Plasma and Urinary Pharmacokinetics of the 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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ABSTRACT

Introduction and Objectives: AQX-1125, a novel SH2-containing inositol-5'-phosphatase 1 (SHIP1) activator represents a novel once-daily oral therapy for IC/BPS. Here we assess the extent of bladder exposure to AQX-1125 over 6 weeks with trough drug levels in plasma and urine. The LEADERSHIP trial was a multicenter, randomized, double-blind, placebo-controlled, Phase 2 clinical trial investigating the ability of 200 mg AQX-1125 to reduce pain in female patients with IC/BPS in North America.

Methods: Blood and urine was collected after 28 and 42 days. Samples were analyzed for concentrations of AQX-1125 via HPLC-MS/MS methods and trough levels calculated.

Results: PK samples where collected from 35 patients randomized to AQX-1125 and the mean/geometric mean plasma concentrations were 252/211 and 225/162 ng/mL for Days 28 and 42, respectively. The mean/geometric mean urine concentrations were 49,863/34,450 and 33,396/22,934 ng/mL for Days 28 and 42, respectively, at least 140-fold higher than the corresponding plasma levels. The trough plasma concentrations are similar to or exceed those anticipated for efficacy from earlier clinical trials and pre-clinical studies.

Conclusions: The novel SHIP1 activator, AQX-1125 reaches the bladder of IC/BPS patients via both the bloodstream and urine. The urinary route of elimination of AQX-1125 as parent compound may be an attractive property of the drug for IC/BPS. If once daily oral AQX-1125 proves effective in ameliorating symptoms of IC/BPS, both systemic and direct exposure of drug to the bladder may contribute to that response. This pharmacokinetic data supports continued development of AQX-1125 as an oral, once daily therapy for IC/BPS.

INTRODUCTION

AQX-1125, Aquinox's lead drug candidate, is a small molecule activator of SHIP1, a regulating 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 pre-clinical studies and seven completed clinical trials.

STUDY DESIGN

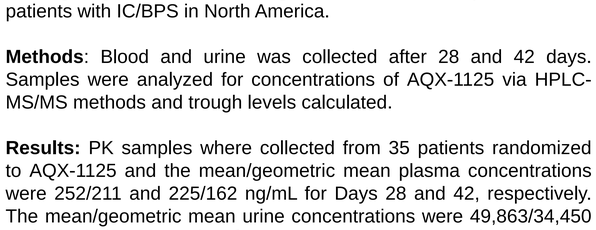

Figure 1. LEADERSHIP Study Design

BACKGROUND

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 BPS questionnaires.

69 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 (ICSI/PI), Bladder Pain IC Symptom Score (BPIC-SS) and Short Form 12 Health Survey questionnaires were administered. Safety data were 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.

Table 1. LEADERSHIP Efficacy Results

Endpoint (Change from baseline at 6 weeks)	AQX-1125 (n=37)	Placebo (n=32)	Difference in LSM (95%CI)	p-value
PAIN (11-point NRS)				
Avg. Daily Pain (e-diary)	-2.4	-1.4	-1.0 (-2.1, 0.0)	0.061
Max. Daily Pain (e-diary)	-2.6	-1.4	-1.3 (-2.5, -0.1)	0.030*
Avg. Daily Pain (clinic)	-2.6	-1.1	-1.6 (-2.8, -0.5)	0.008*
Max. Daily Pain (clinic)	-2.8	-1.1	-1.6 (-3.0, -0.2)	0.028*
SYMPTOM QUESTIONNAIRES				
ICSI	-3.8	-1.4	-2.7 (-4.6, -0.9)	0.005*
ICPI	-3.6	-1.6	-2.5 (-4.5, -0.5)	0.014*
ICSI/ICPI Combined	-7.3	-3.0	-5.1 (-8.8, -1.4)	0.007*
BPIC-SS	-8.8	-4.0	-5.4 (-9.5, -1.3)	0.011*
VOIDING FREQUENCY				
No. voids/24 hours	-3.6	-0.8	-2.8 (-5.5, -0.1)	0.040*

AQX-1125 demonstrated rapid onset of action, with early changes in pain observed. Time course of effect for maximum daily pain (proposed P3 1° endpoint) is represented in Figure 2, with a similar pattern observed for the other pain endpoints.

