The Effects Of AQX-1125, A Selective Oral SHIP1 Activator, On Lipopolysaccharide-Induced Cellular And Biochemical Changes In Sputum From Healthy Volunteers

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Rationale: SH2-containing inositol-5'-phosphatase 1 (SHIP1) down-regulates the pro-inflammatory phosphoinositide 3-kinase (PI3K)/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.

Objectives: 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, two-way cross-over study, 18 healthy volunteers were randomised to one of two treatment sequences (placebo then AQX-1125 or AQX-1125 then placebo) in a double-blind fashion. In each treatment period they 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 hr after aerosol LPS challenge. Secondary endpoints included sputum biomarker and PK analysis, as well as safety and tolerability assessment.

Results: AQX-1125 significantly reduced sputum neutrophil counts 24 hr following the inhaled LPS-challenge when compared to placebo by ANOVA (p=0.014). The absolute sputum cell counts in subjects treated with AQX-1125 (1.4×10^6 cells/gram sputum) were reduced by 67% when compared to sputum cell counts from subjects treated with placebo (4.3×10^6 cells/gram sputum). When baseline sputum neutrophils were included as a covariate in the analysis (ANCOVA), AQX-1125 reduced the 24 hr post-LPS sputum neutrophils by 62% (p=0.0615). The reduction of neutrophils correlated with a 62% reduction in the pre-dose Day 7 sputum IL-6 concentration (p=0.048). AQX-1125 was safe and well tolerated. The most frequent adverse events were related to the inhaled LPS challenge. The time to maximum plasma concentration at steady state ($C_{max,ss}$) indicated that AQX-1125 was rapidly absorbed. The mean $C_{max,ss}$ and AUC_{0-24} values were 1350 ng/mL and 16900 hr.ng/mL respectively.

Conclusions: AQX-1125 has anti-inflammatory effects in healthy volunteers undergoing LPS-induced lung inflammation; reducing the LPS-mediated increases in sputum neutrophilia and suppressing sputum IL-6 concentrations. These clinical data demonstrating efficacy of AQX-1125 in a standard pulmonary inflammation model, coupled with the safety, tolerability and PK data, support the continued clinical development of the SHIP1 activator AQX-1125 for inflammatory disease.

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