up
[e] GI Disorders Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class
[f] Eye Disorders MedDRA System Organ Class

The safety profile of AQX-1125 was also reviewed in the context of gender. While the Leadership study of IC/BPS only included female subjects, approximately half of the subjects in the other Phase 2 studies were male. There was no difference in the incidence of TEAEs between AQX-1125 and placebo in the subsets of male subjects (48% for each treatment; Studies AQX-1125-202 and AQX-1125-204 combined data) or female subjects (62% with AQX-1125 and 61% with placebo; Studies AQX-1125-202 and AQX-1125-204 combined data).

Refer to the AQX-1125 IB for additional details.

5 TRIAL OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to evaluate the effect of 12 weeks of treatment with AQX-1125 (200 mg) administered orally once-daily compared to placebo on the change from Baseline (Visit 2) to Week 12 (Visit 4) in maximum daily pelvic pain (mean) in male subjects with non-bacterial CP/CPPS using a standardized 11-point Numerical Rating Scale (NRS) pain score recorded daily by an electronic diary (eDiary).

5.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- The effects of 12 weeks of treatment with AQX-1125 (200 mg) administered orally once-daily compared to placebo on the change from Baseline (Visit 2) to Week 12 (Visit 4) for each of the following:

  - NIH Chronic Prostatitis Symptom Index (NIH-CPSI) pain subscale and all domains total score
  - Male sexual health as measured using the International Index of Erectile Function Questionnaire, Erectile Function Domain (IIEF-EF)
  - Average daily pelvic pain (eDiary), average and maximum pelvic pain (Paper-based NRS, in clinic), using the standardized 11-point NRS
  - 24-hour voiding frequency (eDiary)
- Time course of effects: AQX-1125 (200 mg) compared to placebo on the change from Baseline (Visit 2) at Week 6 (Visit 3), Week 12 (Visit 4), and Week 16 (i.e. 4 weeks after end of treatment) for each of the pain and symptom scale endpoints
- The overall response to treatment for AQX-1125 (200 mg) compared to placebo as measured by the subject's Global Response Assessment (GRA), Patient's Global Impression of Change scale (PGI-C) and Patient's Global Impression of Severity scale (PGI-S) at Week 12 (Visit 4)
- The proportion of subjects with ≥30% and ≥50% improvement in maximum daily pelvic pain (mean) using the 11-point NRS recorded by eDiary and the NIH-CPSI pain subscale compared to placebo, at Weeks 6 (Visit 3) and 12 (Visit 4)
- Responder analysis: response to treatment defined by any of the following:
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with no change in the amount or strength of concomitant analgesic medications
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with a decrease in the amount or strength of concomitant analgesic medications
- Discontinuation of study medication due to treatment failure (% meeting treatment failure criteria and time to event)

5.3 Safety Objectives

The safety objectives of this study are to evaluate:

- Safety and tolerability of AQX-1125 (200 mg) compared to placebo during the 12-week treatment period
- Ocular safety based upon assessment of lenticular opacification using Lens Opacification Classification System (LOCS) III, best corrected visual acuity (BCVA) using the Logarithm of the Minimum Angle of Resolution (LogMAR) chart, intraocular pressure (IOP), corneal staining, and slit lamp examination

6 INVESTIGATIONAL PLAN

6.1 Overall Trial Design and Plan: Description

In this double-blind, placebo-controlled study, approximately 100 male subjects diagnosed with CP/CPPS will be randomized to either AQX-1125 (200 mg) or placebo in a 1:1 ratio across approximately 30 centers in North America. The study will consist of a screening period of up to 3 weeks, a 12-week treatment period followed by a 4-week Off-Treatment Safety Follow-up period, and an Ophthalmic Safety Follow-up Visit 6 months post last dose, for a total study duration of about 41 weeks. There will also be a follow-up telephone call 3 months after the last dose.

At Screening Visit 1, each subject will complete a set of questionnaires, and receive (and be trained to use) an eDiary. Subjects will record their average and maximum daily pelvic pain score, at approximately the same time each day (in the evening prior to the last dose of pain medication), as well as their daily use of analgesic pain medications. Baseline ophthalmic assessments, including lenticular opacification assessment using LOCS III, can be completed as a separate visit any time during the screening period (any time before Visit 2).

At Baseline (Visit 2), all subjects will return to the clinic for review of eligibility and to complete the efficacy questionnaires and assessments to establish Baseline values. Average daily pelvic pain scores recorded in the eDiary within the 7 days prior to Baseline (Visit 2) will be part of the study entry criteria. If all entry criteria are met, the subject will be randomized (1:1) to receive a single daily oral dose of 2 tablets for 12 weeks as follows:

- AQX-1125 200 mg dose group: 2 AQX-1125 100 mg tablets; or,
- Placebo group: 2 placebo tablets

All enrolled subjects will record the following in the eDiary (from Screening Visit 1 to Week 16 [Off-Treatment Safety Follow-up Visit]):

- Maximum daily pelvic pain: subjects will assess their maximum pelvic pain for that day on a scale of 0 to 10, with 0 indicating ‘no pelvic pain’ and 10 indicating ‘pelvic pain as bad as you can imagine’
- Average daily pelvic pain. Subjects will assess their average pelvic pain for that day on a scale of 0 to 10, with 0 indicating 'no pelvic pain' and 10 indicating 'pelvic pain as bad as you can imagine'
- Analgesic medication taken each day
- 24-hour voiding frequency: voiding frequency will be measured over a 24-hour period, within a 3-day (72 hours) window before the next scheduled visit (Visit 2, 3, 4 and Off-Treatment Safety Follow-up Visit)

At Week 6 (Visit 3), Week 12 (Visit 4) and Week 16 (Off-Treatment Safety Follow-up Visit), during the clinic visit, subjects will complete NIH-CPSI, paper-based 11-point NRS (average and maximum pelvic pain experienced over the last 24 hours), GRA, PGI-C, IIEF, PGI-S, PHQ-9, have vital signs assessed, and return unused study drug (Week 6 and 12). Any adverse events (AEs) are to be recorded.

Subject compliance with the eDiary will be monitored by trained study site personnel at each study visit.

All subjects completing the 12 weeks of treatment (Visit 4) will be considered completers of treatment. Subjects who withdraw from the study during the treatment period should complete an Early Termination Visit. Subjects who discontinue the double-blind treatment for any reason will be encouraged to continue with all subsequent study-related visits and evaluations, with emphasis on obtaining pelvic pain data, analgesic medication data and voiding frequency data to assess efficacy endpoints. Subjects who complete the study or early terminate during the study will be asked to return for the Safety Follow-up Visit 4 weeks after discontinuing study drug, and the Ophthalmic Safety Follow-up Visit 6 months after the last dose. Subjects will also be contacted via telephone for the follow-up telephone call 3 months after their last dose.

6.2 Discussion of Trial Design Including the Choice of Control Group

The randomized, double-blind, placebo-controlled, parallel-group design used for this study is the current standard for interventional human trials.

7 SELECTION OF SUBJECTS

Approximately 100 male subjects at approximately 30 sites in North America are planned.

7.1 Inclusion Criteria

For inclusion into the screening period subjects must meet the following criteria:

1. Provide written informed consent and the willingness and ability to comply with all aspects of the study requirements
2. Males, ≥18 and ≤80 years of age at Screening Visit 1
3. Have pain or discomfort in the pelvic region for at least 3 months in the last 6 months, in the absence of a urinary tract infection or other pelvic/urological cause, and have a physician diagnosis of CP/CPPS (NIH Prostatitis, Category III)
4. NIH-CPSI of ≥15 on the total score
5. Subjects must agree to use a condom for sexual intercourse from Screening Visit 1 until at least 90 days after the last dose of study drug, unless they have been surgically sterilized (vasectomy) for a minimum of 6 months. True abstinence from sexual intercourse in accordance with the preferred and usual lifestyle of the subject is also acceptable
6. Have an average daily pelvic pain score of ≥4 out of 10 on the 11-point NRS pain scale (mean of the average daily pelvic pain score recorded at each of the 7 days prior to Baseline [Visit 2]). A minimum of 5 daily records within 7 days prior to Baseline (Visit 2) must be recorded
7. Must be capable of voiding independently for 30 days prior to screening (to allow completion of 24-hour voiding diary)

7.2 Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for the trial:

1. Diagnosis of NIH Prostatitis Categories I (acute prostatitis) or II (chronic bacterial) prostatitis
2. Diagnosis of IC/BPS with symptoms of pain, pressure, or discomfort perceived to be related to the bladder, and associated lower urinary symptoms for > 6 weeks in the absence of infection or other identifiable causes
3. Relief of pelvic pain after voiding or have >15 voids per day
4. Post-void residual volume >150 mL
5. Have had an unresolved (positive bacterial urine culture) urinary tract infection within 8 weeks (inclusive) prior to Screening Visit 1 (subjects can rescreen [up to 1 time] once infection clears)
6. History of previous prostate or bladder intervention (i.e. prostate biopsy, cystoscopy, or indwelling urinary catheter) within 1 month of Screening Visit 1, history of microwave therapy, transurethral resection of the prostate, transurethral radiofrequency

thermotherapy, transurethral incision of the prostate, transurethral needle ablation, transurethral laser vaporization of the prostate, Urolift®, Rezum, and other urological interventions (e.g., botulinum toxin) within 6 months of Screening Visit 1

