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

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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, 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, cytokine levels 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 1-60 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: The novel SHIP1 activator, AQX-1125 is able to decrease visceral pain and bladder inflammation in a rodent model of cystitis. This compelling data supports development of AQX-1125 as an oral, once-daily therapy for IC/BPS.