

## The Effects Of The Novel SHIP1 Activator AQX-1125 On Allergen-Induced Responses In Mild To Moderate Asthma

### Authors

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**Rationale:** SH2-containing inositol phosphatase-1 (SHIP1) is an endogenous inhibitor of the phosphoinositide-3-kinase pathway that is involved in the activation of inflammatory cells. AQX-1125 is a first-in-class oral SHIP1 activator with a novel anti-inflammatory mode of action. Inhaled allergen challenge (IAC) is useful in studying the allergic inflammatory response in patients with mild to moderate asthma.

**Objectives:** To determine the effect of AQX-1125 on lung function, airway responsiveness to methacholine, sputum eosinophils and fractional exhaled nitric oxide (FeNO) in asthmatic patients after IAC.

**Methods:** A randomized, double-blind, placebo-controlled, 2-way cross-over study was performed in 22 steroid-naïve patients with mild to moderate asthma and documented late phase response to IAC. AQX-1125 (450 mg QD) or placebo were administered orally for 7 days. IAC was performed on day 6 (2 h post-dose), followed by methacholine challenge (day 7), and induced sputum collection.

**Results:** AQX-1125 significantly abrogated the late phase response compared with placebo (FEV<sub>1</sub> 4-10h: mean difference 150 ml, 20%; p=0.026); and significantly increased the minimum FEV<sub>1</sub> during LAR (mean difference 180 ml; p=0.013). AQX-1125 had no effect on the early phase response. AQX-1125 showed a trend in reduction of sputum eosinophils & macrophages although this did not achieve significance as there were only 11 paired samples for analysis. There was no effect on methacholine responsiveness or FeNO. Pharmacokinetic data showed that AQX-1125 was rapidly absorbed with a mean C<sub>max,ss</sub> and AUC<sub>0-24 h,ss</sub> values of 1508 ng/mL and 17228 hr.ng/mL respectively. AQX-1125 was well tolerated but mild GI side effects (dyspepsia, nausea abdominal pain) were described in 5/22 subjects on active treatment. These side effects were mild and self limited. All patients completed the respective dosing periods and there were no withdrawals from the study.

**Conclusion:** Oral AQX-1125, a novel oral SHIP1 activator, significantly reduces the late response to IAC, with a trend to reduce airway inflammation. AQX-1125 was safe and well tolerated.

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