7. Unilateral testicular or scrotal pain as the sole symptom of CP/CPPS
8. Ongoing, symptomatic urethral stricture disease
9. Catastrophizing pain score of ≥30 as determined by the Pain Catastrophizing Scale (PCS)
10. Current major depressive disorder (i.e. Patient Health Questionnaire-9 [PHQ-9] score ≥10)
11. Neurologic disease or disorder affecting the bladder, ability to void spontaneously, or directly contributing to urinary symptoms (e.g., multiple sclerosis, autonomic neuropathy)
12. Severe, excruciating pain during rectal exam (i.e. an "inability to perform the exam")
13. History of chronic substance abuse, dependency or abuse of opioids, or other narcotics within the last 2 years
14. Currently receiving, or expect to receive, any of the following prohibited medications or procedures:
    - **Non-steroidal anti-inflammatory drug or other medication (e.g. alpha-blockers) for CP/CPPS,** unless on a stable dose for ≥30 days prior to Screening Visit 1
    - **Long-acting opioids:** within 2 weeks prior to Baseline (Visit 2) or expected to take any long-acting opioids at any time during the study
    - **Short-acting opioid or opioid-containing analgesics**: more than 10 doses/month, or more than a single dose > 2 days per week, or any short-acting opioids within 3 days prior to randomization
    - **Oral steroid therapy, immunosuppressants/immunomodulators** (including daily phosphodiesterase Type 4 inhibitors) within 30 days prior to Screening Visit 1 and throughout the study
    - Have taken any **investigational drug or device** within 90 days prior to Screening Visit 1, or have had previous exposure to AQX-1125
15. Any prior history of pelvic cancer (e.g., colorectal, genitourinary) or treatment (radiation or chemotherapy) thereof
16. Major surgery within 3 months prior to Screening Visit 1
17. Have any other condition/disease which, in the opinion of the Investigator, could compromise subject safety or interfere with the subject's participation in the study or in the evaluation of the study results. In case of any doubt, the Investigator shall consult the medical monitor
18. Known intolerance to micro-crystalline cellulose (Avicel® PH-102), mannitol or other ingredient of AQX-1125 tablets

7.3 Criteria for Individual Subject Discontinuation of Study Drug

Subjects should be discontinued from study drug, while encouraged to follow all other protocol-specified procedures, for the following reasons:

- Noncompliance with trial or follow-up procedures that in the Investigator's opinion would jeopardize the subject's safety

- Discontinuation of study drug at the Investigator's request for any reason that the Investigator believes continuation of study drug therapy would not be in the subject's best interest
- Subjects may discontinue study drug at any time for drug intolerability, disease progression, availability of other therapeutic options, or subject judgment

7.4 Criteria for Individual Subject Withdrawal from the Trial

Subjects may withdraw from further participation in the study at any time and for any reason without prejudice. The degree to which a subject withdraws can vary and efforts will be made to collect important safety data if feasible and the subject consents. A subject will be considered to be withdrawn from the trial for the following reasons:

- Withdrawn consent from all treatment and follow-up
- Death
- Lost to follow-up
- Termination of the trial by the Sponsor

Any subject who is withdrawn should complete all Early Termination (ET) Visit assessments. Subjects will be asked to return for the Off-Treatment Safety Follow-up Visit 4 weeks after discontinuing study drug, and the Ophthalmic Safety Follow-up Visit 6 months after the last dose. Subjects will also be contacted via telephone for the follow-up telephone call 3 months after their last dose.

8 TREATMENTS

8.1 AQX-1125 Tablet Drug Product

AQX-1125 tablet drug product is supplied as round, white, biconvex, film-coated tablets containing 100 mg AQX-1125 (free base) active ingredient and pharmaceutical grade excipients.

The excipients used in the AQX-1125 100 mg tablet dosage form are: microcrystalline cellulose (Avicel® PH-102), mannitol (Pearlitol® 50C), sodium lauryl sulfate, colloidal silicon dioxide, crospovidone, magnesium stearate, and Opadry II White (coating mixture).

Total tablet weight will be approximately 314 mg.

Further details on the active ingredient of AQX-1125 are provided in the AQX-1125 IB.

8.2 Placebo Tablet Drug Product

Matching placebo is identical in appearance to the test product and contains no active ingredient. Placebo tablet drug product is supplied as weight and appearance matched tablets with the active ingredient component of the tablets substituted with a combination of the 2 main fillers microcrystalline cellulose (Avicel® PH-102) and mannitol (Pearlitol® 200SD).

8.3 Study Drug Administration

Study drug is to be administered only to subjects who have provided written informed consent and have met the criteria outlined in Sections 7.1 and 7.2. Study drug will be administered orally once daily for 12 weeks. (Table 3).

Table 3. Study Drug Dosing

Study Drug Group	Dose	Treatment Regimen
AQX-1125 200 mg	2 AQX-1125 100 mg tablets	2 tablets, once daily
Placebo	2 placebo tablets	

The first dose of study drug will be administered in the clinic at Baseline (Visit 2), once all Baseline procedures are completed and the subject has been randomized. No investigational or commercial agents or therapies other than those described in Section 8.11 may be administered with the intention to treat the subject's condition.

Subjects will be instructed to take the study drug with a glass of water around the same time of day with food, or eat a light meal no more than 4 hours prior to consumption, for 12 weeks. On study visit days, subjects will be instructed not to take the study drug before the visit and to eat a light meal no more than 2 hours prior to the scheduled visit. The study drug will be taken during the study visit after all assessments have been completed. If the subject has inadvertently taken the study drug prior to attending the clinic, the clinic dose should not be given.

If a dose is missed, subjects should take the dose as soon as they remember on the same day. However, if it is the next day, the missed dose should be skipped and next dose taken as normal. Only 1 dose of study drug (2 tablets) should be taken each day and a double dose should not be taken.

Remaining unused study drug will be collected at Week 6 and at the end of the 12-week treatment. Subjects will be instructed to return all used wallets (including partially used and those with unused spare doses) for reconciliation at each study visit.

8.4 Randomization

Randomization will be conducted at Baseline (Visit 2), after verifying that the subject meets all inclusion criteria and has none of the exclusion criteria. Approximately 100 male subjects with diagnosed CP/CPPS will be randomized to either AQX-1125 (200 mg) or placebo in a 1:1 ratio.

A central, permuted block randomization scheme will be used with a selected blocking factor (block size) determined based on the proposed allocation ratio and number of subjects.

An Interactive Web Response System (IWRS) will be used for the randomization to either AQX-1125 (200 mg) or placebo and subsequent wallet assignments. Study staff will log in to the IWRS using appropriate credentials and input subject-specific information (i.e. subject number and other basic identifiers). In accordance with the randomization schedule, the IWRS will assign the randomization number and the unique wallet numbers to the subject. Each subject must be given only the wallets assigned by IWRS. The study staff will document the wallet numbers in the Case Report Form (CRF). Subjects are to be randomized in the order in which they qualify from the screening phase for inclusion in the study.

8.5 Study Drug Blinding

Blinding will be maintained via packaging (Section 8.6) and labelling (Section 8.7). Labels will contain fixed (e.g., protocol number) and variable information (e.g., wallet number) in a manner that protects the blind.

The Investigators, study personnel, subjects, medical monitor, and clinical monitor will remain blinded throughout the study, unless safety concerns necessitate unblinding.

If a medical emergency occurs and a decision regarding the subject's clinical treatment requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Unless the medical emergency is deemed to be life-threatening, the medical monitor must first be consulted before unblinding. The Investigator would then utilize the IWRS for unblinding and the unblinding procedure will be provided in the IWRS Manual. The date, time, and reason for unblinding must be documented in the source documents and on the applicable electronic Case Report Form (eCRF). Investigators should note that the occurrence of a SAE should not routinely trigger immediate unblinding. If the medical monitor was not notified prior to breaking the blind, the Investigator must notify the medical monitor of any and all blinds broken within 24 hours of each occurrence.

8.6 Study Drug Packaging

The tablets are packaged in blister packs, with 2 blister packs containing a total of a 14-day supply and 2 spare doses, assembled into a child-resistant cardboard wallet. Based on a dosing regimen of 2 tablets a day, the wallet design will contain a total of 32 tablets/16 doses.

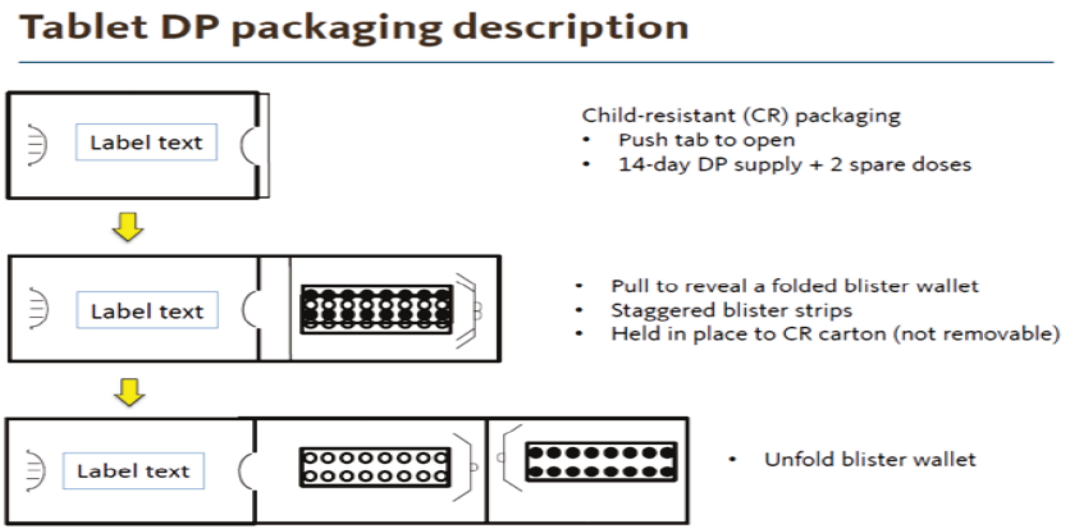

Figure 2. Tablet packaging

Sufficient quantities of wallets will be dispensed to enable the subject to continue to take the medication up to the next study visit. The spare doses will allow the subjects to remain on treatment if their visit is a few days post the target visit date but within predefined acceptable windows.

