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Title: The effect of the novel SHIP1 activator AQX-1125 on allergen-induced responses in mild to moderate asthma

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Body: 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 and safety profile in pre-clinical studies. Objectives: To determine the effect of once daily 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-naive patients with mild asthma. AQX-1125 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 (FEV1 4-10h: mean difference 150ml; p>0.027); and increased minimum FEV1 during LAR (mean difference 180ml; p=0.014); increased FEV1 0-10h (mean difference 97.5ml; p>0.05) but had no effect on the early phase response. AQX-1125 showed a trend in reduction of sputum eosinophils & macrophages & also reduced methacholine responsiveness but these did not achieve significance. There was no effect on FeNO. AQX-1125 was well tolerated with mild self limited GI side effects described in 5/22 subjects on active treatment. Conclusion: AQX-1125, a novel oral SHIP1 activator, significantly reduces the late phase response to IAC, with trends to reduce airway inflammation and hyperresponsiveness.