



Clinical trial results:

The LEADERSHIP 301 Trial: A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, 3 Arm, Parallel-Group, Phase 3 Trial to Evaluate the Efficacy and Safety of 2 Doses of AQX-1125 Targeting the SHIP1 Pathway in Subjects with Interstitial Cystitis/Bladder Pain Syndrome Followed by an Extension Period

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2016-000906-12 |
| Trial protocol | DK HU CZ LV GB BE ES NL |
| Global end of trial date | 06 September 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 03 January 2019 |
| First version publication date | 03 January 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | AQX-1125-301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02858453 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Aquinox Pharmaceuticals (Canada) Inc. |
| Sponsor organisation address | 450 - 887 Great Northern Way, Vancouver, Canada, V5T4T5 |
| Public contact | Clinical Operations, Aquinox Pharmaceuticals (Canada) Inc., +1 6046299223, clinical@aqxpharma.com |
| Scientific contact | Clinical Operations, Aquinox Pharmaceuticals (Canada) Inc., +1 6046299223, clinical@aqxpharma.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 June 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 May 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 September 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of 12 weeks of treatment with 2 different doses of oral AQX-1125 (100 mg or 200 mg) administered once daily compared to placebo on the change from Baseline (Visit 2) to Week 12 (Visit 4) in maximum daily bladder pain in subjects with IC/BPS using a standardized 11-point NRS pain score recorded daily by electronic diary (e-diary).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the "Declaration of Helsinki" and International Council on Harmonisation guideline on Good Clinical Practice (GCP). This clinical trial was reviewed and approved by the appropriate Regulatory Health Agency and Ethics Committee. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects were required to sign the informed consent form.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment | 15 July 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Poland: 33 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Czech Republic: 25 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | Hungary: 26 |
| Country: Number of subjects enrolled | Latvia: 27 |
| Country: Number of subjects enrolled | Canada: 32 |
| Country: Number of subjects enrolled | United States: 188 |
| Country: Number of subjects enrolled | Romania: 73 |
| Worldwide total number of subjects | 433 |
| EEA total number of subjects | 213 |

Notes:

| Subjects enrolled per age group | |
|-------------------------------------------|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 348 |
| From 65 to 84 years | 85 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 12 countries: Belgium, Canada, Czech Republic, Denmark, Hungary, Latvia, Netherlands, Poland, Romania, Spain, United Kingdom and United States.

Pre-assignment

Screening details:

A total of 433 subjects with IC/BPS were enrolled across 86 Clinical Research Centers in North America and Europe. The 12-week Treatment period was followed by an extension period planned for 52 weeks

Period 1

| | |
|------------------------------|-------------------------------------------|
| Period 1 title | 12 Week Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Carer, Assessor, Subject |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

2 placebo tablets (matching AQX-1125 tablets), taken orally, once daily for 12 weeks

| | |
|----------------------------------------|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 placebo tablets, oral, once daily for 12 weeks

| | |
|------------------|-----------------|
| Arm title | AQX-1125 100 mg |
|------------------|-----------------|

Arm description:

2 tablets (1 x AQX-1125 100mg tablet and 1 x matching placebo tablet), taken orally, once daily for 12 weeks

| | |
|----------------------------------------|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | AQX-1125 100 mg |
| Investigational medicinal product code | |
| Other name | rosiptor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 tablets (1 x AQX-1125 100mg tablet and 1 x matching placebo tablet), taken orally, once daily for 12 weeks

| | |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 x placebo tablets, oral, once daily for 12 weeks

| | |
|---------------------------------------------------------------------------------------------------|-----------------|
| Arm title | AQX-1125 200 mg |
| Arm description: 2 tablets (2 x AQX-1125 100mg tablets), taken orally, once daily for 12 weeks | |
| Arm type | Experimental |
| Investigational medicinal product name | AQX-1125 200 mg |
| Investigational medicinal product code | |
| Other name | rospitor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 tablets (2 x AQX-1125 100 mg tablets), taken orally, once daily for 12 weeks

| Number of subjects in period 1 | Placebo | AQX-1125 100 mg | AQX-1125 200 mg |
|---------------------------------------|---------|-----------------|-----------------|
| Started | 144 | 145 | 144 |
| Completed | 134 | 129 | 122 |
| Not completed | 10 | 16 | 22 |
| Consent withdrawn by subject | 8 | 8 | 7 |
| Adverse event, non-fatal | 1 | 4 | 8 |
| Not Specified | 1 | - | 3 |
| Pregnancy | - | 2 | - |
| Non-compliance with study drug | - | 1 | 1 |
| Lost to follow-up | - | - | 1 |
| Randomized, did not take drug | - | 1 | 1 |
| Lack of efficacy | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| 2 placebo tablets (matching AQX-1125 tablets), taken orally, once daily for 12 weeks | |
| Reporting group title | AQX-1125 100 mg |
| Reporting group description: | |
| 2 tablets (1 x AQX-1125 100mg tablet and 1 x matching placebo tablet), taken orally, once daily for 12 weeks | |
| Reporting group title | AQX-1125 200 mg |
| Reporting group description: | |
| 2 tablets (2 x AQX-1125 100mg tablets), taken orally, once daily for 12 weeks | |

| Reporting group values | Placebo | AQX-1125 100 mg | AQX-1125 200 mg |
|----------------------------------------------------|---------|-----------------|-----------------|
| Number of subjects | 144 | 145 | 144 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 117 | 118 | 113 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Adults (65-80 years) | 27 | 27 | 31 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 48.9 | 50.1 | 49.9 |
| standard deviation | ± 15.25 | ± 14.94 | ± 14.90 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 114 | 114 | 113 |
| Male | 30 | 31 | 31 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | 11 | 7 |
| Not Hispanic or Latino | 136 | 134 | 136 |
| Unknown or Not Reported | 2 | 0 | 1 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 2 | 1 |
| Asian | 1 | 2 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 1 |
| Black or African American | 5 | 5 | 4 |

| | | | |
|-----------------------------------|---------|---------|---------|
| White | 137 | 135 | 137 |
| More Than One Race | 0 | 1 | 1 |
| Hunner Lesion | | | |
| Units: Subjects | | | |
| Presence | 34 | 29 | 32 |
| Absence | 110 | 115 | 112 |
| Not Reported | 0 | 1 | 0 |
| BMI | | | |
| Body Mass Index | | | |
| Units: kilogram(s)/square meter | | | |
| arithmetic mean | 27.3 | 26.4 | 27.4 |
| standard deviation | ± 5.98 | ± 5.69 | ± 5.93 |
| Duration of Diagnosis with IC/BPS | | | |
| Units: Years | | | |
| arithmetic mean | 3.90 | 4.93 | 4.55 |
| standard deviation | ± 4.319 | ± 4.721 | ± 4.915 |

| | | | |
|-------------------------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 433 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 348 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Adults (65-80 years) | 85 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 341 | | |
| Male | 92 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 24 | | |
| Not Hispanic or Latino | 406 | | |
| Unknown or Not Reported | 3 | | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 4 | | |
| Asian | 3 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |

| | | | |
|-----------------------------------|-----|--|--|
| Black or African American | 14 | | |
| White | 409 | | |
| More Than One Race | 2 | | |
| Hunner Lesion | | | |
| Units: Subjects | | | |
| Presence | 95 | | |
| Absence | 337 | | |
| Not Reported | 1 | | |
| BMI | | | |
| Body Mass Index | | | |
| Units: kilogram(s)/square meter | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Duration of Diagnosis with IC/BPS | | | |
| Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: 2 placebo tablets (matching AQX-1125 tablets), taken orally, once daily for 12 weeks | |
| Reporting group title | AQX-1125 100 mg |
| Reporting group description: 2 tablets (1 x AQX-1125 100mg tablet and 1 x matching placebo tablet), taken orally, once daily for 12 weeks | |
| Reporting group title | AQX-1125 200 mg |
| Reporting group description: 2 tablets (2 x AQX-1125 100mg tablets), taken orally, once daily for 12 weeks | |
| Subject analysis set title | Placebo (Female Subjects Only) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Primary analysis was conducted on female subjects only | |
| Subject analysis set title | AQX-1125 100 mg (Female Subjects Only) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Primary analysis was conducted on female subjects only | |
| Subject analysis set title | AQX-1125 200 mg (Female Subjects Only) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Primary analysis was conducted on female subjects only | |