8.7 Study Drug Labelling

The wallet will be labelled with a single panel label, with translations provided for official languages of the countries/clinical sites participating in the study. Both packaging and labelling will be conducted as per regulatory guidelines.

Labels will contain fixed (e.g., protocol number) and variable information (e.g., wallet number) in a manner that protects the blind.

8.8 Study Drug Storage

Study drug should be stored at room temperature (15 to 25°C/59 to 77°F with excursions up to 30°C/86°F permitted). Instructions for handling temperature excursions are detailed in the Study Manual. Room temperature readings at site are to be recorded with any deviations outside of the permitted ranged reported. Study drug should be stored in a secure, locked facility accessible only to authorized study personnel until dispensed to the study subject. Instructions for ordering drug will be specified in the Study Manual and will be distributed to the study centers by a centralized distribution service.

8.9 Study Drug Handling and Accountability

Records shall be maintained of the delivery of study drug(s) to the study center(s), the inventory at the study center(s), the use by each subject and the return of unused study drug to the distribution centers (per the Study Manual).

These records shall include dates, quantities, batch numbers, expiry dates and the unique wallet numbers assigned to the study medication and to the study subjects.

The Investigator shall be responsible for ensuring adequate documentation of study drug received, dispensed, and returned.

8.10 Treatment and Electronic Diary Compliance

Treatment compliance will be assessed through tablet counts. The subject will be instructed to bring all dispensed wallets back to the clinic at each visit (even if the wallet is empty). The number of used and remaining tablets will be recorded on the eCRF.

Subject compliance with the eDiary will be monitored by trained study site personnel at each study visit.

8.11 Concomitant Medications

8.11.1 Permitted Medications

The use of stable concomitant therapy is allowed throughout the study, except for those medications prohibited in Section 8.11.2. All concomitant medications must be recorded in the appropriate sections of the eCRF or the eDiary as appropriate, and updated if any changes occur. Concomitant medications should include all medications taken within 30 days prior to Screening Visit 1 and throughout the study.

The following medications are permitted for use during the study:

- Short-acting opioid or opioid-containing analgesics (e.g., acetaminophen + codeine) for treatment of pain, including CP/CPPS symptom flares but treatment per protocol is only

permitted for fewer than 5 days per week or no more than 10 doses per month
- Non-opioid-containing analgesics (e.g., acetaminophen)
- Non-steroidal anti-inflammatory drugs (NSAIDs) only if on a stable dose (i.e. stable pattern and frequency of use) for ≥30 days prior to Screening Visit 1
- Medications for treating diseases other than CP/CPPS are permitted, provided they are not included in the list of prohibited medications listed in Section 8.11.2.
- Medications for treating CP/CPPS are permitted, provided they are not included in the list of prohibited medications listed in Section 8.11.2, and the subject has been on a stable dose for ≥30 days prior to Screening Visit 1 and plans to continue current pattern of usage for the duration of the study.

8.11.2 Prohibited Medications

The following medications are prohibited for use during the study:

- Any long-acting opioids
- Oral steroid therapy, immunosuppressants/immunomodulators (including daily phosphodiesterase type 4 inhibitors)

If a subject requires short-acting opioid analgesics for ≥5 days per week on >1 occurrence during the study or >10 times per month on >1 occurrence during the study, or require a prohibited medication to treat an AE, the subject may remain in the study. The use of the prohibited medication should be captured on the eCRF.

9 STUDY ASSESSMENTS

Refer to Table 1 for scheduling of study assessments.

9.1 Eligibility Only Assessments

9.1.1 Demographics, Baseline Characteristics, Medical/Surgical History

Demographic information, including age, birth year, sex, race and ethnicity.

Baseline characteristics consist of a complete medical history and detailed disease history. Medical history includes prior and ongoing medical diagnoses and conditions, surgical procedures, and medications taken within the previous 30 days. Background incidence of cataracts in subjects noted prior to dosing should be recorded as medical history.

This information will be collected at screening (Visit 1).

9.1.2 Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles Diagnosis

The Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles (UPOINT) system is designed to classify patients with an established diagnosis of CP/CPPS into a clinically relevant phenotype that can rationally guide therapy. Using the website http://www.upointmd.com (Shoskes, et al., 2013), subjects will be classified into the 6 domains of the UPOINT system (Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles). The classification will be done at screening (Visit 1) only.

9.1.3 Pain Catastrophizing Scale

This 13-statement PCS is captured only at screening (Visit 1), (Appendix 1. Pain Catastrophizing Scale) and attempts to elicit the subject's types of thoughts and feeling when in pain. Catastrophizing is defined as an exaggerated negative mental set brought to bear during actual or anticipated painful experience (Sullivan et al., 2001). A subject is excluded from the study if the total score from these questions is ≥30 (Sullivan et al., 1995).

9.1.4 Patient Health Questionnaire 9-Question

The PHQ-9 is a 9-item patient self-reporting tool used to assist study personnel in identifying mood changes by screening for symptoms of depression (Kroenke et al., 2001, Appendix 2. Patient Health Questionnaire 9-Items). Question 9 screens for the presence of suicidal ideation.

A subject with a total score ≥10 from these questions at Screening (Visit 1) or Baseline (Visit 2), or if in the opinion of the Investigator, findings on the Baseline (Visit 2) PHQ-9 indicate newly identified or poorly managed mental health concerns which would put the subject at risk or compromise their ability to participate in the study and comply with study requirements, the subject will be excluded from the study.

Subjects with an overall score on the self-reported PHQ-9 ≥10 or a score on Question 9, related to thoughts of wanting to hurt oneself, of ≥1 have a higher likelihood of the presence of a mood disorder. Any subject with a score above these thresholds will be seen by a member of the clinical study staff prior to leaving that study visit. Study staff will further clinically assess whether the subject is experiencing depressive symptoms, suicidal thoughts or behaviors, and whether these symptoms, if present, are changed from baseline. If the findings represent a change, this change in symptoms/mood, not the PHQ-9 score, will be recorded as an AE, and the subject will be clinically managed by the Investigator. This procedure allows for subjects to be identified and managed in a clinical setting and the data to be captured in the clinical study database as AEs.

This will be performed at Visits 1, 2, 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.1.5 Urine: Bacterial Culture & Sensitivity, Leukocyte Esterase Test

A urine bacterial culture will be obtained at screening (Visit 1) only. A subject will be excluded from the study if the subject has symptoms consistent with a urinary tract infection and a positive urine bacterial culture, defined as $\geq 10^5$ colony forming units (CFU) per mL or $\geq 10^4$ Gram negative rod CFU per mL. A subject can rescreen up to 1 time once the infection clears. A leukocyte esterase test will be conducted by the site at screening (Visit 1) only.

9.2 Efficacy Assessments

9.2.1 11-point Numerical Rating Scale

This scale will be used to determine the primary and secondary NRS pain endpoints (Appendix 3. 11-point Numerical Rating Scale). The subject will be asked to rate both their average and maximum (worst) pelvic pain intensity for the day on a daily basis using the eDiary. Subjects will also be asked to rate both their average and maximum (worst) pelvic pain intensity using the paper version during the in-clinic visits (Visits 1, 2, 3, 4, ET (if needed), and at the Off-

Treatment Safety Follow-up Visit). Subjects will be asked to rate their pelvic pain on a scale of 0-10, by indicating the number that best describes the pain intensity.

9.2.2 National Institutes of Health, Chronic Prostatitis Symptom Index

The NIH-CPSI is a commonly used 13-item questionnaire for the assessment of symptom severity in men with CP/CPPS. For each item, score ranges are 0–1 (6 items), 0–3 (2 items), 0–5 (3 items), 0–6 (1 item), and 0–10 (1 item) (Litwin et al., 1999, Appendix 4. National Institutes of Health Chronic Prostatitis Symptom Index). This will be performed at Visits 1, 2, 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.2.3 International Index of Erectile Function Questionnaire

The 15-question IIEF Questionnaire is a validated, multi-dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials (Rosen et al., 1997). A score of 0-5 is awarded to each of the 15 questions that examine the 5 main dimensions of male sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction (Appendix 5. International Index of Erectile Function Questionnaire). The entire questionnaire will be administered to the subject, however, only the first 5 questions associated with the Erectile Function domain will be used for the efficacy assessments.

