SHIP1 Activation Provides Significant Benefit in Interstitial Cystitis/Bladder Pain Syndrome: Results of a Phase 2 Randomized Placebo Controlled Trial

J. Curtis Nickel,1* Blair Egerdie,2 Edward Davis,3 Robert Evans,4 Heidi Biagi,5 Stephen Shrewsbury6
1 Queen’s University, Kingston, Canada 2 Urology Associates, Kitchener, Canada 3 Citrus Valley Medical Center, Glendora, CA
4 Wake Forest University Health Sciences, Winston Salem, NC 5 Aquinox Pharmaceuticals (Canada) Inc., Vancouver, BC, Canada

INTRODUCTION

AQX-1125 is a novel, small molecule activator of SHIP1, a regulatory component of the PI3K cellular signaling pathway. By increasing SHIP1 activity, AQX-1125 accelerates a natural mechanism that has evolved to maintain homeostasis of the immune system by reducing immune cell activation and migration to sites of inflammation. AQX-1125 has demonstrated safety and favorable drug properties for once daily oral administration in multiple preclinical studies and seven completed clinical trials.

LEADERSHIP 201 TRIAL DESIGN

Methods

We conducted a double-blind, placebo-controlled Phase 2 trial of the safety and efficacy of AQX-1125 (plus existing therapy) in IC/BPS subjects using e-diaries and standardized IC/BPS questionnaires.

69 women with moderate to severe IC/BPS were randomized to daily 200 mg AQX-1125 or placebo for 6 weeks. 21 were already taking Elmiron® (9 placebo, 12 AQX-1125) and 19 already taking amitriptyline (10 placebo, 9 AQX-1125). Daily average and maximum pain scores and voiding frequency were recorded prior to visits and in the clinic for pain. The O’Leary-Sant Interstitial Cystitis Symptom and Problem Index (ICSI), Bladder Pain IC Symptom Score (BPC-SS) and Short Form 12 Health Survey questionnaires were administered. Safety data were collected throughout the course of treatment at the 6-week follow-up.

LEADERSHIP 201 RESULTS

At 6 weeks, all pain and symptom endpoints showed a clinically meaningful benefit, with all but average daily pain being statistically significant versus placebo.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AQX-1125</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN (11-point NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. Daily Pain (e-diary)</td>
<td>-2.4</td>
<td>-1.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Max. Daily Pain (e-diary)</td>
<td>-2.6</td>
<td>-1.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Avg. Daily Pain (clinics)</td>
<td>-2.8</td>
<td>-1.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Max. Daily Pain (clinics)</td>
<td>-2.8</td>
<td>-1.3</td>
<td>0.002</td>
</tr>
<tr>
<td>SYMPTOM QUESTIONNAIRES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICSI</td>
<td>-3.8</td>
<td>-1.4</td>
<td>0.005</td>
</tr>
<tr>
<td>ICPI</td>
<td>-3.6</td>
<td>-1.3</td>
<td>0.014</td>
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<tr>
<td>ICSI/ICPI Combined</td>
<td>-7.3</td>
<td>-3.2</td>
<td>0.007</td>
</tr>
<tr>
<td>BPC-SS</td>
<td>-3.8</td>
<td>-1.3</td>
<td>0.011</td>
</tr>
<tr>
<td>VOIDING FREQUENCY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. voids/24 hours</td>
<td>-3.6</td>
<td>-0.8</td>
<td>0.040</td>
</tr>
</tbody>
</table>

LEADERSHIP 201 EFFICACY

Change from Baseline in Maximum Pain (e-diary) Mean ± SE

LEADERSHIP 201 SAFETY

System Organ Class

Subjects With Any Treatment Emergent Adverse Event (%) 25 (78.1) 19 (51.4)

Adverse Events (%) 11 (34.4) 11 (29.7)

Infections and infestations 6 (18.6) 6 (16.2)

Serious system disorders 5 (15.6) 2 (5.4)

Skin and subcutaneous disorders 4 (12.5) 4 (10.9)

Renal and urinary disorders 5 (15.6) 2 (5.4)

General disorders and administration site conditions 5 (15.6) 1 (2.7)

Investigations 4 (12.5) 2 (5.4)

Eye disorders 0 (0.0) 0 (0.0)

Musculoskeletal and connective tissue disorders 3 (9.4) 2 (5.4)

Reproductive system and breast disorders 3 (9.4) 0 (0.0)

Psychiatric disorders 1 (3.1) 2 (5.4)

No subjects had any AEs occurring >10% in either placebo or AQX-1125 group.

The most frequently reported AEs (≥5%) (up to 3 days after last dose of study drug) and those occurring at a higher frequency in the AQX-1125 group than placebo, were dyspepsia, gastroesophageal reflux disease, and diarrhea. There were no serious adverse events either during treatment, or in the 4-week follow-up period.

CONCLUSIONS

Efficacy: Over 6 weeks, 200 mg AQX-1125 daily demonstrated:

- Reduced maximum daily pain by a clinically meaningful and statistically significant amount.
- Reduced both average and maximum pain reported at clinic by clinically meaningful and statistically significant amounts.
- A trend to reduce average daily pain by e-diary.
- Clinically meaningful and statistically significant improvements in ICSI, ICPI, ICSI/ICPI, BPC-SS and urinary frequency.

Safety and Tolerability: AQX-1125 was well-tolerated in this population of moderate-severe IC/BPS women with frequent comorbid conditions and concomitant medication.

ASSOCIATED POSTERS AT THIS CONFERENCE

- Abstract ID: 16-2182
  - Effect of AQX-1125 on Urinary Bladder Inflammation and Pain Induced by Cyclophosphamide in Rats, Targeting the SHIP1 Pathway
- Abstract ID: 16-2222
  - Plexus and Urinary Pankreatochromaffin of a Novel, Oral SHIP1 Activator, AQX-1125 in Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS) - Results of the Phase 2 LEADERSHIP Trial

ACKNOWLEDGEMENTS

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Stephen Shrewsbury
Email: salesh@aquinox.com