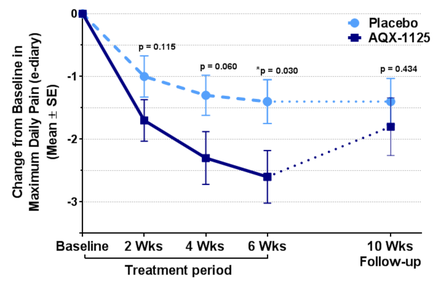

Figure 2. Change from baseline in the maximum daily bladder pain scores (11-point NRS, e-diary)

SAFETY

AQX-1125 was well tolerated for the 6-week duration of treatment in this trial. The proportion of subjects reporting TEAE was greater for placebo compared to AQX-1125 treatment (78% vs 51%). The most frequently reported TEAEs (>5%), and that occurred at a higher frequency in the AQX-1125 group than placebo, were dyspepsia, gastroesophageal reflux disease, and sinusitis. There were no serious adverse events either during treatment, or in the 4-week follow-up period.

PK MATERIALS AND METHODS

Pharmacokinetic blood and urine samples were collected prior to drug administration at Week 4 and Week 6 clinic visits approximately 24 hrs 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 and urine for storage periods ≥ 1 yr during their respective method validation.

PK RESULTS

Mean trough plasma concentrations were 252 ng/mL at Week 4 and 225 ng/mL at Week 6. The mean trough urine concentrations at Week 4 (49,863 ng/mL) and at Week 6 (33,396 ng/mL) were 140–200 times higher than the corresponding mean plasma concentrations. Finding high AQX-1125 levels in the urine demonstrates that AQX-1125 is eliminated via renal clearance.

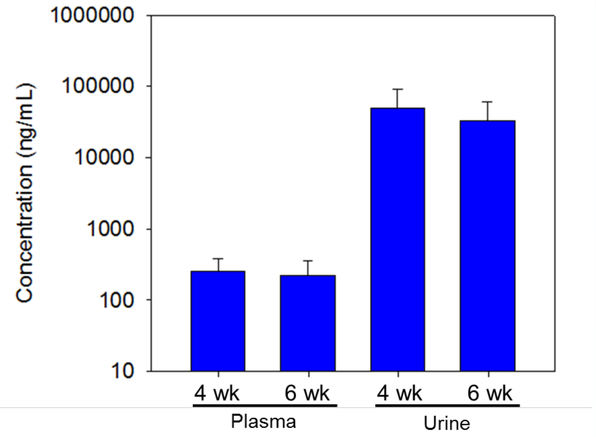

Figure 3. Trough Concentrations from the LEADERSHIP Trial

Ad hoc comparison of Week 4 vs Week 6 concentrations showed no significant difference therefore demonstrating that these concentrations were at steady-state. The drug levels in plasma and urine in IC/BPS patients demonstrate both systemic and urinary exposure at the site of action in subjects with IC/BPS and further supports a once-daily AQX-1125 oral dose administration.

RESULTS

Table 2. Trough* Concentration from the LEADERSHIP Trial

	Plasma (ng/mL)		Urine (ng/mL)	
	Week 4	Week 6	Week 4	Week 6
N	32	33	26	31
Mean	252	225	49,863	33,396
Geo mean	211	162	34,450	22,934
SD	129	127	40,630	27,873
CV	51	57	81	83

* Subjects that took drug just prior to sample collection were excluded

CONCLUSION

Pharmacokinetics:

- Steady state trough plasma concentration observed in the LEADERSHIP trial is consistent with previous 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
- AQX-1125 is eliminated via renal clearance and is consistent with animal studies

REFERENCES

Humphrey L, Arbuckle R, Moldwin R, et al. The bladder pain interstitial cystitis symptom score: development, validation and identification of a cut score. Eur Urol. 2012; 61:271-279.

O'Leary MP, Sant GR, Fowler FJ, et al. The interstitial cystitis symptom index and problem index. Urology. 1997; 49 (5A Suppl): 58-63.

Stenton G, Mackenzie L F, Tam P, et al. Characterization of AQX-1125, a small molecule SHIP activator: Part 1. Effect on inflammation cell activation and chemotaxis in vitro and pharmacokinetic characterization in vivo. Br J Pharmacol. 2013; 168(6): 1506-18.

Stenton G, Mackenzie L F, Tam P, et al. Characterization of AQX-1125, a small molecule SHIP activator: Part 2. Efficacy studies in allergic and pulmonary inflammation models in vivo. Br J Pharmacol. 2013; 168(6): 1519-29.

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