SHIP1 Activation

**Rationale:** SH2-containing inositol-5-phosphatase 1 (SHIP1) down-regulates the pro-inflammatory phosphatidylinositol 3-kinase/Akt pathway by metabolizing PI(3,4,5)P3 to PI(3,4)P2. SHIP1 activation is an established pharmacological approach for the control of inflammatory disorders.

**Objective:** To determine the effects of SHIP1 activation by AQX-1125 on lipopolysaccharide (LPS)-induced lung inflammation in healthy volunteers.

**Methods:** In this single-center, placebo-controlled, double-blind, crossover study, 24 healthy volunteers were randomized to one of two treatment sequences (placebo then AQX-1125 or AQX-1125 then placebo) in a 28-day blinded fashion. In each treatment period, subjects received either oral AQX-1125 (450 mg) or matching placebo once-daily, for 7 days. The wash-out period was 28 days between the two treatment periods. The primary endpoint was the effect of AQX-1125 on sputum neutrophilia 24 h after aerosol LPS challenge. Secondary endpoints included sputum biomarkers and PK analysis, as well as safety and tolerability assessment.

**Results:** AQX-1125 significantly reduced sputum neutrophil counts 24 h following the inhaled LPS challenge when compared to placebo by ANCOVA. AUC exposure to sputum cell counts in subjects treated with AQX-1125 (1.4 x 10^6 cells/gram sputum) were reduced by 67% when compared to sputum cell counts from subjects treated with placebo (4.3 x 10^6 cells/gram sputum). When baseline sputum neutrophile levels were included as a covariate in the analysis (ANOVA), AQX-1125 reduced the 24 h post-LPS sputum neutrophils by 62% (p<0.0161). The reduction of neutrophiles correlated with a 62% reduction in the pre-/post-Day 7 sputum IL-6 concentration (p=0.048). AQX-1125 was safe and well tolerated. The most frequent adverse events related to the inhaled LPS challenge. The time to maximum plasma concentration at steady state (Cmax,ss) indicated that AQX-1125 was rapidly absorbed. The mean Cmax,ss and AUC0-24 values were 1350 ng/mL and 16900 h.ng/mL respectively. AQX-1125 mediated a 62% reduction (p=0.048) in sputum IL-6 concentrations at 24 h hours induced by inhaled LPS challenge.

**Conclusion:** AQX-1125 has anti-inflammatory effects in healthy volunteers undergoing LPS-induced lung injury, reducing the LPS-mediatied increase in sputum neutrophiles and sputum IL-6 concentrations. This clinical data demonstrates the efficacy of AQX-1125 in a standard pulmonary inflammation model and coupled with the safety, tolerability and PK data support the continued clinical development of the SHIP1 activator AQX-1125 for inflammatory disease.

**Clinical Development of AQX-1125**

**Current Phase II Studies:**

- Interstitial Cystitis/Bladder Pain Syndrome “LEADSHIP” Study
- Parallel group, randomized, double-blind, placebo-controlled, multicenter study
- 6 weeks dosing
- Bladder pain and BPS symptom endpoints
- COPD Evaluation “HYDRA” Study
- Parallel group, randomized, double-blind, placebo-controlled, multicenter study
- 12 weeks dosing
- Exacerbation and COPD symptom endpoints

**Human and animal pharmacodynamic study results are presented in the posters titled:**

- “The Effects Of The Novel SHIP1 Activator AQX-1125 On Asthma”
- “Pharmacological Or Therapeutic AQX-1125, A Small Molecule SHIP1 Activator, Inhibits Bleomycin-induced Pulmonary Fibrosis”

**Summary:** AQX-1125 is a small molecule that controls PKR-driven cellular migration and activation. SHIP1’s preferential expression in hematopoietic cells and low degree of homology with SHIP2 reduces the likelihood of off-target, off-tissue toxicities. AQX-1125, a small molecule allosteric SHIP1 activator, with PK properties suited to once per day dosing, inhibits the PKR pathway resulting in an inhibition of Akt phosphorylation and reduced chemotaxis. AQX-1125 has high water-solubility, good oral bioavailability, minimal metabolism, and distributes to the lung at high concentrations.

In this study, once daily orally administered AQX-1125 inhibited the LPS-induced pulmonary inflammatory response as measured by the significant inhibition of sputum neutrophil accumulation following inhaled challenge with LPS. The magnitude of effect on sputum neutrophil was 67% reduction (ns placed at the 24 h timepoint) and this effect correlated with a statistically significant reduction (65% vs placebo) in sputum IL-6 concentrations. Together with the safety and pharmacokinetics, this study demonstrated a favorable risk-benefit profile and support for further development of AQX-1125 for the treatment of inflammatory respiratory diseases.

**REFERENCES:**

1. Pellegato et al. Targeted disruption of SHIP leads to hematopoietic perturbations, lung inflammation in animal models.