This information will be collected at Visits 2, 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.2.4 Global Response Assessment

Assessment of the subject's global symptoms, compared with Baseline symptoms, will be performed by the subject using a 7-item scale (Appendix 6. Global Response Assessment). This information will be collected at Visits 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.2.5 Patient's Global Impression of Change Scale

Assessment of the subject's overall status since Baseline, will be performed by the subject using a 7-item scale (Appendix 7. Patient's Global Impression of Change Scale). This information will be collected at Visits 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.2.6 Patient's Global Impression of Severity Scale

Assessment of the subject's current symptoms will be performed by the subject using a 5-item scale (Appendix 8. Patient's Global Impression of Severity Scale). This information will be collected at Visits 2, 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.2.7 Twenty-four Hour Voiding Frequency

Voiding frequency will be measured over a 24-hour period, within a 3-day (72 hours) window before scheduled visits (Visit 2, 3, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.3 Safety Assessments

9.3.1 Physical Examination, Vital Signs

A complete general physical examination categorized by body system (e.g., head, eyes, ears, nose throat; neck; chest; lungs; back; abdomen; digital rectal exam [at Screening Visit 1 only]; extremities; and neurological), and vital signs, will be assessed and recorded at Visits 1, 2, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit. Vital signs will also be taken at Visit 3. Weight will be done at Visits 1, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit. Height will be measured at Visit 1. Seated blood pressure (BP) (mmHg), heart rate (HR) (beats per minute) and temperature (degrees Celsius) will be measured after the subject has been sitting for at least 5 minutes.

9.3.2 Ophthalmic Assessments

Ophthalmic assessments will be performed during the study. Screening ophthalmic assessments can be performed any time within the screening window (Visit 1a). Post-Baseline ophthalmic assessments (Visit 4, ET [if needed], Off-Treatment Safety Follow-up Visit, and Ophthalmic Follow-up Visit) should occur within the specified Visit windows.

The assessments will include the following:

- BCVA using the LogMAR chart (i.e., after manifest refraction)
- IOP, preferably measured by Goldmann tonometry, before and after dilation with mydriatic agent
- Corneal staining
- Slit lamp examination
- Lenticular opacification using LOCS III

Background incidence of cataracts in subjects noted prior to dosing should be recorded as medical history. Any clinically significant ocular findings must be reported as AEs. Refer to Section 9.3.5.5 for specific details concerning ocular AEs and definition of ocular SAEs.

9.3.3 12-lead Supine Electrocardiogram

Subjects will be resting supine for at least 5 minutes before the electrocardiogram (ECG) recording. The Investigator will determine if any abnormal ECG results are clinically significant and if so, record these on the appropriate source document and on the AE CRF page. This assessment will be performed at Visits 1, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit.

9.3.4 Clinical Chemistry & Hematology, Urinalysis

Blood samples will be collected for clinical laboratory tests and processed by a central laboratory. Subjects do not need to be fasting for the blood draw. This assessment will be performed at Visits 1, 2, 4, ET (if needed), and at the Off-Treatment Safety Follow-up Visit. The following laboratory tests will be assessed (Table 4):

Table 4. Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
▪ Urea ▪ Glucose ▪ Aspartate aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Alkaline phosphatase (AP) ▪ Lactate dehydrogenase (LDH) ▪ Sodium ▪ Phosphate ▪ Potassium ▪ Chloride ▪ Creatine phosphokinase (CPK) ▪ Globulin ▪ Cholesterol ▪ Creatine ▪ Serum calcium ▪ Total bilirubin ▪ Triglyceride ▪ Gamma glutamyl transpeptidase (GGT) ▪ Uric acid	▪ Hematocrit ▪ Hemoglobin ▪ Red Blood Cell Count ▪ White Blood Cell Count with Differential ▪ Platelet Count ▪ Mean corpuscular volume ▪ Mean corpuscular hemoglobin ▪ Mean corpuscular hemoglobin concentration	▪ pH ▪ Protein ▪ Glucose ▪ Ketones ▪ Bilirubin ▪ Specific Gravity ▪ Blood ▪ Nitrites ▪ Urobilinogen ▪ Bacterial culture & sensitivity, leukocyte esterase test (Screening Visit only)

The central laboratory will provide a laboratory manual and appropriate supplies (containers and labels). Laboratory values that are out of range will be identified and may be repeated at the Investigator's discretion. The Investigator will determine if any out-of-range laboratory values are clinically significant and if so, record these on the appropriate source document and on the AE CRF page. All clinically significant out-of-range laboratory values will be followed until they return to normal, or become medically stable.

9.3.5 Adverse Event Definitions/Reporting Requirements

An AE (also known as an "adverse experience") is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality.

All clinical AEs noted during the study will be reported on the appropriate AE page of the eCRF.

AEs that are serious, unexpected, and at least possibly related to study participation will be reported to the Institutional Review Board (IRB) or IEC and to the United States (US) Food and Drug Administration (FDA) or Health Canada within the timelines described below. All other AEs, such as those that are expected, or not related to the study participation, are to be reported annually to the institution's IRB/IEC at the time of the annual Continuing Review and to FDA as part of regular data submission at the time of annual Investigational New Drug (IND) report.

9.3.5.1 Expected Events

Expected events are those that have been previously identified as resulting from administration of the study drug. An AE is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current IB.

9.3.5.2 Suspected Adverse Reaction

A suspected adverse reaction is a subset of all AEs for which there is a reasonable possibility (i.e. evidence to suggest a causal relationship between the drug and the AE) that the drug caused the event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

9.3.5.3 Adverse Reaction

An adverse reaction is a subset of all suspected adverse reactions, and is defined as any AE caused by a drug.

9.3.5.4 Serious Adverse Event Definitions / Reporting Requirements

9.3.5.4.1 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered serious if, in the view of *either the Investigator or Sponsor*, it results in any of the following outcomes:

Death:
This includes any death that occurs while the subject is on study and/or within 28 days after the last dose of study drug. An autopsy will be requested, and if performed, results will be submitted to the Sponsor.

A life-threatening AE:
An AE or suspected adverse reaction is considered life-threatening if, *in the view of either the Investigator or Sponsor*, its occurrence places the subject at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.

Inpatient hospitalization or prolongation of existing hospitalization:
In the absence of an AE, hospitalization or prolongation of hospitalization should not be reported as an SAE in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center
- Hospitalization for survey visits or annual physicals
- For a hospitalization planned (and documented) before the start of the study for a pre-existing condition which has not worsened

A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

A congenital anomaly/birth defect

An important medical event:

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples 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 the development of drug dependency or drug abuse.

The Sponsor should be notified within 24 hours of the Investigator becoming aware of a SAE and the event documented on the eCRF.

9.3.5.4.2 Serious Unexpected and Suspected Adverse Reaction

An unexpected AE (or SUSAR) is any AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed, or, if an IB is not required/available, is not consistent with the risk information described in the general investigational plan. This also refers to AEs or suspected adverse reactions mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug. A SUSAR requires mandatory expedited reporting to the applicable regulatory authority(ies) (refer to Section 9.3.5.8). The Sponsor will forward the formal notification describing the SUSAR to Investigators. Each Investigator must then notify his/her IRB/IEC of the SUSAR, in accordance with the IRB/IEC's policy.

9.3.5.5 Ophthalmic Event Reporting

All clinically significant ocular findings must be reported as AEs.

Ocular Treatment Emergent Adverse Events of Special Interest

The following Ocular AEs will be treated as treatment emergent AEs of special interest (TEAESIs)

- A Class II or Class III grading shift in LOCS III as defined in the Ophthalmology Manual compared to Baseline
- A reduction of 2 lines or more on the LogMAR chart in BCVA compared to Baseline
- Ocular AEs without clear etiology
- Ocular AEs considered possibly or probably related to study drug

Ocular AEs with clear etiology will be reviewed on a case by case basis to determine if they should be treated as TEAESIs.

Adjudication

Ocular TEAESIs will be assessed by an independent, blinded adjudicator.

Reporting of TEAESI

TEAESIs will be communicated to the Drug Safety Manager to expedite Sponsor review of events. Investigators must designate whether the event is an AE or whether it meets the criteria of an SAE (Section 9.3.5.4.1).

9.3.5.6 Recording Adverse Events

For the purposes of this study, any detrimental change in the subject's condition, from signing of informed consent up to completion of the treatment period should be considered an AE (i.e. for up to 28 days after last dose of investigational product has been taken).

AEs should be captured wherever possible as a diagnosis and it is the Investigator's responsibility to ensure this is done. If a precise diagnosis cannot be made, a syndrome can be recorded. Rarely should it be necessary to record one or more individual symptoms.

All ongoing non-ocular AEs should be followed up until the Off-Treatment Safety Follow-up Visit (for 28 days after the last administration of study drug), with the exception of any ongoing study drug-related AEs, which should be followed until resolution, unless in the Investigator's opinion the AE is unlikely to resolve due to the subject's underlying disease. Ongoing ocular AEs will be queried at the Follow-up call 3 months post last dose and at the Ophthalmic Safety Follow-up Visit 6 months post last dose.

Ocular AEs must be followed until the 6-month Ophthalmic Safety Follow-up Visit.

Any new SAEs occurring up to 28 days after the last administration of study drug should be reported to the drug safety manager.

At any time after the Off-Treatment Safety Follow-up Visit, if an Investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the drug safety manager.

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page(s) of the eCRF. The Investigator will carefully evaluate each AE to determine:

- duration (start and end dates)
- intensity (grade)
- seriousness
- relationship to study drug (Unlikely, Possible, Probable)
- action taken with study drug (study drug modification or interruption, study drug discontinuation)
- action taken (none, medication, medical intervention)
- outcome (resolved without sequelae, resolved with sequelae, ongoing)

The Investigator will evaluate all AEs and SAEs with regard to maximum intensity and relationship to study drug. Maximum intensity should be assigned using one of the severity grades as outlined in the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0. If the AE is not specifically listed in Common Terminology Criteria for Adverse Events v4.0, the following grades will be used:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening or disabling
- Grade 5: death

9.3.5.7 Determining Relationship of Adverse Events to Study Drug

The Investigator must attempt to determine if an AE or SAE is related to the use of the study drug. This relationship should be described as follows:

Probable A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on study drug withdrawal may be lacking or unclear.

