Aquinox Pharmaceuticals (Canada), Inc.
Protocol #: AQX-1125-205

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

Protocol Version 3.0/Amendment 2.0

Statistical Analysis Plan

Created by: Clinical Trial Data Services, Inc.
40 Nagog Park, Suite #210
Acton, MA 01720

By signing the following, I agree to the contents in the Statistical Analysis Plan and its associated attachments. Any modifications to the SAP made after signing will result in a change order.

Approved by:

Name	Title	Signature	Date
Brian Wiens, Ph.D.	Senior Director, Biostatistics Aquinox Pharmaceuticals, Inc		
James MacDougall, Ph.D.	Senior Biostatistician, CTDS		25Jun18
Terri Sampo, MPH	Principal Consultant, CTDS		6/25/2018
Jill Young	Clinical Project Manager, ProTrials Research, Inc.		

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence Interval
CMH	Cochran-Mantel Haenszel Test
CP/CPPS	Chronic Prostatitis/Chronic Pelvic Pain Syndrome
CRF	Case Report Form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ET	Early Termination
FDA	Food and Drug Administration
GRA	Global Response Assessment
HR	Heart Rate
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	Institutional Ethics Committee
IIEF-EF	International Index of Erectile Function Questionnaire, Erectile Function Domain
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LogMAR	Logarithm of the Minimum Angle of Resolution
LOCS III	Lens Opacification Classification System III
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MAR	Missing at Random
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
MNAR	Missing not at random
NIH	National Institutes of Health
NIH-CPSI	National Institutes of Health, Chronic Prostatitis Symptom Index
NRS	Numerical Rating Scale
PCS	Pain Catastrophizing Scale
PGI-C	Patient's Global Impression of Change
PGI-S	Patient's Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TEAESI	Treatment Emergent Adverse Event of Special Interest
UPOINT	Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles

Table of Contents

1 Protocol Synopsis

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

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

Methodology [Study Design]:

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:

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
    - **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
  - 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 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

2 Statistical Methodology

2.1 General Considerations

The objective of this double-blind Phase II study is to evaluate the efficacy and safety of AQX-1125 (200 mg) in male subjects with chronic prostatitis/chronic pelvic pain Syndrome (CP/CPPS). This study uses a randomized (1:1, AQX-1125: Placebo), double-blind, placebo-controlled, parallel group design. Randomization will be conducted at Baseline (Visit 2), after verifying that the subject meets all inclusion criteria and has none of the exclusion criteria. Two tablets of AQX-1125 or placebo will be administered orally once daily for 12 weeks. The study will consist of a screening period of up to 3-weeks a 12-week treatment period followed by a 4-week off drug 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.

All subjects screened into the study will be assigned a subject identifier number during screening that will be used on all subject documentation. The subject identifier number will contain the site number and the subject number assigned in numerical order at the screening visit. Subject numbers will be assigned in ascending order at each site starting with 01. All data will be listed in subject data listings sorted by site and subject number unless otherwise noted. Data tabulations will be prepared as described in the sections below.

All statistical analyses will be performed using SAS Version 9.4 or higher. The following summary statistics will be reported for continuous data: number of subjects, mean, median, standard deviation, quartiles, minimum, and maximum. Confidence intervals (CIs) will be provided where appropriate. For categorical data, the number and percentage of subjects within each treatment group will be reported.

For weekly scores that are based on daily subject assessments, a subject's score for a week will be the average (mean) of the daily scores across that week. Baseline lab test results or vital sign results will be the last non-missing value before dosing. Change from baseline will be defined as the post-baseline visit value minus the baseline value unless otherwise specified. Assessments performed at the Early Termination visit will be summarized descriptively.

2.2 Subject Population

2.2.1 Sample Size Justification

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 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.

2.2.2 Study Assessment Time Points

All enrolled subjects will record the maximum and average daily pelvic pain in the eDiary from Screening Visit 1 to Week 16, as well as analgesic medication taken each day. Subjects will record 24-hour voiding frequency prior to scheduled visits at baseline, Week 6, Week 12 and Week 16. Visits are scheduled at the following timepoints:

- Visit 1/Screening
- Visit 1a/ Baseline ophthalmic assessments (at any time before Visit 2)
- Visit 2/Baseline (Week 1)
- Visit 3 (Week 6)
- Visit 4 (Week 12)
- Early Termination: 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 a visit at Week 12 to assess efficacy endpoints.
- Off Treatment (Week 16) 4-week off drug Safety Follow-up period
- Ophthalmic Safety Follow-up Visit 6-months post last dose: Ophthalmic assessments and AE collection (ophthalmic related AEs only)
- Follow-up telephone call 3 months after the last dose: AE collection (ophthalmic related AEs only)
- Unscheduled Visits: Unscheduled visits may occur when subject needs to make a visit in between the scheduled visit dates due to an AE, difficulty complying with the study protocol requirements, or a significant change in their disease state. Unscheduled visits may be conducted at any time during the study and should include the same assessments as Week 16.

2.2.3 Schedule of Events

Event	Screening Period[a]		Baseline	Treatment Period			Safety Follow-up		
Assessment	Visit 1	Baseline Ophthal. 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	✓								

Event	Screening Period[a]		Baseline	Treatment Period			Safety Follow-up		
Assessment	Visit 1	Baseline Ophthal. 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)
24-hour voiding frequency[h]			✓	✓	✓	✓	✓		
AE collection	✓		✓	✓	✓	✓	✓	✓[l]	✓[l]
Concomitant medications	✓		✓	✓	✓	✓	✓		
Study drug dispensing[i]			✓	✓					
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.

2.2.4 Randomization/Unblinding

2.2.4.1 Randomization Methodology

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. The block size will be specified in the randomization plan.

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 unique credentials and input subject-specific screening and baseline information. In accordance with the randomization schedule, the IWRS will assign the randomization number and unique wallet numbers to the subject. Each subject must be given only the wallets assigned by IWRS. The study staff will document the wallet number in the Study Drug Accountability electronic Case Report Form (eCRF). Subjects are to be randomized in the order in which they qualify from the screening phase for inclusion in the study. The randomization plan will be executed in accordance with CTDS' SOP DM016: Generation of Randomization Schemes/Unblinding.

2.2.4.2 Unblinding

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 eCRF Completion Guidelines. The date, time, and reason for unblinding must be documented in the source documents and on the applicable unblinding form in the IWRS. 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.

2.2.5 Study Populations for Analysis

The following are the analysis populations to be used:

2.2.5.1 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 which the subject was randomized to receive.

2.2.5.2 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.

2.2.5.3 Per-Protocol (PP) Population

The PP Population will include all ITT subjects who do not have any major protocol deviations that possibly affect interpretation of the primary efficacy endpoint and have non-missing Baseline and Week 12 assessments of maximum daily pelvic pain (i.e. the primary efficacy assessment). Determination of which subjects to be included in the PP population will be performed by a blinded review committee prior to database lock. In the event of study drug administration error, the subject will be omitted from the PP population.

2.2.6 Baseline Characteristics/Medical History

Demographics – age (years), race, ethnicity and baseline height, weight BMI and baseline maximum daily pelvic pain will be summarized by treatment group and overall for the ITT, Safety, and PP Populations.

Medical History will be coded using the MedDRA dictionary terms and will be summarized by SOC and PT by treatment group and overall for the ITT Population.

2.2.7 Subject Disposition

All subjects enrolled into the study that are issued a subject number will be accounted for in Subject Disposition. Data will be tabulated by treatment group and overall and the numbers and percentages of subjects in each treatment group

who are enrolled, randomized and treated, who comprise each of the analysis populations, who complete the study or discontinue from treatment or discontinue from the study prematurely along with the reason for discontinuation will be presented. The number of subjects who were seen at each specified study visit will also be tabulated by treatment group and by site.

Reasons for any early withdrawals and the last date of dosing completed prior to discontinuation will be provided in a listing.

2.2.8 Protocol Deviations

Protocol deviations (major and minor) will be defined prospectively prior to database lock by a review committee who is blinded to treatment assignment. Deviations will not be entered by the clinical sites into the EDC database. Instead, they will be tracked separately by the ProTrial's clinical personnel. This process will be defined in detail in the ProTrial's separate Protocol Deviation Plan document. Major protocol deviations as well as those deviations that could possibly affect the interpretation of the primary endpoint (subset of major deviations) will be tabulated by treatment group and overall. All deviations will be presented in listings. All deviations will be classified and excluded from the PP analysis.

2.2.9 Dose Regimen

Two AQX-1125 100 mg tablets will be administered orally once daily, around the same time of day, with food or eat a light meal no more than 4 hours prior to consumption, for 12 weeks. Matching placebo is identical in appearance to the test product and contains no active ingredient and will be administered the same as AQX-1125. Tabulations of exposure to study medication are described in Section 2.2.15.1, Extent of Exposure. Details of study medication use will be provided in a subject data listing.

2.2.10 Methods for Handling Missing Data

2.2.10.1 Missing Daily Data in the Weekly Scores

For endpoints which are the average of a daily score across a week (e.g., maximum daily pain and average daily pain), if the subject has 4 or more non-missing values in that week, the weekly mean score will be calculated as the average of the non-missing values, otherwise the weekly mean score will be set to missing for that week.

2.2.10.2 Imputation Methods

The primary endpoint analysis method is a mixed model for repeated measures (MMRM) ANCOVA. This is an observed case approach to missing data and assumes the missing data is missing at random (MAR).

Sensitivity analyses for the primary efficacy analysis will include imputing the missing data using two multiple imputation (MI) methods (described below). Any sensitivity analyses performed will be considered supportive analyis.

- Multiple Imputation Assuming Missing at Random: Missing post-baseline weekly maximum daily pelvic pain (mean) change from baseline scores at Weeks 6 and 12 will be imputed via MI assuming (MAR). SAS Proc MI using the linear regression method will be the method for the imputation if the missing data pattern follows a monotonic pattern. If the data does not follow a monotonic pattern a sequential approach to imputing the variables to produce a monotone missing data pattern as described in Alut (2012) will be applied.

  A default random number generator of 345353 will be used and 100 imputed datasets will be created. Each of the imputed datasets will be analyzed via the same model as the primary efficacy endpoint analysis (See Section 2.2.13.1). The range of the imputed pain values will be set between 0 and 10 via the SAS Proc MI Maximum and Minimum options. The results across the multiple imputed data sets will be combined using SAS Proc MIANALZYE.

  The following are the set of variables to be used in the MI model:
  - treatment group (placebo/AQX-1125)
  - age group (<65, 65-<75, ≥75 years)
  - race (White/Non-White)
  - baseline daily pelvic pain score
  - experienced a severe AE (yes/no) (CTCAE grade 3-5, severe, life-threatening or death)
  - duration of exposure [last day-first day] +1

  For the ‘experienced a severe AE’ imputation variable, if a subject experiences a severe AE from baseline to Week 6 the value will be ‘yes’ for the imputation of the Week 6 time-point, ‘no’ otherwise. Similarly, if a subject experiences a severe AE from Baseline to Week 12 the value will be ‘yes’ for the imputation of the Week 12 time-point, ‘no’ otherwise.

Note: if the MI model does not converge or produce estimates (i.e., due to over-specification) the set of imputation variables may be modified.

- Multiple Imputation Assuming Missing Not at Random: For this imputation the missing weekly maximum daily pelvic pain (mean) change from baseline scores will be imputed at Weeks 6 and 12 assuming the data follow a Missing Not at Random (MNAR) pattern. The imputation of weekly mean change from baseline pain scores in the AQX-1125 treatment group will be based on the distribution in the placebo group. This method assumes that the trajectory of withdrawals from the AQX-1125 treatment arm follows the distribution of the placebo subjects. Placebo-based imputation will be implemented by the sequential modelling approach via PROC MI (O'Kelly & Ratitch., 2014). Missing change from baseline endpoint values will be imputed using the distribution of the non-missing placebo group values. SAS Proc MI using the linear regression method will be the method for the imputation if the missing data pattern follows a monotonic pattern. If the data does not follow a monotonic pattern a sequential approach to imputing the variables to produce a monotone missing data pattern as described in Alut (2012) will be applied.

  A default random number generator of 345354 will be used and 100 imputed datasets will be created. Each of the imputed datasets will be analyzed via the same model as the primary efficacy endpoint analysis (See Section 2.2.13.1). The range of the imputed pain values will be set between 0 and 10 via the SAS Proc MI Maximum and Minimum options. The results across the multiple imputed data sets will be combined using SAS Proc MIANALZYE.

  The set of variables for the MI model is the same set as defined for the MAR MI imputation.

  Note: if the MI model does not converge or produce estimates (i.e., due to over-specification) the set of imputation variables may be modified.

2.2.11 Safety Monitoring

No safety monitoring committees are planned for the study.

2.2.12 Interim Analysis

There are no formal interim analyses planned for this study, however, there will be an interim database freeze/lock of the study data after all subjects have completed their Off-Treatment Safety Follow-up Visit (Week 16). After this interim freeze/lock occurs, unblinding will occur and CTDS will produce the unblinded TLFs, except for the safety ophthalmic follow-up results. Once the final data has been collected and cleaned, the database will be locked and the ophthalmic safety results will be produced using the final, locked data. Blinded data review will occur periodically throughout the study (i.e. 50% of subjects who completed week 16, 75% of subjects who completed week 16) and any results that are produced will be clearly marked as "Blinded".

2.2.13 Efficacy Analyses

The primary efficacy analysis population will be the ITT Population.

2.2.13.1 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 numerical rating scale (NRS) pain score recorded daily by an eDiary.

Average maximum pain scores will be summarized by week for each of the planned 12 weeks of treatment, for each treatment group. The results will be reported in a table and also graphically.

The primary analysis will use data from week 6 and week 12, based on actual clinic visit dates. If a subject has at least 4 recorded maximum pelvic pain scores in the 7 days prior to a clinic visit, the mean of the available scores will be calculated to be that subject's value in the primary efficacy analysis. These values will differ slightly from the weekly reported pain score, if a subject's clinic visit is not on the exact target date.

Comparison of AQX-1125 to placebo at Week 12 for the primary efficacy endpoint will use MMRM. SAS PROC MIXED will be used with the observed change from baseline score at Week 6 and Week 12 as dependent variables. The model will include the baseline NRS score as a fixed effect covariate with fixed effect categorical factors for treatment group, visit and baseline×visit and treatment×visit interactions. The interactions will remain in the model regardless of significance. Treatment group comparisons at each visit (including the primary analysis endpoint at the Week 12 visit) will be estimated by least squares (LS) means differences with accompanying p-values and 95% CIs.

An unstructured covariance pattern will be used to estimate the variance–covariance of the within-subject repeated measures. Sample SAS code for the primary efficacy endpoint analysis is provided in Appendix B – Sample MMRM Code.

2.2.13.2 Supplementary Analysis to the Primary Endpoint

The following supplementary analysis will be provided to support the primary efficacy analysis.

- The primary efficacy analysis will be performed on the PP Population
- The primary efficacy analysis will be performed on the ITT Population based on MI MAR data imputation (see Section 2.2.10.2)
- The primary efficacy analysis will be performed on the ITT Population based on MI MNAR data imputation (see Section 2.2.10.2)
- The primary analysis will be repeated using each observed daily value of pelvic pain score, through day 84. For this analysis, weekly average pain score will not be used, but reported daily values will be to estimate daily change from baseline values. This analysis will be an MMRM on the PP Population using Observed Cases. The model will include the baseline NRS score as a fixed effect covariate with fixed effect categorical factors for treatment group, visit and baseline×day and treatment×day interactions. Here visit is a weekly level variable. Treatment group comparisons at each day will be estimated by least squares (LS) means differences with accompanying p-values and 95% CIs. Treatment group comparisons at each day will be estimated by least squares (LS) means differences with accompanying p-values and 95% CIs. The model will adjust for the multiple subject observations using a REPEATED statement in SAS Proc Mixed

  An unstructured covariance pattern will be used to estimate the variance–covariance of the within-subject repeated measures. If the model does not converge a different covariance structure (i.e., one with less parameters to estimate) will be applied.
- The weekly maximum daily pelvic pain (mean) scores and change from baseline values will be summarized by treatment group for each of the 12 weeks in the treatment period. This summary may differ slightly from the primary analysis, since the primary analysis uses the values at week 6 and week 12 from the 7 days prior to the actual clinic

visit, while this analysis will use values from the weekly visits (days 1-7, days 8-14, days 15-21, etc.).

2.2.13.3 Secondary Endpoints

P values for secondary endpoints will be used for descriptive purposes rather than for statistical inference; therefore, no adjustments for multiplicity will be utilized.

The following four change from Baseline to Week 12 endpoints will be analyzed in a manner similar to the primary efficacy analysis as described in Section 2.2.13.1:

(1) NIH-CPSI pain subscale (pain, urinary symptoms and quality of life impact) and all domains total score
- Total score (score range 0-43)
- Pain: Total of items 1a, 1b, 1c, 2a, 2b, 3, 4 (score range 0-21)
- Urinary Symptoms: total of items 5 and 6 (score range 0-10)
- QoL Impact: total of items 7,8 and 9 (score range 0-12)

NIH-CPSI data are collected on a paper form at each planned clinic visit.

(2) Male sexual health as measured using the International Index of Erectile Function Questionnaire, Erectile Function domain (IIEF-EF): The IIEF-EF score is the sum of the ordinal responses to the 5 items

IIEF-EF data are collected on a paper form at each planned clinic visit.

(3) Mean of average daily pelvic pain scores (eDiary), average pelvic pain (in clinic), and maximum daily pelvic pain (in clinic).

Average and maximum daily pelvic pain are collected on the eDiary, and also on a paper form at each planned clinic visit. Analysis of data collected on paper at the planned clinic visits will be used to confirm results from the analysis of data collected on the eDiary.

(4) 24-hour voiding frequency
For each of the scheduled assessment periods, the voiding frequency will be the last 24-hour period in which voiding is collected (i.e., if voiding is collected in more than one 24-hour period).

The following four-time course secondary endpoints will be assessed by MMRM model where 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) is the dependent variable:

(1) Mean of maximum daily pelvic pain score (eDiary)

(2) NIH-CPSI pain subscale and all domains total score

(3) IIEF-EF

(4) Mean of average daily pelvic pain scores (eDiary), average and maximum pelvic pain (Paper-based NRS in clinic)

The MMRM model to assess time course will have treatment as a factor, the corresponding baseline value as a covariate, a linear term for time (in weeks), and a time×treatment interaction effect term. The model will allow for a subject random intercept and slope over time with an unstructured correlation matrix. Sample SAS code for the time course MMRM is provided in Appendix B – Sample MMRM Code.

For response to treatment as measured by the GRA and PGI-C at Week 12 (Visit 4), the frequency distribution of each response scale will be presented by treatment group and assessed using a chi-square row mean score difference test.

- The GRA response is a 7-point Likert scale (range: -3 to 3) with a score of -3 indicating "Markedly Worse", a score of 0 indicating "No Change", and a score of 3 indicating "Markedly Improved" to the question: *As compared to when you started the study drug, how would you rate your Chronic Prostatitis / Chronic Pelvic Pain Syndrome symptoms now?*

- The PGI-C response is a 7-point Likert scale (range: 1 to 7) with a score of 1 indicating "Very much improved", a score of 4 indicating "No change", and a score of 7 indicating "Very much worse" to the item: *Choose the response that best describes the overall change your pelvic pain since you started the study*.

- The PGI-S response is a 5-point ordinal scale with a score of 1 being "None" and a score of 5 being "Very Severe" to the item: *Choose the response that best described the severity of your chronic prostatitis / chronic pelvic pain symptoms over the past week*.

For response to treatment as measured by the PGI-S at Week 12 (Visit 4), the frequency distribution of each response scale will be presented by treatment group and the change from baseline will be assessed by an ANCOVA model with treatment as a factor and baseline PGI-S as a covariate.

For the following two dichotomous secondary efficacy endpoints the rates for each treatment group and difference between the treatment groups will be presented with corresponding 95% CIs. A CMH test will be used to test for differences in rates between the treatment groups controlling for baseline pelvic pain. The baseline pelvic pain will be stratified into 2 categories (4-7 and >7):

(1) Treatment response as defined by meeting either of the following:
- Decrease in maximum daily pelvic pain (mean) from Baseline to Week 12 using a standardized 11-point NRS with no change in the amount or strength of concomitant analgesic medications (as defined in Section 2.2.14).
- 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 (as defined in Section 2.2.14).

(2) A ≥30% and ≥50% improvement (decrease) in maximum daily pelvic pain (mean) (using the 11-point NRS recorded by eDiary and the NIH-CPSI pain subscale), at Weeks 6 (Visit 3) and 12 (Visit 4).

For the Discontinuation of study medication due to treatment failure endpoint, only summary statistics will be provided for the percent meeting treatment failure criteria and the time to event (no inferential analyses will be performed). Time to discontinuation of study medication due to treatment failure will be summarized and presented graphically using Kaplan-Meier methods (i.e., SAS PROC LIFETEST stratifying on treatment group).

The frequency distribution of the 5-category IIEF-EF score will be presented by treatment group for Week 12 as well as a shift table from Baseline. The 5 categories are no erectile dysfunction (score: 26-30), mild erectile dysfunction (score: 22-25), mild to moderate erectile dysfunction (score: 17-21), moderate erectile dysfunction (score: 11-16) and severe erectile dysfunction (score: 1-10). Responses to all items must be completed to calculate anIIEF-EF score. Any response with missing values will be excluded from the analyses. Treatment group difference

with corresponding 95% CIs in the 5-category IIEF-EF will be assessed by a Cochran-Mantel-Haenszel (CMH) test using row mean scores controlling for Baseline IIEF-EF score.

Data from both treatment arms will be used to calculate a meaningful change threshold (MCT), which reports a change in the primary endpoint (change in maximum daily pelvic pain) by anchoring to other outcomes (including PGI-S and/or PGI-C) to determine a change in maximum pelvic pain that provides a meaningful benefit to patients. The determination of the MCT will be made outside of the methods documented in this SAP prior to database lock. Once the MCT is determined, the proportion of subjects who have an improvement of at least the MCT will be summarized by treatment group and compared using a chi-square test as an exploratory analysis.

2.2.14 Concomitant Analgesic Medication Change Definitions

Concomitant analgesic medication use for each subject will be programmatically categorized from the eDiary data using the following definitions:

(1) No change in the amount or strength of concomitant analgesic medications
- For each concomitant analgesic medication the subject is taking at Baseline, the average daily dose change from Baseline to Week 12 is within 15% of the average daily dose in the 7 days prior to Baseline *and*
- No new concomitant analgesic medications are started at any time after baseline until week 12 *and*
- No concomitant analgesic medications are discontinued at any time after baseline until week 12

(2) Decrease in the amount or strength of concomitant analgesic medications
- For at least one concomitant analgesic medication the subject is taking at Baseline, the average daily dose change from Baseline to Week 12 has decreased by at least 15% of the average daily dose in the 7 days prior to Baseline *and*
- For all other concomitant analgesic medication the subject is taking at Baseline, the average daily dose change from Baseline to Week 12 does not increase by >15% of the average daily dose in the 7 days prior to Baseline *and*
- No new concomitant analgesic medications are started at any time after baseline until week 12 unless a non-opioid analgesic

medication is added and an opioid analgesic is discontinued (i.e., a non-opioid replaces an opioid analgesic medication as described below).

(3) Increase in the amount or strength of concomitant analgesic medications

- For at least one concomitant analgesic medication the subject is taking at Baseline, the average daily dose change from Baseline to Week 12 is >15% of the average daily dose in the 7 days prior to Baseline *or*
- A new concomitant analgesic medication is started at any time after baseline until week 12, unless a non-opioid analgesic medication is added and an opioid analgesic is discontinued (i.e., a non-opioid replaces an opioid analgesic medication as described below).

If any non-opioid analgesic is added but simultaneously (within two days) an opioid analgesic is permanently discontinued, this will not be considered an increase in the amount or strength of concomitant analgesic medications; instead, it will be considered a decrease.

A separate blinded assessment of concomitant analgesic use will be provided following a manual review. For this manual review, a charter will be prepared describing the process. Individuals with knowledge and training will review concomitant analgesic data from each individual subject and classify each subject as having a decrease, no important change, or an increase in concomitant medications. This assessment will be used in a separate analysis supportive of the programmatic assessment.

2.2.15 Safety Analyses

Safety analyses will be based on the Safety Population and be presented by treatment groups. Only descriptive statistics will be presented and inferential statistical testing will not be performed.

2.2.15.1 Extent of Exposure and Compliance

Extent of exposure to study medication will be tabulated by treatment group. Duration of exposure will be calculated as last day of exposure minus the first day of exposure +1. Exposure will be summarized by treatment group for the safety population.

Compliance will be assessed by pill counts. The number of tablets dispensed and the number of tablets returned will be calculated. Compliance will be calculated by subtracting the number of returned

tablets (number of tablets taken) from the number of tablets dispensed (minus extra tablets dispensed) and then dividing the difference by the number of tablets that should have been taken (two for each day on study). The result will be multiplied by 100%. Compliance will be calculated over the entire duration of exposure.

2.2.15.2 Adverse Events

Counts and percentages of subjects who experienced any of the following will be presented by treatment group and overall: any AE, any drug related AE, discontinuations of study participation due to an AE, any serious adverse events (SAE), deaths, drug related SAEs, and treatment-emergent AE of special interest (TEAESI). Only those adverse events determined to be treatment emergent (TEAE) will be presented. Treatment emergent adverse events are those events with the date and time of AE onset being greater than the date and time of first dosing, and (other than TEAESIs) only those with an onset date within 28 days after the last date of dosing.

Verbatim terms on the case report forms will be linked to preferred terms and related body systems using the MedDRA Coding Dictionary version 20.0. The number and percentage of subjects who experience treatment-emergent adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall. Adverse events will be counted only once for a subject within each Preferred Term and System Organ Class; thus, since a subject may have more than one Preferred Term within an SOC, percentages of PT may not sum to the percentage in the SOC. If a subject reports an AE with a Preferred Term multiple times with differing severities, only the most severe is counted. If a subject reports an AE with a Preferred Term multiple times with differing relationships to study medication, only the one related to study drug is counted. Drug-related adverse events are defined as having a causality rating of being probable or possible.

All reported AEs will be tabulated as described above. For the overall AE table, number of adverse events will also be presented. In addition, a tabulation of adverse events that occur at a frequency of 2% or greater in any active treatment group at the SOC or PT level will be prepared.

AEs will also be tabulated by intensity/severity of the event (Grade 1 – mild/ Grade 2 – moderate/ Grade 3 – severe/ Grade 4 – life-threatening or disabling/ Grade 5 - death) and by Investigator's assessment of relationship to study medication (Probable, Possible or Unlikely). Adverse events judged by the Investigator to be Serious Adverse Events

(SAEs), SAEs resulting in death, AEs (regardless of seriousness) that require modification to study medication dosing (interruption or discontinuation) will also be tabulated by SOC and PT.

2.2.15.2.1 Serious Adverse Events

The number and percentage of subjects experiencing a Serious Adverse Event (SAE) will be tabulated by SOC and PT by treatment group and overall. SAEs will be counted only once for a subject within each PT and SOC.

2.2.15.2.2 Deaths

A listing of subjects who die while on study will be prepared along with the adverse event associated with the cause of death.

2.2.15.2.3 Interruptions or Discontinuations of Study Medication Due to an AE

A listing of subjects who have changes to their study medication dosing will be prepared.

2.2.15.2.4 Ocular Treatment Emergent AEs of Special Interest

As defined in protocol Section 9.3.5.5 the following Ocular AEs will be treated as TEAESIs:

- A Class II or Class III grading shift in LOCS III as defined in the Ophthalmology Manual compared to Baseline. A class II or III grading shift will be programmatically derived from the fields captured on the eCRFs in accordance with the Rosiptor Ophthalmology Manual which is the following:
    - Class II: Increase in LOCS III grade of ≥ 0.9 (NO), ≥ 1.0 (C), or ≥ 0.9 (P)
    - Class III: Increase in LOCS III grade of ≥ 1.2 (NO), ≥ 1.5 (C), or ≥ 1.5 (P)
- 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. Ocular TEAESIs will be assessed by an independent, blinded adjudicator.

The number and percentage of subjects who experience a TEAESI will be tabulated by System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall.

2.2.15.2.5 Ophthalmic Safety

Ophthalmic safety will be summarized by treatment groups and overall at Baseline, Week 12, Week 16 and 6 months post last dose: assessment of lenticular opacification using LOCS III grading system, best corrected visual acuity (BCVA) using the LogMar chart (i.e., after manifest refraction), and Intraocular Pressure (IOP) before and after dilation. Summaries will also be provided at early termination, although such summaries are acknowledged to not be a representative sample of the distribution. Number and percentage of subjects detected with corneal stain and abnormal slit lamp examination results will be presented at Baseline, Week 12 and 6 months post last dose.

2.2.15.2.6 Analysis of LOCS III

Change from baseline in LOCS III score to each scheduled visit will be summarized by treatment group. Incidence of class events (Class I, Class II and Class III) will be summarized. Incidence of cumulative events (at least a Class I event, at least a Class II event and a Class III event) will be summarized and p-values will be provided for descriptive purposes, using a chi-square test. The definition of class I, II and III events are described in the Rosiptor Ophthalmology Manual.

The LOCS III grading system values will also be analyzed by means of a longitudinal MMRM model which accounts for the between-eye correlation. The details of this MMRM is provided in Appendix C – LOC III Grading System MMRM Analysis.

2.2.15.3 Laboratory Data

Shift tables will be presented showing the shift in (Normal/Low/High) from baseline to Week 12, off treatment follow-up and early termination visit by treatment group.

2.2.15.4 Vital Signs, 12-Lead ECG, physical examination and Other Observations Related to Safety

Vital signs include blood pressure and heart rate. Actual values and change from baseline will be tabulated by treatment group at baseline and each post-baseline.

Shift tables will be provided for ECG data (Normal/Abnormal) from Screening Visit to Week 12, off treatment follow-up and early termination visit by treatment group.

Physical Examination Findings will be presented in the listings but not tabulated.

2.2.15.5 Concomitant Medications

Concomitant Medications will be coded per the WHO Drug Dictionary B3 Global (version effective March 2017). Concomitant Medications will be tabulated by treatment group, Drug Class (pharmacological level, ATC3) and Drug Name (chemical substance level, ATC5). These data will be provided in subject data listings along with the verbatim drug term and usage details.

Use of concomitant analgesic medication will be summarized with the percentage (%) of subjects taking each class of medication using subjects who took any such medication on at least 1 of the 7 days prior to the Baseline, Week 6 or Week 12 Visit).

References

O'Kelly, M., & Ratitch, B. (2014). *Clinical Trials with Missing Data: a Guide for Practitioners.* Wiley.

Alut, K. *Multiple Imputation for Ordinal Variables: A Comparison of SUDAAN PROC IMPUTE and SAS® PROC MI*, SESUG 2012, Paper SD-12, 2012.

3 Document Version Control

Revision History:

REVISION	RELEASE DATE	AUTHOR	SUMMARY OF CHANGES
A	June 25, 2018	Jim MacDougall, PhD	Initial Release

Appendix A - Programming Specifications for Tables and Listings

The following specifications will be used in the production of tables and listings.

1. Page Setup

   Unless otherwise noted, tables and listings will use landscape orientation. Margins will be at least 1.5 inches on the bound side and at least 1 inch on the other three sides.
   The following header information should be included:
   - Upper left: Sponsor name and protocol number
   - Center: CONFIDENTIAL
   - Upper right: Page number shown as Page n of N. Page numbers should be sequential within a table or listing.

   The footer should include:
   - The name of the SAS program used to generate the output along with the run date/time and the words "by CTDS".
   - For tables, the corresponding listing number(s).
   - For figures, the corresponding table number.

2. Footnotes

   Unless otherwise specified, footnotes should appear on all pages within the table.

3. Font

   Font will be 8-point Arial, or smaller if needed for space constraints. If possible, small tables should appear on one page. If tables continue on to multiple pages, there should be a page break after an assessment so that all the statistics for an assessment appear on the same page.

4. Tables

   Table titles should reflect the content of the table. Under the main title, in parentheses, the name of the analysis population being summarized should appear.

   4.1 Summary Statistics - Continuous Data

   Unless otherwise noted, the mean and median and confidence interval (CI) of a set of values should be printed out to one decimal place more than the original value. The standard deviation should be printed out to 2 decimal places more than the original value. The number of subjects on whom the parameter is assessed should appear. Minimum and maximum should be consistent with the original value. P-values will be

expressed as 4 decimal places. Any p-values that get calculated as 0.00005 or less should be expressed as P <0.0001.

4.2 Summary Statistics - Categorical Data

Numbers of subjects are reported as whole numbers. Null counts are represented as 0. Table percentages should be reported to one decimal. Null percentages will be suppressed (i.e., just showing the null count of 0).

For all categories, the total number of subjects with data will be presented as N and the number of subjects with non-missing data will be used as the denominator for the calculation of the percentages, unless otherwise stated in a footnote.

5. Subjects Included in Listings

In general, subject data listings should include all subjects who signed the informed consent. If a listing includes a subset of subjects who meet a certain condition (e.g., subjects with SAEs) then this should be clear from the title of the listing. If there are no subjects who meet the condition (e.g. no subjects with SAEs) for either the tables or the listings, then a page marker should appear stating that no subjects met the criteria.

Appendix B – Sample MMRM Code

The following is sample SAS Proc Mixed code to be used for the primary endpoint analysis.

```
**-------------------------------------------------------**;
** usubjid: subject identifier                           **;
** visit: visit identifier                               **;
** trt: treatment identified                             **;
** chg: change from baseline value                       **;
** base: baseline value                                  **;

proc mixed data=xxxx;
  class usubjid visit trt(ref='0');
  model chg = base visit trt base*visit trt*visit/s;
  repeated /subject=usubjid type=un;
  ** note: LS Mean analysis is primary analysis **;
  lsmeans trt trt*visit / diff cl;
  ods output LSMeans=LSMeans Diffs=diffs;
  where visit >0;
run;
```

The following is sample SAS Proc Mixed code for the MMRM to assess time course

```
**-------------------------------------------------------**;
** usubjid: subject identifier                           **;
** visit: visit identifier (numeric)                     **;
** trt: treatment identified                             **;
** chg: change from baseline value                       **;
** base: baseline value                                  **;

proc mixed data=xxxx;
  class usubjid trt(ref='0');
  model chg = base visit trt trt*visit/s;
  random intercept visit /subject=usubjid type=un;
  where visit >0;
run;
```

Appendix C – LOC III Grading System MMRM Analysis

The analysis of the LOCS III lens opacification data will use the following model:
Let y_{ijk}= LOCS III grade for the ith subject at the jth time point for the kth eye,

i = 1,…,100; j = 1,…,4; k = 1,2;
the visits corresponding to the values of j are:
1= Week 1 (baseline)
2=Week 12
3=Week 16
4=Week 38.

Note: if the subject has an early termination visit, that value will be included in the week corresponding to the next scheduled visit (i.e., either Week 12, 16, or 38).

Let t_j = time (weeks) at the jth time point;

t_j =0 if j=1
t_j =12 if j=2
t_j =16 if j=3
t_j =38 if j=4.

Let k = 1 for the right eye (OD), k= 2 for the left eye (OS).

Let x_i=1 if the ith subject is in the active treatment group, x_i= 0 if in the placebo group.

Let z_{il} = value of the ith covariate for the lth subject at baseline, where i = 1 for age (years).

Separately for each cataract type, the following MMRM will be fit:

$$y_{ijk} = \alpha + \beta_1 x_i + \beta_2 t_j + \underline{\beta_3} \underline{z_i} + \underline{\gamma_1} x_i t_j + \underline{\gamma_2} z_i t_j + e_{ijk}$$

where:

α	is the intercept parameter
β_1	is the difference in mean LOCSIII grade at baseline between the active and placebo groups
$\underline{\beta_2}$	is the rate of increase in LOCS III grade in the placebo group for each visit (Weeks 12, 16, and 38)
$\underline{\beta_2}+ \underline{\gamma_1}$	is the rate of increase in LOCS III grade in the active group for each visit (Weeks 12, 16, and 38)
$\underline{\beta_3}$	are the effects of covariates on baseline LOCS III grade
$\underline{\gamma_2}$	are the effects of covariates on the rate of change of LOCSIII grade over time for each visit (Weeks 12, 16, and 38).

note: underlining indicates a vector.

The primary parameter of interest is γ_1, the difference in the rate of increase in LOCS III grade between the active group and placebo group for post-baseline each scheduled visit (i.e., Weeks 12, 16, 38). A contrast statement, testing for a trend across time will also be calculated.

SAS PROC MIXED will be used to fit the model in based on the eye as the unit of analysis using the REPEATED option with a UN@UN correlation structure. This will enable control for correlation between-eyes and across time:

(a) Between LOCS III grade for two eyes of the same person at the same time
(b) Between LOCS III grade for the same eye over time
(c) Between LOCS III grade for one eye (e.g., OD) at one time and the fellow eye (e.g., OS) at a different time.

This analysis will be performed separately for each type of cataract (NO, C, P).

Sample SAS code is provided below:

```
**-------------------------------------------------------**;
** usubjid: subject identifier                           **;
** eye: eye identifier                                   **;
** trt: treatment                                        **;
** time: week of assessment                              **;
** aval: LOCS III Grade                                  **;

proc mixed data=xxxx;
  class usubjid eye(ref=1') time(ref='0') trt(ref='0');
  model aval = trt time age
               trt*time age*time /s;
  repeated time eye/subject=usubjid type=un@un;
   ** note: linear contrast statement for estimating the **;
   **       trend when the visits are 0, 6, 12, 16, 38   **;
   **       contrast constrained that sum of contrasts   **;
   **       coefficients =0, squared sum =1               **;
   estimate 'slope: trt-x-time'
        time -0.163771768 -0.018196863 0.782465115 -0.600496483
        trt*time -0.163771768 -0.018196863 0.782465115 -0.600496483 0 0 0 0
    /e;
run;
```