AQX-1125, a SHIP1 Activator, Inhibits Chemotaxis In Vitro and Exerts Pleiotropic Anti-Inflammatory Effects in a Rodent Model of Endothelium-Induced Pulmonary Inflammation

**Rationale:** Pharmacological modulation of the phosphatase-3 kinase (PI3K)/Akt pathway is an established approach to controlling inflammatory disorders. PI3K-containing module-5 phosphatase-1 (SHIP) metabolizes PI3P to PI(3,5)P2. SHIP1-deficient mice exhibit pulmonary inflammation, characterized by significant pulmonary edema recruitment into the lung. Preclinical pharmacological activation of SHIP1 by the small molecule AQX-1125, is reported herein as an emerging innovative therapy for pulmonary inflammatory diseases.

**Methods:** AQX-1125 was tested in an in vivo essay utilizing a recombinant human SHIP1 enzyme (wild-type and mutant enzyme lacking the C2 domain). As phosphoinositide signaling plays a key role in chemotaxis, the effect of AQX-1125 was tested on leukocyte chemotaxis using Boyden chambers. In vivo, the efficacy of AQX-1125 was tested in a model of endothelial LPS challenge in the rat. Pharmacokinetic studies were also performed in rats.

**Results:** AQX-1125 displayed a concentration-dependent increase in the catalytic activity of recombinant SHIP1, an effect, that was absent after deletion of the C2 domain of the enzyme, indicating an allosteric mode of activation. AQX-1125 exerted an inhibitory effect on leukocyte chemotaxis. The greatest effect was against monocyte and B cell chemotaxis, which had IC50 of 28 and 28 mM respectively. AQX-1125 administered to rats exhibited high oral bioavailability (85% ± 30 mg/kg), a terminal half-life of approximately 5h, and high concentrations in a number of parenchymal tissues, including the lung. Consistent with its inhibitory effect on chemotaxis, the compound afforded a dose-dependent reduction of leukocyte infiltration into the bronchoalveolar lavage fluid (BALF) in a rat pulmonary inflammation model induced by LPS (43% inhibition of neutrophil influx at 30 mg/kg). This effect was associated with reduced gene expression of systemic pro-inflammatory mediators, cytokines and growth factors, with a characteristic signature different from that of the reference compound dexamethasone.

**Conclusion:** The SHIP1 activator AQX-1125 potently inhibits leukocyte chemotaxis in vitro, inhibits LPS-induced pulmonary inflammation and inflammatory mediator release in vivo and exhibits pharmacokinetics suitable for once per day dosing. Thus, AQX-1125 may have clinical potential for treatment of pulmonary inflammatory diseases. Proof-of-concept clinical efficacy of AQX-1125 is currently being initiated to assess the utility of the SHIP1 activator, AQX-1125, in human pulmonary inflammation.

**INTRODUCTION**

**Targeting SHIP1:**
- **PI3K pathway:** An established target for drug development.
- **PI3K/SHIP1 pathway:** A key role in regulating cell migration and activation.
- **Targeting SHIP1:** An alternative way of modulating the PI3K pathway.

**PI3K** expression restricted to hematopoietic derived cells - limited target toxicity.

**SHIP1** activation redirects cellular PI3K signaling, rather than preventing it.

**SHIP1 Activation**
AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators1, but has improved drug solubility and superior side effect profiles. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain, and are anti-inflammatory in cellular and murine models.

**Background**

**Challenge**

**Results**

**Conclusion**

**Summary**

**Phase I Clinical Development of AQX-1125**

**Phase I:** Pharmacokinetics of AQX-1125 in healthy human volunteers
- **AQX-1125 is well tolerated in HHV’s (SAD/MAD)**
- PK is dose-proportional
- Terminal half-life is ~22hr
- No food effects detected on AUC
- Oral bioavailability is high
- PK supports once-a-day dosing

**Phase II:** Allergen and LPS Challenge
- **Allergen Challenge:** Clinical Trials Group, London, UK - PIs: Dr. Leaker & O’Connor
- Cross-over study (1 active dose + placebo), 22 mild asthmatics, 7 days dosing.
- Lung function, sputum leukocytes and analyte endpoints

**Phase III Clinical Data are presented:** AQX-1125, A SHIP1 Activator in Clinical Development For Pulmonary Inflammation: Pharmacokinetics, Metabolism And Tolerability in Healthy Human Volunteers

**References**


**AQX Pharmaceuticals Inc., Richmond, BC, Canada**