Unlikely A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

9.3.5.8 Reporting Deaths and Other Serious Adverse Events

9.3.5.8.1 Events to Be Reported and Timeframe

Any death or other SAE experienced by the subject during treatment or within 30 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 28 days after receiving study drug and is believed to be study drug-related, must be promptly reported to the Sponsor (*within 24 hours of the Investigator becoming aware of the event*) by telephone, telefax, or e-mail transmission.

9.3.5.8.2 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the Sponsor is responsible for informing the FDA and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US Code of Federal Regulations [CFR], Title 21 Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor is required to submit written documentation, in the form of an IND Safety Report, on the following:

- SUSARs
- Findings from other studies that suggest a significant risk to humans exposed to drug
- Findings from animal or in vitro testing that suggest a significant risk to humans exposed to drug
- Increased rate of occurrence of serious suspected adverse reactions from what is reported in the IB or the protocol

Written submission must be made by the Sponsor to the FDA/other regulatory authorities (and by the Investigator to the IRB/IEC) as soon as possible, and in no event later than **15 calendar**

days after the Sponsor determines that the information qualifies for reporting. The Sponsor shall also inform all Investigators.

In addition, the Sponsor is further required to report, by either telephone or facsimile transmission or in writing to the FDA/other regulatory authorities the occurrence of any unexpected fatal or life-threatening event associated with the use of the drug (SUSARs) no later than **7 calendar days** after notification of the event, followed by a written report **no later than 15 calendar days** after the initial report receipt date. The Sponsor shall also inform all Investigators.

The Sponsor will provide expedited reports of the following SUSARs to the Investigators for reporting to their IRB/IEC:

- SUSARs that have arisen in the clinical trial that was assessed by the IRB/IEC
- SUSARs that have arisen in other clinical trials of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the IRB/IEC

Investigators are required to promptly report to the IRB/IEC all unanticipated problems involving risk to human subjects, including AEs that should be considered unanticipated problems (21 CFR 312.53(c)(1)(vii), 312.66, and 21 CFR 56.108(b)(1)).

9.3.5.9 Initial Information Provided by the Investigator

The Investigator must transmit sufficient initial information to the Sponsor (or designee) should an SAE report meet the criteria for completion of an IND Safety Report. As much of the following information about the subject and the event will be requested:

- Subject identification code, gender, and age or date of birth
- Underlying diagnosis and extent of disease
- Lot number and expiration date of study drug (if available)
- Dose, route, frequency, and duration of study drug administered
- Date of last study drug administration
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimens and indications)
- Pertinent laboratory data/diagnostic study (including dates)
- Pertinent medical history
- Study drug status (dose interrupted, discontinued)
- Did event abate after interruption of study drug administration (if applicable)?
- Did event recur after study drug was reintroduced (if applicable)?
- Severity of the AE
- Relationship of the AE to study drug
- Outcome of the AE

9.3.5.10 Follow-up Information

Follow-up data concerning the SAE (e.g., diagnostic test reports, physician's summaries, etc.) must also be submitted to the Sponsor as they become available, preferably by telefax or e-mail, as soon as they become available, and until the event resolves or stabilizes.

9.3.5.11 Serious Adverse Event and Serious and Unexpected Suspected Adverse Reaction Review and Potential Impact on Trial Conduct

The Investigator will review each SAE report and evaluate further the relationship of the SAE to study drug and to the subject's underlying disease.

Based on the Investigator's and Sponsor's assessment of causality of the AE and discussions with the medical monitor, a decision will be made by the Sponsor concerning the need for further action with respect to the future conduct of the study. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new AE related to study drug raises concern over the safety of its continued administration to subjects, the Sponsor will take immediate steps to notify the FDA, other regulatory authorities, and all Investigators participating in clinical studies with the study drug.

Further action required may include any of the following:

- Alteration of the existing research program by modification of the protocol
- Discontinuation or suspension of the study
- Alteration of the informed consent process by modification of the existing Informed Consent Form (ICF) and informing current study participants of new findings
- Modification of previously identified expected suspected adverse reaction lists to include AEs newly identified as study drug-related

9.4 Timing of Assessments

9.4.1 Screening Period

9.4.1.1 Visit 1

- Informed consent
- Inclusion/Exclusion criteria
- Demographics
- Medical/Surgical history
- Physical examination
- UPOINT classification
- NIH-CPSI
- Paper-based 11-point NRS
- PCS
- PHQ-9
- 12-lead supine ECG

- Vital signs (HR, BP, temperature)
- Height
- Weight
- Clinical chemistry (does not need to be fasting), hematology, urinalysis
- Urine: bacterial culture & sensitivity, leukocyte esterase test
- AE collection
- Review concomitant medication
- eDiary issue/train

9.4.1.2 Baseline Ophthalmic Testing (Visit 1a)

Ophthalmic assessment at Visit 1a may occur at any time during the Screening period.

Ophthalmic assessments include:

- BCVA using the LogMAR chart (i.e. after manifest refraction)
- IOP (preferably measured by Goldmann tonometry before and after dilation with mydriatic agent)
- Corneal staining
- Slit lamp examination
- Lenticular opacification using LOCS III

9.4.2 Baseline (Visit 2)

- NIH-CPSI
- Paper-based 11-point NRS
- PHQ-9
- IIEF
- PGI-S
- Review Inclusion/Exclusion criteria
- eDiary review for Inclusion/Exclusion criteria
- Physical examination
- Vital signs (HR, BP, temperature)
- Clinical chemistry (does not need to be fasting), hematology, urinalysis
- Voiding frequency measured over a 24-hour period, within a 3-day (72 hours) window before the scheduled Visit
- AE collection
- Review concomitant medication
- Randomization after confirming subject continues to meet eligibility criteria
- Study drug dispensing
- Administration of first dose of study drug (after all assessments performed)

9.4.3 Treatment Period

9.4.3.1 Visit 3

- NIH-CPSI
- Paper-based 11-point NRS
- PHQ-9
- GRA
- PGI-C
- IIEF
- PGI-S
- Voiding frequency measured over a 24-hour period, within a 3-day (72 hours) window before the scheduled visit
- Vital signs (HR, BP, temperature)
- AE collection
- Review concomitant medication
- Study drug dispensing
- Study drug compliance check
- Study drug accountability
- eDiary review

9.4.3.2 Visit 4

- NIH-CPSI
- Paper-based 11-point NRS
- PHQ-9
- GRA
- PGI-C
- IIEF
- PGI-S
- Voiding frequency measured over a 24-hour period, within a 3-day (72 hours) window before the scheduled visit
- Physical examination
- Ophthalmic assessments (BCVA, IOP, corneal staining, slit lamp, LOCS III)
- 12-lead supine ECG
- Vital signs (HR, BP, temperature)
- Weight
- Clinical chemistry (does not need to be fasting), hematology, urinalysis
- AE collection
- Review concomitant medication
- Study drug compliance check

- Study drug accountability
- eDiary review

9.4.4 Early Termination

- NIH-CPSI
- Paper-based 11-point NRS
- PHQ-9
- GRA
- PGI-C
- IIEF
- PGI-S
- Voiding frequency measured over a 24-hour period, within a 3-day (72 hours) window before the scheduled visit
- Physical examination
- Ophthalmic assessments (BCVA, IOP, corneal staining, slit lamp, LOCS III)
- 12-lead supine ECG
- Vital signs (HR, BP, temperature)
- Weight
- Clinical chemistry (does not need to be fasting), hematology, urinalysis
- AE collection
- Review concomitant medication
- Study drug compliance check
- Study drug accountability
- eDiary review

9.4.5 Safety Follow-up

9.4.5.1 Off-Treatment Safety Follow-up

- NIH-CPSI
- Paper-based 11-point NRS
- PHQ-9
- GRA
- PGI-C
- IIEF
- PGI-S
- Voiding frequency measured over a 24-hour period, within a 3-day (72 hours) window before the scheduled visit
- Physical examination (only needed if there are outstanding safety concerns from Week 12)

- Ophthalmic assessments (only needed if there are outstanding safety concerns from Week 12)
- 12-lead supine ECG (only needed if there are outstanding safety concerns from Week 12)
- Vital signs (HR, BP, temperature)
- Weight
- Clinical chemistry (does not need to be fasting), hematology, urinalysis (only needed if there are outstanding safety concerns from Week 12)
- AE collection
- Review concomitant medication
- eDiary review/collect

9.4.5.2 Telephone Call

- AE collection (ophthalmic related AEs only)

9.4.5.3 Ophthalmic

- Ophthalmic assessments
- AE collection (ophthalmic related AEs only)

9.4.5.4 Unscheduled Visit

Unscheduled visits may be conducted at any time during the study and may include the same assessments as Week 12 (Visit 4).

10 STATISTICAL METHODS AND PLANNED ANALYSES

Statistical methods and conventions are described in this section. Full details on the analysis methods and presentation of study results will be provided in the statistical analysis plan (SAP). The SAP will be finalized prior to unblinding of the trial.

10.1 General Considerations

All statistical analyses will be performed using SAS® Version 9.4 or higher.

All clinical study data will be presented in subject data listings. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated by treatment group for continuous variables. Confidence intervals (CIs) will be provided where appropriate.

Frequencies and percentages will be presented by treatment group for categorical and ordinal variables.

Means, medians, and CIs will be reported to 1 decimal place more than the data reported on the eCRF or by the laboratory/vendor. Standard deviations will be reported to 2 decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places displayed on the eCRF or by the laboratory/vendor. *P* values will be reported to 4 decimal places.

10.2 Sample Size Determination

Sample size was calculated using the 2-sample means statement in the POWER procedure in SAS. A sample size of 45 subjects per treatment group will provide 80% power to detect a 1.2-point difference in the change from Baseline maximum pelvic pain score between AQX-1125 and placebo assuming a between-subject standard deviation of 2.0 and a 2-sided 5% significance level.

Assuming a 10% rate of discontinuation from study drug, the total number of subjects to be randomized is approximately 100. Subjects who discontinue will be included in the primary analysis, resulting in a slight decrease in power if the discontinuing subjects in the placebo group have no additional change after discontinuation of study drug while the discontinuing subjects in the AQX-1125 group have a loss of efficacy after discontinuing study drug.

10.3 Study Populations

The following are the analysis populations to be used:

- Intent-to-Treat (ITT) Population: The ITT Population will include all randomized subjects. In the event of study drug administration error, analyses on the ITT Population will be performed according to the treatment to which the subject was randomized to receive.
- Safety Population: The Safety Population will include all subjects who received any amount of study drug. In the event of study drug administration error, analyses on the Safety Population will be performed according to the treatment the subject actually received.
- Per-Protocol (PP) Population: The PP Population will include all ITT subjects who do not have any major protocol deviations and have non-missing Baseline and Week 12 assessments of maximum daily pelvic pain (i.e. the primary efficacy assessment). In the event of study drug administration error, analyses on the PP Population will be performed according to the treatment the subject actually received.

10.4 Statistical Analyses

10.4.1 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition (enrollment, randomization, study completion) and reasons for not completing the study will be presented by treatment group and overall. Additionally, the number of subjects in each of the analysis populations (Section 10.3) will be presented by treatment group and overall.

Subject demographics and baseline characteristics will be summarized by treatment group and overall for the ITT, Safety, and PP Populations. Descriptive statistics will be provided for age, height, and weight. Frequencies and percentages will be tabulated for sex, race, and ethnicity.

10.4.2 Efficacy Data

The primary efficacy analysis population will be the ITT Population. Sensitivity analysis for selected endpoint analyses will be performed on the PP Population.

10.4.2.1 Weekly Scores based on Daily Assessments

For weekly scores that are based on daily subject assessments (e.g., maximum daily pelvic score recorded daily by the eDiary) a subject's score for a week will be the average (mean) of the daily scores across that week.

10.4.2.2 Primary Efficacy Endpoint

The primary endpoint is the change from Baseline (Visit 2) to Week 12 (Visit 4) in the maximum daily pelvic pain (mean) using a standardized 11-point NRS pain score recorded daily by an eDiary.

10.4.2.3 Primary Efficacy Endpoint Analysis

Comparison of AQX-1125 to placebo at Week 12 for the primary efficacy endpoint will use mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) to compare change from Baseline in NRS score (dependent variable) between treatment arms (AQX-1125 and placebo). The model will include the Weeks 6 and 12 change from baseline scores for each subject. The MMRM model will have factors for Visit, Visit×Treatment interaction, and a Visit×Baseline interaction covariate. The treatment effects for each group and the treatment group difference will be estimated by least-squares means for Week 12 and tested at the 2-sided 0.05 level.

The least-squares means treatment group estimates and the difference between treatment groups will be presented for all Weeks 1 through 12 with corresponding confidence intervals.

10.4.2.4 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The change from Baseline to Week 12 for each of the following:
  - NIH-CPSI pain subscale and all domains total score
  - Male sexual health as measured using the IIEF-EF
  - Mean of average daily pelvic pain scores (eDiary), average and maximum daily pelvic pain (paper-based NRS in clinic)
  - 24-hour voiding frequency (eDiary)
- Time course of effects: AQX-1125 (200 mg once-daily) compared to placebo on the change from Baseline (Visit 2) to Week 6 (Visit 3), Week 12 (Visit 4), and Week 16 (i.e. 4 weeks after end of treatment) for each of the following:
  - Mean of maximum daily pelvic pain score (eDiary)
  - NIH-CPSI pain subscale and all domains total score
  - IIEF-EF
  - Mean of average daily pelvic pain scores (eDiary), average and maximum pelvic pain (Paper-based NRS in clinic).
  - 24-hour voiding frequency (eDiary)
- Response to treatment as measured by the GRA, PGI-C, and PGI-S at Week 12 (Visit 4).

- A ≥30% and ≥50% improvement in maximum daily pelvic pain (using the 11-point NRS recorded by eDiary and the NIH-CPSI pain subscale) compared to placebo, at Week 6 (Visit 3) and Week 12 (Visit 4).
- Responder analysis: Response to treatment defined by any of the following:
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with no change in the amount or strength of concomitant analgesic medications
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 (eDiary) with a decrease in the amount or strength of concomitant analgesic medications
- Discontinuation of study medication due to treatment failure (% meeting treatment failure criteria and time to event)

10.4.2.5 Secondary Efficacy Endpoints Analyses

For the following dichotomous secondary efficacy endpoints, the rates for each treatment group and the difference between the treatment groups will be presented with corresponding 95% CIs. A Cochran–Mantel–Haenszel test will be used to test for differences in rates between the treatment groups controlling for baseline pelvic pain.

- Treatment response as defined by meeting either of the following:
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 using a standardized 11-point NRS with no change in the amount or strength of concomitant analgesic medications
  - Decrease in maximum daily pelvic pain from Baseline to Week 12 using a standardized 11-point NRS with a decrease in the amount or strength of concomitant analgesic medications
- A ≥30% and ≥50% improvement in maximum daily pelvic pain (using the 11-point NRS recorded by eDiary and the NIH-CPSI pain subscale), at Weeks 6 (Visit 3) and 12 (Visit 4).
- Discontinuation of study medication due to treatment failure (% meeting treatment failure criteria and time to event)

The following change from Baseline to Week 12 endpoints will be analyzed in a manner similar to the primary efficacy analysis as described in Section 10.4.2.3.

- NIH-CPSI pain subscale and all domains total score.
- Male sexual health as measured using the IIEF-EF.
- Mean of average daily pelvic pain scores (eDiary), daily pelvic pain (in clinic), and maximum daily pelvic pain (in clinic).
- 24-hour voiding frequency

Additionally, for the IIEF-EF domain endpoint, the frequency distribution of the 5 category IIEF-EF score (i.e. described in Appendix 5. International Index of Erectile Function Questionnaire) will be presented by treatment group for Week 12 as well as a shift table from Baseline. Treatment group difference in the 5-category IIEF-EF will be assessed by a Cochran-Mantel-Haenszel (CMH) test controlling for Baseline IIEF-EF score.

The following time course secondary endpoints will be assessed by MMRM ANCOVA model where the change from Baseline is the dependent variable and linear trends across time (i.e., visit) are assessed.

Time course of effects: AQX-1125 (200 mg once-daily) compared to placebo on the change from Baseline (Visit 2) to Week 6 (Visit 3), Week 12 (Visit 4) and Week 16 (i.e. 4 weeks after end of treatment) for each of the following:

- Mean of maximum daily pelvic pain score (eDiary).
- NIH-CPSI pain subscale and all domains total score.
- IIEF-EF.
- Mean of average daily pelvic pain scores (eDiary), daily pelvic pain (in clinic), and maximum daily pelvic pain (in clinic).
- 24-hour voiding frequency.

For the following secondary endpoints, the frequency distribution of each response scale will be presented by treatment group. For the GRA and PGI-C, treatment group differences will be assessed by means of a chi-square test. For the PGI-S, treatment differences will be assessed by means of a CMH test controlling for Baseline PGI-S.

- Response to treatment as measured by the GRA, PGI-C, PGI-S at Week 12 (Visit 4).

10.4.2.6 Control for Multiplicity

The Type 1 error rate for the primary endpoint analysis is at the 0.05 level (2-sided). The Type I error rate will not be controlled for the secondary efficacy endpoints.

10.4.2.7 Interim analyses

There are no interim analyses planned for this trial.

10.4.3 Safety Data

Safety analyses will be based on the Safety Population. Safety data will be presented by treatment groups. Descriptive statistics will be presented; inferential statistical tests will not be performed.

The safety assessments include AEs, clinical laboratory tests, physical examination, vital signs, and ECG assessments. Change from Baseline will be summarized for safety laboratory tests, vital signs, and ECG assessments. Shift tables for the lab tests (high, low or normal) will also be presented.

All AEs will be classified according to the MedDRA dictionary. AEs will be summarized by the number and percentage of subjects experiencing any AE, any SAE, and any AE leading to study discontinuation during the treatment period. AEs will also be summarized by 1) System Organ Class (SOC) and Preferred Term (PT); 2) SOC, PT, and severity; and 3) SOC, PT, and relationship to study drug.

Ophthalmic safety will be summarized by treatment groups including: assessment of lenticular opacification using LOCS III, BCVA using the LogMAR chart, IOP, corneal staining, and slit lamp examination at Baseline and 6 months post last dose, and at ET.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Assurance (QA) and Quality Control systems will be implemented and maintained with Standard Operating Procedures, as appropriate, to ensure that this clinical study is conducted and data are generated, documented and reported in compliance with the protocol, ICH E6 GCP, and applicable regulatory requirements.

Before enrolling any subjects in this study, a Sponsor representative and the Investigator will review the protocol, IB, eCRFs and instructions for their completion, as well as the procedures for obtaining informed consent and for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone and email. During site visits, the study monitor will assure accurate and reliable data collection by verifying the information recorded on the eCRFs against source documents and medical records (i.e. source document verification).

