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 10 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	- 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	- 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	- 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: