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

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Primary ObjectiveThe 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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON45365

Source
ToetsingOnline

Brief title
The LEADERSHIP 301 Trial (AQX-1125-301)

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
bladder pain syndrome, Interstitial cystitis

Research involving
Human

Sponsors and support

Primary sponsor: Aquinox Pharmaceuticals (Canada) Inc.
Source(s) of monetary or material Support: the sponsor as indicated in part B of the ABR form.

Intervention

Keyword: AQX-1125, Interstitial Cystitis/Bladder Pain Syndrome, Phase 3, SHIP1 Pathway

Outcome measures

Primary outcome

The change from Baseline (Visit 2) at Week 12 (Visit 4) for AQX-1125 100 mg or

200 mg compared to placebo in the maximum daily bladder pain score based on a

standardized 11 point NRS recorded by e-diary as measured by the mean of the

maximum scores recorded once daily for a minimum of 5 of the 7 days prior to

each visit.

Secondary outcome

The key secondary endpoints are:

* The mean change from Baseline (Visit 2) at Week 12 (Visit 4) for AQX-1125 100

mg or 200 mg compared to placebo in the following:

o Voiding frequency measured over a 24-hour period, within a 3 day (72 hours)

window before Baseline (Visit 2) and again before Week 12 (Visit 4).

o ICSI.

o BPIC-SS.

* Overall response to treatment for AQX-1125 100 mg or 200 mg compared to placebo as measured by the subject*s GRA at Week 12.

Safety endpoints:

* The frequency and severity of AEs will be reported for the TP phase, the 52-week EP, and TP and EP combined, and will include:

o Abnormal, clinically significant vital signs, laboratory tests, ECG, weight, or findings on physical examinations.

* Ophthalmic examination, as defined in Section 12.6.

Exploratory endpoints:

* Evaluation of the proportion of subjects improving by the derived MCID in the maximum pain assessment at Week 12, for which an anchor based analysis using the GRA for anchoring will be conducted to derive the MCID.

* The change from Baseline (Visit 2) at Week 6 (Visit 3) for AQX-1125 100 mg or 200 mg compared to placebo in:

o Maximum daily bladder pain based on an 11-point NRS recorded by e-diary as measured by the mean of the maximum pain scores recorded once daily for a minimum of 5 of the 7 days prior to each visit.

o Voiding frequency measured over a 24-hour period, within a 3-day (72 hours) window before Baseline (Visit 2) and again before Week 6 (Visit 3).

o ICSI.

o BPIC-SS.

* Overall response to treatment for AQX-1125 100 mg or 200 mg compared to placebo as measured by the subject*s GRA at Week 6.

* The change from Baseline (Visit 2) at Week 6 (Visit 3) and Week 12 (Visit 4) for AQX 1125 100 mg or 200 mg compared to placebo in the following:

o ICPI.

o Average daily pain based on an 11-point NRS recorded by e-diary as measured by the mean of the average pain scores recorded for a minimum of 5 of the 7 days prior to each visit.

* The proportion of subjects with reduction from Baseline (Visit 2) for AQX-1125 100 mg or 200 mg compared to placebo, in maximum daily bladder pain as measured by the mean of the maximum pain scores recorded for a minimum of 5 of the 7 days prior to each visit:

o Of *30% at Week 12 (Visit 4) and Week 6 (Visit 3).

o Of *50% at Week 12 (Visit 4) and Week 6 (Visit 3).

* The change from Baseline (Visit 2) at Week 12 (Visit 4) for AQX 1125 100 mg or 200 mg compared to placebo in the following:

o EuroQol 5-Dimension 5-Level (EQ-5D-5L).

o Nocturia (number of episodes that subject had to wake and void).

* Overall response to treatment for AQX-1125 100 mg or 200 mg as measured by the subject*s GRA at Week 64. (Visit 10).

* Frequency (proportion of days) of daily use of rescue pain medications (during TP).

* Proportion of subjects who withdraw due to treatment failure (during TP).

Study description

Background summary

IC/BPS is a chronic condition of unknown etiology that involves bladder pain and usually urinary urgency, frequency and nocturia, with no evidence of infection. Although the disease is more prevalent in women (3.3 to 7.9 million) than men (2.1 to 4.6 million) in the United States (US), its frequency seems to be increasing with more defined approaches to diagnosis. IC/BPS results in a negative impact on quality of life (QoL), increased risk of mental health disorders and suicidal ideation, and increased health care costs. Several pharmacological treatments have been evaluated for IC/BPS; however, with conflicting results, there remains a large unmet need.

Study objective

Primary Objective
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 interstitial cystitis/bladder pain syndrome (IC/BPS) using a standardized 11-point numerical rating scale (NRS) pain score recorded daily by electronic diary (e-diary).

Secondary Objectives
The secondary objectives of this study are 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) for each of the following:
o Urinary voiding frequency over a 24-hour period.
o O*Leary-Sant Interstitial Cystitis Symptom Index (ICSI).
o Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS).
* Overall response to treatment for AQX-1125 (100 mg or 200 mg) compared to placebo as measured by the subject*s Global Response Assessment (GRA) at Week 12.

Safety Objectives
* The safety objectives of this study are to evaluate:
* Safety and tolerability of AQX-1125 compared to placebo during the 12-week treatment period (TP).
* 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 Objectives
The exploratory objectives of this study are to evaluate:
* 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. .
* The effect of treatment with once daily AQX-1125 (100 mg or 200 mg) compared to placebo on the change from Baseline (Visit 2) to Week 6 (Visit 3) for each of the following:
o Maximum daily bladder pain (using the 11-point NRS recorded by e-diary).
o Urinary voiding frequency over a 24-hour period.
o ICSI.
o BPIC-SS.
* Overall response to treatment for AQX-1125 (100 mg or 200 mg) compared to placebo as measured by the subject*s GRA at Week 6.
* The effect of treatment with once daily AQX-1125 (100 mg or 200 mg) compared to placebo on the change from Baseline (Visit 2) at Week 6 (Visit 3) and Week 12 (Visit 4) for each of the following:
o O*Leary-Sant Interstitial Cystitis Problem Index (ICPI).
o Average daily bladder pain score (using the 11-point NRS recorded by e-diary).
* The effect of treatment with once daily AQX-1125 (100 mg or 200 mg) compared to placebo on the proportion of subjects with reduction from Baseline (Visit 2) in maximum daily bladder pain (using the 11-point NRS recorded by e-diary):
o Of *30% at Week 12 (Visit 4) and Week 6 (Visit 3).
o Of *50% at Week 12 (Visit 4) and Week 6 (Visit 3).
* The effect of treatment with once daily AQX-1125 (100 mg or 200 mg) compared to placebo on the change from Baseline (Visit 2) at Week 12 (Visit 4) for each of the following:
o Subjects* quality of life (QoL), assessed by the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire.
o Nocturia (number of episodes that subject had to wake and void).
* Overall response to treatment for AQX-1125 (100 mg or 200 mg) as measured by the subject*s GRA at Week 64 (Visit 10).
* Daily use of rescue pain medication during the 12-week treatment period (during TP).
* Withdrawal due to treatment failure (% meeting treatment failure criteria and time to event) (during TP).

Study design

This multi-center Phase 3 trial includes a 12-week randomized, double-blind, placebo controlled, parallel-group, treatment phase (TP) to compare the efficacy and safety of 2 doses (100 mg or 200 mg) of AQX-1125 versus placebo in up to 600 subjects with IC/BPS from approximately 140 Clinical Research Centers in North America and Europe. The 12-week TP is followed by an extension period of 52 weeks.

Intervention

In the treatment phase (TP) subjects are randomized (1:1:1) to receive a single daily oral dose of 2 tablets for 12 weeks as follows:
1. AQX-1125 200 mg dose group: AQX-1125 2 x 100 mg tablets or,
2. AQX-1125 100 mg dose group: AQX-1125 1 x 100 mg + 1 x placebo tablets or,
3. Placebo group: 2 x placebo tablets.

During the 52-week extension period (EP), subjects randomized to AQX-1125 in TP will continue on their assigned dose. Subjects who received placebo will be randomized (1:1) to one of the 2 following treatment arms:
1. AQX-1125 200 mg dose group: AQX-1125 2 x 100 mg tablets in EP or,
2. AQX-1125 100 mg dose group: AQX-1125 1 x 100 mg + 1 x placebo tablets in EP.

Study burden and risks

The results from the previous study (AQX-1125-201) suggest that subjects treated with AQX-1125 may experience a reduction in maximum daily bladder pain and an improvement in the most important IC/BPS symptoms over a 12-week treatment period. During the TP, one-third of subjects will receive placebo and thus not benefit from potential positive effects of AQX-1125. The 52 week EP will provide subjects with access to potentially beneficial study treatment for up to 15 months in total.

Based on the safety profile and potential treatment effect of AQX-1125, the proposed study is considered to have an acceptable benefit/risk ratio.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For inclusion in to 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/females, *18 and *80 years of age at Screening Visit 1.;3. Subjects who have consistently had symptoms of bladder pain in addition to urinary urgency and/or urinary frequency for more than 6 months (to ensure a properly established diagnosis).;4. Have had the clinical diagnosis, or history consistent with the diagnosis, of IC/BPS for >3 months but *20 years (to ensure a properly established diagnosis).;5. BPIC-SS minimum score as per the study protocol.;6. ICSI minimum score as per the study protocol.;7. Pelvic floor pain maximum score as per the study protocol on the 11-point NRS pain scale following a pelvic pain assessment (to discriminate between bladder pain and perineal/pelvic floor pain masquerading as bladder pain).;8. Must be capable of voiding independently (to allow completion of voiding diary over a 24 hour period).;9. Subjects must fulfil at least one of the following criteria:;* Males/females surgically sterile for a minimum of 6 months; or;o Females: Post-menopausal for a minimum of 1 year; or ;o If of child bearing potential, must have a negative pregnancy test and agree to avoid pregnancy and use a highly effective method of contraception with one additional barrier method of contraception from Screening Visit 1 to the final Follow-up Visit of the study (or until at least 28 days after the last dose of study drug has been taken). ;o Acceptable methods of highly effective contraception include non-hormonal intrauterine device, intrauterine hormone-releasing system or hormonal contraception (patch, injectable or implantable). Acceptable barrier methods include male condom, diaphragm, cap or sponge, or vasectomy of sole sexual partner.;o If using oral hormonal contraception, the barrier method used must include spermicide.;o True abstinence can be used as a method of contraception, when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.;o Males: Must use a condom for sexual intercourse from Screening Visit 1 until at least 90 days after last dose of study drug has been taken, unless they have been surgically sterilized (vasectomy).;10. Women of child bearing potential must have a negative pregnancy test at Screening Visit 1, Baseline (Visit 2) and throughout

the study.;11. Females are non-lactating (Screening Visit 1, Baseline [Visit 2] and throughout the study).;For inclusion into TP, subjects must meet the following criteria at Baseline (Visit 2):;12. Have minimum average daily pain score as per the study protocol on the 11-point NRS pain scale (mean of the average daily pain score recorded at each of the 7 days prior to Baseline [Visit 2]).;13. Minimum number of urinary voids as per the study protocol in a 24-hour period recorded within 3 days (72 hours) prior to Baseline (Visit 2).;14. Have undergone a cystoscopy within the last 36 months (inclusive) prior to Baseline (Visit 2). For cystoscopies performed prior to Screening Visit 1, results of that cystoscopy must be available and include presence or absence of Hunner Lesion and additional pathology.;* If the cystoscopy was performed for non-therapeutic purposes, it must have been performed at least 14 days prior to Screening Visit 1. ;* If the cystoscopy involved therapeutic hydrodistension, it must have been performed at least 3 months prior to Baseline (Visit 2). The results of that cystoscopy must be available and the information, particularly the presence or absence of Hunner Lesion will be collected; or;* If no cystoscopy has been performed prior to Screening Visit 1, the results are unavailable or do not meet the requirements of the protocol, the subject will have a cystoscopy (without hydrodistension) at Screening Visit 1a, within 14 days of Screening Visit 1 (with Baseline [Visit 2] occurring a minimum of 14 days and a maximum of 28 days after the screening cystoscopy at Screening Visit 1a).

Exclusion criteria

Subjects meeting any of the following criteria at Screening Visit 1 will not be eligible for study participation. However, subjects fulfilling criterion 2 will be eligible for rescreening:;1. Catastrophizing pain score over maximum score allowed per the study protocol as determined by the Pain Catastrophizing Scale (PCS).;2. Have had a urinary tract infection (UTI) including bacterial cystitis within the past 30 days (inclusive) or presence on laboratory C&S at Screening Visit 1. Subjects with current infection may be treated according to standard of care and rescreened at least 10 days after resolution of infection (and have a repeat urine C&S that was documented as clear).;3. Microscopic hematuria that has not been adequately evaluated per local standard of care.;4. History of chronic substance abuse, dependency or abuse of opiates, or other narcotics within the last 2 years. ;5. Currently receiving any of the following prohibited medications or procedures:;* Taken antihistamine or NSAID unless on a stable dose for *30 days prior to Screening Visit 1. ;* Taken any long-acting opiates within 2 weeks prior to Baseline (Visit 2) and throughout the study, or more than 10 short-acting opiates/month. If (short-acting) opiate analgesics are taken during the screening period they should be limited to a maximum of 2 days per week and not within 3 days prior to randomization. ;* Oral steroid or cyclosporine therapy within 30 days prior to Screening Visit 1 and throughout the study.;* Had treatment with intravesical therapy within 60 days prior to Screening Visit 1.;* Bladder hydrodistension and/or fulguration within 3 months prior to Screening Visit 1 and throughout the study.;* Have taken any investigational drug within 90 days prior to Screening Visit 1 or have had previous exposure to AQX-1125.;6. History of previous procedure(s) (augmentation cystoplasty, cystectomy, cystolysis, botulinum toxin or bladder catheterization) that has significantly affected bladder function.;7. History of cyclophosphamide or chemical cystitis, urinary tuberculosis or radiation cystitis.;8. Females: History of bladder tumors or uterine, cervical, vaginal or urethral cancer.;9. Males:

History of prostate surgery (transurethral resection of the prostate [TURP], transurethral radiofrequency thermotherapy [TURT], transurethral incision of the prostate [TUIP], transurethral needle ablation [TUNA], etc.), a history of prostate cancer, or currently being treated for chronic bacterial prostatitis. ;10. 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.;11. Major surgery within 3 months prior to Screening Visit 1.;12. Known intolerance to micro-crystalline cellulose (Avicel® PH-102), mannitol or other ingredient of AQX-1125 tablets.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AQX-1125
Generic name:	AQX-1125

Ethics review

Approved WMO Date:	01-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000906-12-NL
ClinicalTrials.gov	NCT02858453
CCMO	NL60005.056.17