Plasma and Urinary Pharmacokinetics of a Novel, Oral SHIP1 Activator, AQX-1125 in Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS) – Results of the Phase 2 LEADERSHIP Trial


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#16-2232

BACKGROUND

AQX-1125, Aquinox’s lead drug candidate, is a small molecule activator of SHIP1, a regulating component of the PKB 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.

In non-clinical animal studies, the rat was chosen as one of the species for investigation of the efficacy and ADM (adsorption/ distribution/ metabolism/ excretion) properties of AQX-1125. Rats dosed intravenously with radiolabelled AQX-1125 (14C)-AQX-1125) showed that the urinary and fecal routes were the major routes of excretion (see Table 1).

Table 1. Mass Balance of [14C]-AQX-1125 in Rats

<table>
<thead>
<tr>
<th></th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
</tr>
</tbody>
</table>

Upon repeat daily oral administration in female rats, AQX-1125 urine concentration at trough was several fold higher than the corresponding plasma levels (see Table 2).

Table 2. Trough Concentrations from 7-Day Repeat Dose Study in the Rat

<table>
<thead>
<tr>
<th>Dose Group (mg/kg)</th>
<th>Mean Plasma (ng/mL)</th>
<th>Mean Urine (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>195</td>
<td>102,000</td>
</tr>
<tr>
<td>150</td>
<td>471</td>
<td>533,000</td>
</tr>
<tr>
<td>450</td>
<td>1553</td>
<td>1,539,000</td>
</tr>
</tbody>
</table>

In humans, it was predicted that AQX-1125 would be excreted in the urine with higher concentrations than in plasma.

INTRODUCTION

LEADERSHIP 201 Trial:

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-daries and standardized IC/BPS questionnaires.

Sixty-nine women with moderate to severe IC/BPS were randomized to daily 200 mg AQX-1125 or placebo for 6 weeks. Daily average and maximum pain scores and urinary frequency were recorded prior to visits. The O’Leary-Sant Interstitial Cystitis Symptom and Problem Indexes (O-SIP), Bladder Pain IC Symptom Score (IPIC-S) and Short Form 12 Health Survey questionnaires were administered. Safety data was collected through treatment and at the 4-weeks follow-up.

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

LEADERSHIP 201 TRIAL DESIGN

Day 0 - 21: Visit 1

Day 2 Phase Visit

Day 14 24 28 42 70

Figure 1. LEADERSHIP 201 Trial Design

MATERIALS AND METHODS

Pharmacokinetic blood and urine samples were collected prior to drug administration at Week 4 and Week 6 clinic visits approximately 24 h post-dose. Plasma was isolated from the blood samples at the clinic and frozen at -20°C prior to analysis for AQX-1125 using a validated LC-MS/MS method. Urine was collected in 60 mL urine collection bottles and samples stored frozen at -20°C until analysis for AQX-1125 using a validated LC-MS/MS method. AQX-1125 was previously shown to be stable in plasma for storage periods ≥ 1 yr and in urine for storage periods up to 11 months during their respective method validation.

LEADERSHIP 201 RESULTS

AQX-1125 was detected in both plasma and urine samples collected from the trial. Mean trough plasma concentrations were 252 ng/mL (8.7-757 ng/mL) at Week 4 and 225 ng/mL (0.23-554 ng/mL) at Week 6. The mean trough urine concentrations at Week 4 was 49,863 ng/mL (29,707-155,000 ng/mL) and at Week 6 was 53,396 ng/mL (32,400-116,000 ng/mL) (see Table 3). Ad hoc comparison of Week 4 vs Week 6 concentrations showed no significant difference therefore demonstrating that these concentrations were at steady-state.

Table 3. Trough Concentration from the LEADERSHIP 201 Trial

<table>
<thead>
<tr>
<th>Plasma (ng/mL)</th>
<th>Urine (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>Week 6</td>
</tr>
<tr>
<td>N</td>
<td>32</td>
</tr>
<tr>
<td>Mean</td>
<td>252</td>
</tr>
<tr>
<td>Geo mean</td>
<td>211</td>
</tr>
<tr>
<td>SD</td>
<td>129</td>
</tr>
<tr>
<td>CV</td>
<td>51</td>
</tr>
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</table>

There is a 140-200 times difference between corresponding mean urine and plasma concentrations. Finding high AQX-1125 levels in the urine demonstrates that AQX-1125 is eliminated via renal clearance. These results are consistent with findings in the rat, that upon repeat dose administration, mean trough urine concentrations were many fold higher than corresponding plasma concentrations.

CONCLUSIONS

Pharmacokinetics:

- Steady state trough plasma concentration observed in the LEADERSHIP 201 trial is consistent with previous studies.
- AQX-1125 is eliminated via renal clearance and is consistent with animal studies.
- Trough urinary AQX-1125 was approximately 140-200 times higher than corresponding plasma levels.
- The results show systemic and urinary exposure at site of action occurs in subjects with IC/BPS and further support a once-daily AQX-1125 oral dose administration.

ASSOCIATED POSTERS AT THIS CONFERENCE

Abstract ID: 16-2182
Effect of AQX-1125 on Urinary Bladder Inflammation and Pain induced by Cyclophosphamide in Rats. By Targeting the SHIP1 Pathway

Abstract ID: 16-2074
SHIP1 Activation Provides Significant Benefit in Interstitial Cystitis/Bladder Pain Syndrome: Results of a Phase 2 Randomized Placebo Controlled Trial

ACKNOWLEDGEMENTS

The study was sponsored by: Aquinox Pharmaceuticals (Canada) Inc. Website: http://aqxpharma.com

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