Effect of AQX-1125 on Urinary Bladder Inflammation and Pain Induced by Cyclophosphamide in Rats, by Targeting the SHIP1 Pathway

J.L. Cross, C. Harwig, P. Tam, J. Toews and L.F. Mackenzie
Aquinox Pharmaceuticals (Canada) Inc., Vancouver, BC, Canada

ABSTRACT

Introduction and Objectives: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic inflammatory syndrome characterized by pain, pressure or discomfort in the bladder and accompanied by urinary symptoms of frequency and urgency. AQX-1125, a novel SH2-containing inositol-5-phosphatase 1 (SHIP1) activator with broad anti-inflammatory properties, represents a potential once-daily, oral therapy for IC/BPS. In rats, a single injection of cyclophosphamide (CYP) induces a chemical cystitis with similar features of IC/BPS, including inflammation of the bladder, visceral pain and an increase in urinary frequency. The aim of this study was to evaluate the effect of AQX-1125 (0.3, 3 and 30 mg/kg doses) on visceral pain, inflammation and cystometric parameters in acute-CYP-induced cystitis in rats.

Methods: Cystitis was induced in female Sprague Dawley rats by a single intraperitoneal injection (150 mg/kg) of CYP. For cystitis studies, AQX-1125 was administered once-daily for four days, with the final dose given two hours prior to CYP challenge. Von Frey testing measured visceral pain at 4 hours post-challenge and bladders were excised to measure bladder wall thickness, cystometrical results and to score the extent of edema and hemorrhage. For cystometry studies, AQX-1125 was dosed five times at 30 mg/kg and urodynamic function was assessed at 48 hours post-CYP administration.

Results: AQX-1125, at 0.3, 3 and 30 mg/kg, reduced visceral pain, assessed from von Frey 1-4 g, with maximal inhibitions occurring in the 1-6 g range (49%, 95% and 92%, respectively, as compared to the CYP/vehicle group). The AQX-1125 reduction in visceral pain (von Frey 1-60 g), was the same at 3 and 30 mg/kg (31%), and was comparable to the reference standard ibuprofen (37% at 300 mg/kg). AQX-1125 at 3 mg/kg also significantly decreased the inflammatory parameters of bladder wall thickness and the edema score. At 30 mg/kg, AQX-1125 also showed a positive trend in decreasing the intercontraction interval, evaluated during cystometry.

Conclusions: This novel SHIP1 activator, AQX-1125 is able to decrease visceral pain and bladder inflammation in a rodent model of cystitis. This compelling data supports the development of AQX-1125 as an oral, once-daily therapy for IC/BPS.

INTRODUCTION

AQUINOX: A Small Molecule Targeting SHIP1

Figure 1. Targeting SHIP1 to Reduce Inflammation
- P38K/SHP1 pathway is an established target for drug development
- P38K/SHP1 pathway plays a key role in regulating cell migration and activation
- SHIP1 activation redirects cellular P38K signaling, rather than preventing it

AQX-1125 is found at high levels in the urine and bladder of rodents

AQX-1125 significantly reduced cyclophosphamide-induced visceral pain

RESULTS

Figure 5. Effect of AQX-1125 on Bladder Inflammation
- AQX-1125, at 3 mg/kg, significantly decreased bladder edema scores and bladder wall thickness in CYP-treated rats. Data are the mean ± SEM (n=10), **p<0.01, *p<0.05 as compared to vehicle.

Figure 6. Effect of AQX-1125 on Urodynamic Function
- AQX-1125, at 30 mg/kg, showed a positive trend in increasing urodynamic function in CYP-treated rats as measured by intercontraction interval. Data are the mean ± SEM (n=12-13).
- Data support the use of AQX-1125 in IC/BPS to reduce pain and urinary symptoms of IC/BPS

ASSOCIATED POSTERS AT THIS CONFERENCE

Abstract ID: 16-2232
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

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

REFERENCES


CONTACT
Aquinox Pharmaceuticals (Canada) Inc.
403-887 Great Northern Way
Vancouver, BC, Canada, V7T 4L5
Website: http://aquinoxpharma.com

Jennifer Cross
Email: jcross@aquinoxpharma.com