Measures will be undertaken to protect the confidentiality of records that could identify subjects respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

12 DOCUMENTATION AND INSPECTIONS

12.1 Study Monitoring

The Sponsor has responsibility to governing regulatory authorities to take all reasonable steps to ensure the proper conduct of the study with respect to trial ethics, protocol adherence, and data integrity and validity.

This trial will be closely monitored by Sponsor representatives throughout its duration. Monitoring will be in the form of personal visits with the Investigator and staff as well as any appropriate communications by telephone, telefax, mail, or e-mail transmission. The purpose of these contacts is to review trial progress, Investigator and subject adherence to the protocol, and to determine if there are any problems associated with the conduct of the study. The following may be assessed during site monitoring visits:

- Required regulatory documentation
- Signed ICFs
- Subject accrual and follow-up
- Study drug inventory records
- Investigator and subject compliance to the study protocol
- Concomitant medication use
- AE documentation
- Protocol deviation documentation
- Data are accurate, complete, and verifiable when compared to source documents

The Investigator and study staff are expected to cooperate with monitors during such visits and provide all relevant study documents.

12.2 Audits and Inspections

All documentation pertaining to this clinical trial may be subject to a QA audit by the Sponsor, or Regulatory Authorities (e.g., the FDA). Upon request, the auditor will have access to inspect, copy, review, and audit all source documents, eCRFs, medical records, correspondence, and ICFs pertaining to the subjects in the trial. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documents and eCRFs. Other documentation subject to QA audit includes the IRB/IEC files, certification and quality control of supporting laboratories, and records relevant to the trial in any supporting pharmacy facilities. Conditions of storage of study materials are also subject to inspection. Sponsor representatives may observe the conduct of any aspect of the clinical trial or its supporting activities both within and outside of the Investigator's institution.

13 ETHICAL AND LEGAL ISSUES

13.1 Ethical Conduct/Good Clinical Practice

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with ICH GCP and applicable regulatory requirements.

13.2 Institutional Review Board/Independent Ethics Committee

This study must be reviewed and approved by the IRB/IEC representing the institution prior to enrolling patients. The IRB/IEC must be appropriately constituted and meet all requirements as described in Part 56, Title 21 of the CFR and local laws and regulations, as applicable. The review must include both the protocol and the ICF for the trial. A copy of the Letter or Notice of Approval from the IRB/IEC must be received by the Sponsor prior to shipment of drug supplies to the Investigator. The IRB/IEC membership list must be submitted to the Sponsor with the written IRB/IEC approval and updated lists, if applicable.

The Investigator must promptly report all changes in the research activity and all unanticipated problems involving risk to the subjects or others to their IRB/IEC. The Investigator will provide progress reports as required by the IRB/IEC. The Investigator is responsible for assuring continuing review and approval of the clinical study on an annual basis and submitting documentation of renewal to the Sponsor. The Investigator will give notice to the IRB/IEC when participation in the study has been completed.

13.3 Written Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the subjects entered into the study, including obtaining written informed consent prior to performing any study-related procedures and informing each subject that the study drug is being used for investigational purposes. A copy of the IRB-approved ICF to be used during the study must be submitted for Sponsor review prior to study initiation.

Prior to entry into the study, the purpose and nature of the study and possible adverse effects must be explained to each patient. All questions about the study should be answered to the patient’s satisfaction or the patient’s legal representative. It is the responsibility of the Investigator or designee to obtain written informed consent from each patient, thereby attesting

that consent was freely given. A copy of the signed and dated ICF will be given to the patient. Documentation of the informed consent process must be evident in the patient's clinical files, and the original executed ICF must be available for review by the study monitor.

In the event that modifications in the experimental design, dosages, tests and assessments, subject selection, etc., of the protocol are indicated or required, and in the event that such modifications substantially alter the study design or increase the potential risk to subjects, revisions to the existing ICF are also required. Such a revision will be reviewed and approved by the appropriate IRB, and documentation of this approval will be forwarded to the Sponsor for submission to the appropriate regulatory body.

In addition, all current study participants, as well as subsequent study candidates, will be informed of the study design modification or increase in potential risk, and written informed consent will be obtained.

13.4 Records and Case Report Forms

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the study drug. Data reported on the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All requested information must be entered on the eCRF in the fields provided.

13.5 Protocol Deviations

The study is to be conducted as described in this protocol without deviation unless there is a safety concern. The protocol should not be modified for any subject without the prior consent of the Sponsor and, if necessary, the IRB/IEC responsible at the investigative site.

In the event of a violation, a report will be submitted to the IRB/IEC (as applicable).

13.6 Termination of the Study

Should the Sponsor and/or the Investigator discover conditions during the course of the trial that indicate that the study should be discontinued, an appropriate procedure for termination will be instituted.

Reasons for the closure of a study site or termination of a study by the Sponsor may include (but are not limited to) the following:

- Successful completion of the study at the study site
- The required number of subjects for the study has been recruited
- Failure of the Investigator to comply with the protocol, GCP guidelines or regulatory requirements
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

13.7 Retention of Records

The Investigator/Institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. Canadian federal

law requires all records created during the conduct of a clinical trial for 25 years under Division 5 of the Health Canada Food and Drug Regulations. US federal law requires that the Investigator retain copies of all files pertaining to the trial (i.e. medical records, laboratory reports, drug inventory/disposition records, signed ICFs, eCRFs, all correspondence, dates and reports of monitoring visits) for a period of 2 years following the date of marketing application approval of the drug for the indication investigated in the study, and until there is no pending or contemplated marketing application, or for 2 years following the Sponsor's discontinuing worldwide clinical development of the study drug, as notified by the Sponsor, whichever is longer.

If the Investigator relocates, retires, or withdraws for any reason from the study, trial records may be transferred to an acceptable designee, such as another Investigator within the institution. Prior notice of such transfer will be provided in writing to the Sponsor. The Investigator must obtain written permission from the Sponsor prior to disposing of any records.

14 INVESTIGATOR RESPONSIBILITIES

An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in the US CFR, Title 21 Part 312, ICH GCP guidelines, as well as local laws and regulations.

The Investigator:

- Will personally conduct or supervise the conduct of the study. The Investigator will ensure that all sub-Investigators and others assisting in the trial are adequately informed about the protocol, the study drug, and their trial-related duties and functions.
- Will make changes to the conduct of the trial only after receiving the Sponsor's approval, except to protect the safety, rights, or welfare of subjects.
- Will not disclose any goods, materials, information (oral or written) and unpublished documentation provided by the Sponsor (including this protocol, the subject eCRFs, and the IB) to any unauthorized person without the Sponsor's prior written consent.
- Will maintain a Subject Screening Log listing all subjects entered into the trial, those considered for trial entry and subsequently excluded, and the reason for exclusion.
- Will store study drug in a secure location, under the conditions indicated in Section 8.9, and will maintain a Drug Inventory Form. Will destroy used supplies in an appropriate manner according to institutional policy and document such destruction. At the completion of the trial, the Investigator will return all unused trial materials to the Sponsor, unless otherwise authorized in writing.
- Will record trial data on eCRFs for each subject who receives any amount of study drug, including those who withdraw before completion of the trial. Will ensure the accuracy, completeness, legibility, and timeliness of the data reported on the eCRF and in required reports. Will review eCRFs for completeness and accuracy prior to submission for data entry.
- Will include source documents such as hospital, clinic, or office charts; laboratory reports; trial worksheets; and signed ICFs in the Investigator's files along with subject trial records. Will include in the ICF a statement allowing the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data reported on the eCRF.

- Will permit direct monitoring and auditing by the Sponsor or Sponsor's representatives and inspection by the appropriate regulatory authorities.
- Will provide the Sponsor with the normal laboratory ranges for the laboratories to be used in the trial as well as the laboratory certification number. Will provide copies of any additional records pertinent to the trial (e.g., radiology reports, chart summaries, autopsy reports) to the Sponsor or regulatory authorities, if requested, with due precaution taken to ensure subject confidentiality.
- Will maintain subject confidentiality at all times during the trial by using coded identifiers when referring to a particular subject (including in any publications).
- Will inform subjects that the study drug is being used for investigational purposes
- Will report to the Sponsor any AEs that occur during the trial in accordance with ICH, CFR 21 Part 312.64 and local laws.

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16 APPENDICES

Appendix 1. Pain Catastrophizing Scale

PCS

Age:_____ Sex: M(__) F(__)

Everyone experiences painful situations at some point in their lives. These experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Thirteen statements are listed below describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain...

1 ☐ I worry all the time about whether the pain will end.

2 ☐ I feel I can't go on.

3 ☐ It's terrible and I think it's never going to get any better.

4 ☐ It's awful and I feel that it overwhelms me.

5 ☐ I feel I can't stand it anymore.

6 ☐ I become afraid that the pain will get worse.

7 ☐ I keep thinking of other painful events.

8 ☐ I anxiously want the pain to go away.

9 ☐ I can't seem to keep it out of my mind.

10 ☐ I keep thinking about how much it hurts.

11 ☐ I keep thinking about how badly I want the pain to stop.

12 ☐ There's nothing I can do to reduce the intensity of the pain.

13 ☐ I wonder whether something serious may happen.

...Total

Appendix 2. Patient Health Questionnaire 9-Items

Aquinox AQX-1125-205
Subject Screen Number/ Randomization Number _____
Visit Date_____ Visit Number _____

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ **DATE:**_____

Over the last *2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns _____ + _____ + _____

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

TOTAL: _____

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

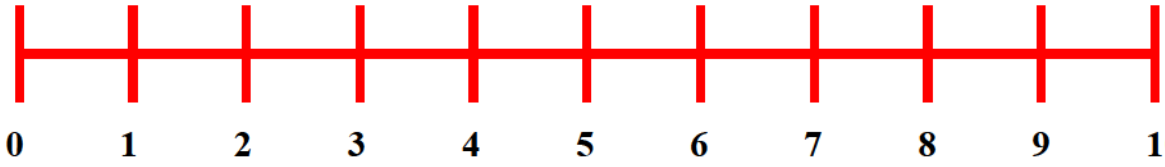
A2662B 10-04-2005

Appendix 3. 11-point Numerical Rating Scale

11-Point Numerical Rating Scale for Pain* (Clinic)

PELVIC PAIN CLINIC ASSESSMENT

Please assess your average and worst pelvic pain for each day on a scale of 0-10:



No Pelvic Pain — **Pelvic Pain as bad as you can imagine**

What number would you give your average pelvic pain over the last 24 hours?

No Pelvic Pain ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Pelvic Pain as bad as you can imagine

What number would you give your worst pelvic pain over the last 24 hours?

No Pelvic Pain ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Pelvic Pain as bad as you can imagine

*Adapted from McCaffery, M. Beebe A, et al. (1989). Pain: Clinical manual for nursing practice, Mosby St. Louis, M

Appendix 4. National Institutes of Health Chronic Prostatitis Symptom Index

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

		Yes	No
a.	Area between rectum and testicles (perineum)	❑1	❑0
b.	Testicles	❑1	❑0
c.	Tip of the penis (not related to urination)	❑1	❑0
d.	Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

		Yes	No
a.	Pain or burning during urination?	❑1	❑0
b.	Pain or discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ 0 Never
❑ 1 Rarely
❑ 2 Sometimes
❑ 3 Often
❑ 4 Usually
❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑
0 1 2 3 4 5 6 7 8 9 10
NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?
❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

8. How much did you think about your symptoms, over the last week?
❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑0 Delighted
❑1 Pleased
❑2 Mostly satisfied
❑3 Mixed (about equally satisfied and dissatisfied)
❑4 Mostly dissatisfied
❑5 Unhappy
❑6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and =_____

Urinary Symptoms: Total of items 5 and 6 =_____

Quality of Life Impact: Total of items 7, 8, and 9 =_____

Appendix 5. International Index of Erectile Function Questionnaire

These questions ask about the effect your erection problems have had on your sex life **over the past 4 weeks**. Please answer these questions as honestly and as clearly as possible. Please answer every question by checking the appropriate box [□]. If you are unsure about how to answer, please give the best answer you can.

In answering these questions, the following definitions apply:

* **Sexual intercourse**

Is defined as sexual penetration (entry) of the partner.

** **Sexual Activity**

Includes intercourse, caressing, foreplay and masturbation.

*** **Ejaculate**

Is defined as the ejection of semen from the penis (or the sensation of this).

**** **Sexual stimulation**

Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

1. **Over the past 4 weeks** how often were you able to get an erection during sexual activity**?
   Please check one box only.

   No sexual activity ..... □
   Almost always or always ..... □
   Most times (much more than half the time) ..... □
   Sometimes (about half the time) ..... □
   A few times (much less than half the time) ..... □
   Almost never or never ..... □

2. **Over the past 4 weeks** when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?
   Please check one box only.

   No sexual stimulation ..... □
   Almost always or always ..... □
   Most times (much more than half the time) ..... □
   Sometimes (about half the time) ..... □
   A few times (much less than half the time) ..... □
   Almost never or never ..... □

The next 3 questions will ask about the erections you may have had during sexual intercourse*.

3. **Over the past 4 weeks** when you attempted sexual intercourse* how often were you able to penetrate (enter) your partner?
   Please check one box only.

   Did not attempt intercourse ..... ☐
   Almost always or always ..... ☐
   Most times (much more than half the time) ..... ☐
   Sometimes (about half the time) ..... ☐
   A few times (much less than half the time) ..... ☐
   Almost never or never ..... ☐

4. **Over the past 4 weeks** during sexual intercourse* **how often** were you able to maintain your erection after you had penetrated (entered) your partner?
   Please check one box only.

   Did not attempt intercourse ..... ☐
   Almost always or always ..... ☐
   Most times (much more than half the time) ..... ☐
   Sometimes (about half the time) ..... ☐
   A few times (much less than half the time) ..... ☐
   Almost never or never ..... ☐

5. **Over the past 4 weeks** during sexual intercourse* **how difficult** was it to maintain your erection to completion of intercourse?
   Please check one box only.

   Did not attempt intercourse ..... ☐
   Extremely difficult ..... ☐
   Very difficult ..... ☐
   Difficult ..... ☐
   Slightly difficult ..... ☐
   Not difficult ..... ☐

* **Sexual intercourse**: Is defined as sexual penetration (entry) of the partner.
** **Sexual activity**: Includes intercourse, caressing, foreplay and masturbation.
*** **Ejaculate**: Is defined as the ejection of semen from the penis (or the sensation of this).
**** **Sexual stimulation**: Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

6. **Over the past 4 weeks** how many times have you attempted sexual intercourse*?
Please check one box only.

No attempts	☐
1-2 attempts	☐
3-4 attempts	☐
5-6 attempts	☐
7-10 attempts	☐
11 + attempts	☐

7. **Over the past 4 weeks** when you attempted sexual intercourse* how often was it satisfactory for **you**?
Please check one box only.

Did not attempt intercourse	☐
Almost always or always	☐
Most times (much more than half the time)	☐
Sometimes (about half the time)	☐
A few times (much less than half the time)	☐
Almost never or never	☐

8. **Over the past 4 weeks** how much have you enjoyed sexual intercourse*?
Please check one box only.

No intercourse	☐
Very highly enjoyable	☐
Highly enjoyable	☐
Fairly enjoyable	☐
Not very enjoyable	☐
Not enjoyable	☐

* **Sexual intercourse**: Is defined as sexual penetration (entry) of the partner.
** **Sexual activity**: Includes intercourse, caressing, foreplay and masturbation.
*** **Ejaculate**: Is defined as the ejection of semen from the penis (or the sensation of this).
**** **Sexual stimulation**: Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

9. **Over the past 4 weeks** when you had sexual stimulation**** **or** intercourse* how often did you ejaculate***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

10. **Over the past 4 weeks** when you had sexual stimulation**** **or** intercourse* how often did you have the feeling of orgasm with or without ejaculation***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

* **Sexual intercourse**: Is defined as sexual penetration (entry) of the partner.
** **Sexual activity**: Includes intercourse, caressing, foreplay and masturbation.
*** **Ejaculate**: Is defined as the ejection of semen from the penis (or the sensation of this).
**** **Sexual stimulation**: Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

The next 2 questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (e.g. masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.

11. **Over the past 4 weeks** how often have you felt **sexual desire**?
Please check one box only.

- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

12. **Over the past 4 weeks** how would you rate your level of **sexual desire**?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low or none at all ☐

* **Sexual intercourse**: Is defined as sexual penetration (entry) of the partner.
** **Sexual activity**: Includes intercourse, caressing, foreplay and masturbation.
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this).
**** **Sexual stimulation**: Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

13. **Over the past 4 weeks** how satisfied have you been with your overall **sex life**?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

14. **Over the past 4 weeks** how satisfied have you been with your **sexual relationship** with your partner?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

15. **Over the past 4 weeks** how would you rate your **confidence** that you could get and keep an erection?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low. ☐

* **Sexual intercourse**: Is defined as sexual penetration (entry) of the partner.
** **Sexual activity**: Includes intercourse, caressing, foreplay and masturbation.
*** **Ejaculate**: Is defined as the ejection of semen from the penis (or the sensation of this).
**** **Sexual stimulation**: Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

Appendix 6. Global Response Assessment

Global Response Assessment (GRA)

"As compared to when you started the study drug, how would you rate your Chronic Prostatitis/Chronic Pelvic Pain Syndrome symptoms now?"

-3: ☐ MARKEDLY WORSE

-2: ☐ MODERATELY WORSE

-1: ☐ SLIGHTLY WORSE

0: ☐ NO CHANGE

+1: ☐ SLIGHLTY IMPROVED

+2: ☐ MODERATELY IMPROVED

+3: ☐ MARKEDLY IMPROVED

Nickel JC, Atkinson G, Krieger JN et al.: Preliminary Assessment of Safety and Efficacy in Proof-of-Concept, Randomized Clinical Trial of Tanezumab for Chronic Prostatitis/Chronic Pelvic Pain Syndrome. Urology. 2012Nov; 80(5):1105-10.

Appendix 7. Patient's Global Impression of Change Scale

PGI-C Questionnaire

PGI-C Questionnaire Completed?

—

Date PGI-C Questionnaire Completed
month ____ day ____ year _____

Please choose the response below that best describes the overall change in your pelvic pain since you started the study

- ☐ 1. Very much improved
- ☐ 2. Much improved
- ☐ 3. Minimally improved
- ☐ 4. No change
- ☐ 5. Minimally worse
- ☐ 6. Much worse
- ☐ 7. Very much worse

Appendix 8. Patient's Global Impression of Severity Scale

PGI-S Questionnaire

PGI-S Questionnaire Completed?

—

Date PGI-S Questionnaire Completed
month ____ day ____ year _____

Please choose the response that best described the severity of your chronic prostatitis, chronic pelvic pain symptoms over the past week

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe