A Phase II Study of the Efficacy and Safety of the Novel Oral SHIP1 Activator AQX-1125 in Subjects with Moderate to Severe Interstitial Cystitis/Bladder Pain Syndrome

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Purpose: In this 6-week, randomized, double-blind, placebo controlled, multicenter trial we assessed the effect of the novel SHIP1 (SH2-containing inositol-5′-phosphatase 1) activator AQX-1125 on bladder pain and urinary symptoms in patients with interstitial cystitis/bladder pain syndrome.

Materials and Methods: Women with interstitial cystitis/bladder pain syndrome and a mean pain score of 5 or greater on an 11-point scale despite treatment were randomized to AQX-1125 or placebo orally once daily for 6 weeks. Average and maximum pain scores (daily) and urinary frequency (before visits) were recorded by e-diary and at clinic visits. The O'Leary-Sant ICSI (Interstitial Cystitis Symptom Index) and ICPI (Interstitial Cystitis Problem Index), BPIC-SS (Bladder Pain Interstitial Cystitis Symptom Score) and SF-12v2® questionnaires were administered. Safety was monitored through 6 weeks of treatment and 4 weeks of followup.

Results: A total of 37 patients received oral AQX-1125 and 32 received placebo. At 6 weeks average daily pain on an e-diary decreased by 2.4 points for AQX-1125 vs 1.4 for placebo ($p = 0.061$), while average pain at clinic decreased by 2.6 vs 1.1 ($p = 0.008$), maximum daily pain on e-diary diary decreased by 2.6 vs 1.4 ($p = 0.030$) and maximum pain at clinic decreased by 2.8 vs 1.1 ($p = 0.028$). AQX-1125 reduced ICSI by 3.8 points vs 1.4 for placebo ($p = 0.005$), ICPI by 3.6 points vs 1.6 ($p = 0.014$) and BPIC-SS by 8.8 points vs 4.0 ($p = 0.011$). Urinary frequency decreased on AQX-1125 by 3.6 voids per 24 hours vs 0.8 for placebo ($p = 0.040$). Adverse event rates were similar for AQX-1125 and placebo (51.4% and 78.1%, respectively). No serious adverse events were reported.

Conclusions: Women with moderate to severe interstitial cystitis/bladder pain syndrome who were treated with the oral SHIP1 activator AQX-1125 reported significantly reduced bladder pain and improved urinary symptoms at 6 weeks. AQX-1125 was well tolerated. AQX-1125 may be a potential new treatment for interstitial cystitis/bladder pain syndrome. It warrants further investigation.

Key Words: urinary bladder; cystitis, interstitial; pain; questionnaires; 4-(4-(aminomethyl)-7a-methyl-1-methylideneoctahydro-1H-inden-5-yl)-3-(hydroxymethyl)-4-methylcyclohexan-1-ol

Abbreviations and Acronyms

AE = adverse event
BMI = body mass index
IC/BPS = interstitial cystitis/bladder pain syndrome
LS = least square
NRS = numerical rating scale
TEAE = treatment emergent AE

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INTERSTITIAL cystitis/bladder pain syndrome is a chronic condition of unknown etiology involving bladder pain and usually urinary urgency, frequency and nocturia.[1] It is often misdiagnosed as urinary tract infection or bacterial cystitis but there is no evidence of infection and antibiotics are generally ineffective.[2] The disease is more prevalent in women (3.3 to 7.9 million)[3] than in men (2.1 to 4.6 million)[4] in the United States and its frequency seems to be increasing with more defined approaches to diagnosis.[5–8] It results in negative impact on quality of life,[8–12] increased risk of mental health disorders and suicidal ideation,[13,14] and increased health care costs.[15] Several pharmacological treatments have been evaluated for IC/BPS but with conflicting results there remains a large unmet need.[1,16]

AQX-1125 represents a new pharmaceutical class of compounds that activate SHIP1 protein, a modulator of phosphoinositide signaling for diverse processes, including cell growth, activation and immune/inflammatory regulation. In vitro data demonstrated that SHIP1 activation modulates the inflammatory process through its antichemotactic activity and inhibition of activation of multiple immune cell types.[17] In vivo anti-inflammatory activity was found in human airway challenge studies[18] in preclinical models[19] of carrageenan induced inflammatory pain, colitis and mast cell anaphylaxis, and cyclophosphamide mediated cystitis (unpublished data). We hypothesized that oral administration of AQX-1125 may provide benefit in the treatment of IC/BPS.

MATERIALS AND METHODS

This randomized, double-blind, placebo controlled, phase 2 clinical trial (ClinicalTrials.gov NCT01882543) enrolled women between July 2013 and January 2015 from 19 Canadian and 12 American sites. The trial was approved by a central institutional review board.

During screening subjects were asked to record average and maximum daily pain each evening on an electronic e-diary (HealthDiary, Toronto, Ontario, Canada) with 0 indicating no pain and 10 indicating pain "as bad as you can imagine." Within 3 days before the return to clinic for the baseline assessment (visit 2) they recorded frequency and voiding volumes in a 24-hour period.

Subjects who met all enrolment criteria were centrally randomized to receive a single daily capsule of 200 mg AQX-1125 or matched placebo for 6 weeks. Clinic visits were scheduled during treatment at 2, 4 and 6 weeks with a followup visit at 10 weeks.

In addition, a full ophthalmic examination, including slit lamp examination of the ocular lens, was included as part of safety monitoring due to preclinical toxicological findings of lens fiber swelling, mainly in the female rat. Examinations were done at baseline and 6 weeks, and 4 weeks after the last dose if any change was detected at week 6.

Study Population

Women 18 to 75 years old with a diagnosis of IC/BPS for greater than 6 months but 15 years or less and bladder pain for 12 months or more were eligible for enrolment in a screening period of 9 to 21 days if they met inclusion criteria, including baseline mean pain 5 or greater on an 11-point scale, BPIC-SS score 19 or greater,[20] baseline combined O'Leary-Sant ICSI/PI[21] score 8 or greater, at least 8 urinary voids per 24 hours and a history of cystoscopy within 36 months revealing signs consistent with a IC/BPS diagnosis including but not restricted to Hunner lesion. Cystoscopy data were not collected. Women were excluded from analysis if they had pelvic floor pain greater than 5 of 10 as assessed by the investigator, BMI less than 18 or greater than 39 kg/m^2, or recent cystoscopy with therapeutic hydrodistension within 3 months or bladder surgery within 3 years. Subjects were allowed to enroll and remain on stable doses of most IC/BPS medications in this trial. The 2 most common medications were pentosan polysulfate sodium (Elmiron®) and amitriptyline (table 1). The supplementary material (http://jurology.com/) shows complete selection criteria.

Assessments

Efficacy. The primary end point was the change from baseline at 6 weeks in the average daily bladder pain score using a standardized 11-point NRS recorded on the e-diary each day.

Secondary end points were the change from baseline at each time point in maximum daily pain recorded on e-diary; average and maximum bladder pain score recorded at each clinic visit; BPIC-SS, ICSI/PI and SF-12v2

Table 1. *Demographics and baseline characteristics*

	Placebo	AQX-1125
No. pts	32	37
Mean ± SD age	53.1 ± 12.9	52.1 ± 14.9
No. race (%):		
White	30.0 (93.8)	31.0 (83.8)
Black	1.0 (3.1)	1.0 (2.7)
Asian	1.0 (3.1)	3.0 (8.1)
Other	0.0	2.0 (5.4)
No. nonHispanic or Latino ethnicity (%)	32.0 (100.0)	37.0 (100.0)
Mean ± SD wt (kg)	76.5 ± 16.3	67.3 ± 12.4
Mean ± SD BMI (kg/m^2)	29.1 ± 5.6	26.2 ± 4.7
Mean ± SD diagnosis duration (mos)	76.3 ± 57.3	63.5 ± 54.4
No. concomitant medication (%):		
Elmiron	9 (28.1)	12 (32.4)
Amitriptyline	10 (31.3)	9 (24.3)
Baseline NRS pain:		
Mean ± SD	6.7 ± 1.01	6.4 ± 0.88
No. 5.0—less than 6.5 (%)	15 (46.9)	20 (54.1)
No. 6.5 or greater—less than 8.0 (%)	13 (40.6)	15 (40.5)
No. 8.0 or greater (%)	4 (12.5)	2 (5.4)
Mean ± SD baseline max pain	7.9 ± 1.05	7.6 ± 1.04
Mean ± SD O'Leary-Sant ICSI/PI	30.2 ± 4.40	27.3 ± 5.04
Mean ± SD ICSI	16.1 ± 2.87	14.4 ± 2.94
Mean ± SD ICPI	14.1 ± 1.92	12.9 ± 2.36
Mean ± SD BPIC-SS	31.6 ± 3.28	29.6 ± 3.62
Mean ± SD SF-12v2 component:		
Mental	41.3 ± 12.46	46.4 ± 8.14
Physical	36.1 ± 11.96	41.4 ± 8.64
Mean ± SD voiding frequency/24 hrs	16.8 ± 7.14	15.7 ± 7.36
Mean ± SD voiding vol (ml/24 hrs)	1,876 ± 1,000	1,823 ± 951