Primary: Change from Baseline of Maximum Daily Bladder Pain Score

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| End point title | Change from Baseline of Maximum Daily Bladder Pain Score |
| End point description: Change from Baseline for AQX-1125 100 mg or 200 mg compared to placebo in the maximum daily bladder pain score based on a standardized 11-point numeric rating scale (NRS) recorded by electronic diary (e-diary). The 11-point NRS ranges from 0-10 with 0 indicating 'no pain' and 10 indicating 'worst pain' | |
| End point type | Primary |
| End point timeframe: Baseline to 12 Weeks | |

| End point values | Placebo (Female Subjects Only) | AQX-1125 100 mg (Female Subjects Only) | AQX-1125 200 mg (Female Subjects Only) | |
|--------------------------------------|--------------------------------------|----------------------------------------------|----------------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 101 | 98 | 91 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -2.52 (± 2.681) | -2.07 (± 2.227) | -2.26 (± 2.635) | |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Mixed-Effects Growth Curve Model |
| Comparison groups | AQX-1125 100 mg (Female Subjects Only) v AQX-1125 200 mg (Female Subjects Only) v Placebo (Female Subjects Only) |
| Number of subjects included in analysis | 290 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4052 ^[1] |
| Method | t-test, 2-sided |

Notes:

[1] - Global Test p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from the signing of the informed consent until the 4 week safety follow up visit post last dose

Adverse event reporting additional description:

Adverse events were any unfavourable medical occurrence reported by the subject during the study. In addition, abnormal findings noted during the vital signs, ECG, physical or ophthalmology examinations deemed by the Investigator to be clinically significant were captured as adverse events.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

2 placebo tablets (matching AQX-1125 tablets), taken orally, once daily for 12 weeks

| | |
|-----------------------|-----------------|
| Reporting group title | AQX-1125 100 mg |
|-----------------------|-----------------|

Reporting group description:

2 tablets (1 x AQX-1125 100mg tablet and 1 x matching placebo tablet), taken orally, once daily for 12 weeks

| | |
|-----------------------|-----------------|
| Reporting group title | AQX-1125 200 mg |
|-----------------------|-----------------|

Reporting group description:

2 tablets (2 x AQX-1125 100mg tablets), taken orally, once daily for 12 weeks

| Serious adverse events | Placebo | AQX-1125 100 mg | AQX-1125 200 mg |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 144 (2.08%) | 4 / 144 (2.78%) | 3 / 143 (2.10%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 144 (0.69%) | 0 / 144 (0.00%) | 0 / 143 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Hernia | | | |
| subjects affected / exposed | 0 / 144 (0.00%) | 0 / 144 (0.00%) | 1 / 143 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Cataract nuclear | | | |
| subjects affected / exposed | 0 / 144 (0.00%) | 0 / 144 (0.00%) | 1 / 143 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 2 / 144 (1.39%) | 2 / 144 (1.39%) | 2 / 143 (1.40%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 144 (0.00%) | 1 / 144 (0.69%) | 0 / 143 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 144 (0.00%) | 1 / 144 (0.69%) | 0 / 143 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | AQX-1125 100 mg | AQX-1125 200 mg |
|-------------------------------------------------------|------------------|------------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 144 (8.33%) | 11 / 144 (7.64%) | 8 / 143 (5.59%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 144 (3.47%) | 8 / 144 (5.56%) | 5 / 143 (3.50%) |
| occurrences (all) | 5 | 8 | 5 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 144 (5.56%) | 4 / 144 (2.78%) | 3 / 143 (2.10%) |
| occurrences (all) | 9 | 4 | 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 June 2016 | <ul style="list-style-type: none">- Inclusion Criteria 9 is changed from requiring that males must use a condom for sexual intercourse until at least 28 days after the last dose of study drug, to requiring that males must use a condom for sexual intercourse until at least 90 days after the last dose of study drug.- Exclusion criterion 1 is changed from a catastrophizing pain score of 30 to ≥ 30.- Update to O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) Question 4- Pregnancy section 12.1.1.1.1 is updated to specify that male subjects, whose partner becomes pregnant during the study and up to 90 days after the last dose of study drug, are instructed to notify the Investigator. Investigators and other site personnel must report any pregnancy that occurs in female subjects and partners of male subjects within 24 hrs of when he or she becomes aware of it to Drug Safety and pregnant partners will be followed until the end of the pregnancy. |
| 19 October 2016 | <ul style="list-style-type: none">- Removal of 14-week extension period (EP) from protocol. All subjects will be eligible to continue into the 40-week open-label extension.- Addition of additional company signatory.- Expansion of potential study participant numbers (minimum of 300 female subjects randomized and maximum of 600 total subjects) and potential study sites to approximately 140 sites.- Recalculation of study timelines.- Addition of an Exploratory Objective to determine the Minimally Clinically Important Difference (MCID) for maximum pain using an anchor based analysis with a Global Response Assessment (GRA) as the anchor.- Add clarity to the definition of Treatment Failure and the Exploratory Objectives assessing proportion of subjects meeting this criterion.- Narrow required specific recorded findings on cystoscopy reports.- Added clarity around follow-up visit timing for subjects participating in the extension period.- Clarity and specificity added to Inclusion Criteria #9 regarding complete abstinence and acceptable methods of contraception.- Updated language in Exclusion Criteria #3 regarding microscopic hematuria- Exclusion Criteria #5 updated to further restrict use of cyclosporine.- From Exclusion Criteria #7, 8 and 9, removed 5-year historical limitation on exposure to some excluded medications or presence of some exclusionary medical conditions.- Table 9.3 Removal of "Expected" from Treatment Emergent Adverse Events table title.- Section 9.5.5 Study Discontinuation language modified based on regulatory requirements.- Section 19 Publication Policy added reference to posting of the trial results to the European Union (EU) Clinical Trials Register |

| | |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 April 2017 | <ul style="list-style-type: none"> - Extension of the 40-week extension period (EP) to 52 weeks for all treatment arms. All subjects will be eligible to continue into the 52-week extension. - Added 64-week visit (Visit 10) to perform end of treatment activities previously planned for Visit 9. Updated throughout protocol. - Safety objectives updated to the following: Safety and tolerability of AQX-1125 during the 52-week extension period (EP). Safety and tolerability of AQX-1125 over 64 weeks of treatment (combined TP and EP). -Exploratory objective updated to the following: "Evaluation of the proportion of subjects improving by the derived minimum clinically important difference (MCID) in the maximum pain assessment at Week 12 by conducting an anchor-based analysis using the GRA for anchoring to derive the MCID". - Planned study period updated to reflect updated timelines. - Addition of GRA at Week 64 (Visit 10). - Added clarification and specificity to ocular adverse event reporting - Addition of a Follow-up Telephone Call 3 months post dose. - Addition of an Ophthalmology Safety Visit 6 months post dose. - Addition of the PHQ-9 questionnaire as a screening tool to all study visits up to completion of the EP. - Analysis of the primary efficacy endpoint is changed to analysis using a mixed-effects growth-curve model adjusting for fixed and random covariates (individual, change trajectory, baseline demographic values, and the stratification factors). |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only results for the primary endpoint are provided. As the global test for this endpoint was not statistically significant, confirmatory hypothesis testing was stopped and all subsequent treatment comparison performed was considered non-confirmatory.

Notes: