AQX-1125 inhibits the asthmatic response following inhaled allergen challenge in subjects with mild to moderate asthma.

**Introduction**

**Targeting SHIP1**
- PI3K pathway is an established target for drug development.
- PI3K/SHIP1 pathway plays a significant role in allergy and asthma.
- Targeting SHIP1 is an alternative way of modulating the PI3K pathway.
- SHIP1 expression is restricted to hematopoietic derived cells - limits off-target toxicity.
- SHIP1 activation redirects cellular PI3K signaling, rather than preventing it.

**SHIP1 Activation**
- A small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.

**Methods**
- A randomized, double-blind, placebo-controlled, 2-way cross-over study was performed in 22 steroid-naive 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 alleviated the late phase response compared with placebo (FEV1: 4.1% vs mean decrease 3.5% +/− 20%; p=0.026), and significantly increased the minimum FEV1 during LAR (mean increase 240 mL; p<0.001). AQX-1125 did not affect the early phase response. AQX-1125 showed a trend in reduction of sputum eosinophils + neutrophils, although this did not achieve significance as there were only 31 paired sputum samples for analysis. There was no effect on methacholine responsiveness or FENO. Pharmacometric data showed that AQX-1125 was rapidly absorbed with mean Cmax,ss and AUC0-24h,ss values of 1508 mg/mL and 1728 h·mg/L, respectively. AQX-1125 was well tolerated but had a few side effects (dyspepsia, nasopharyngitis and abdominal pain) were described in 5/22 subjects on active treatment. These side effects were mild and self limited.

**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 rapidly absorbed with mean Cmax,ss and AUC0-24h,ss values of 1508 mg/mL and 1728 h·mg/L, respectively. AQX-1125 was well tolerated but had a few side effects (dyspepsia, nasopharyngitis and abdominal pain) were described in 5/22 subjects on active treatment. These side effects were mild and self limited.

**AQX-1125 inhibits the asthmatic response following inhaled allergen challenge in subjects with mild to moderate asthma.**

**Methods**

**Background**

**SHIP1 Activation**
- A small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.

**Methods**
- An initial Phase 1 trial was conducted in healthy human subjects to study the safety, tolerability and pharmacokinetics of AQX-1125. Healthy, non-smoking adults (N=106) were randomized into 5 treatment groups. Subjects were administered ascending doses (100-542 mg for 10 days) and food effects (200 mg) of AQX-1125. The results showed that AQX-1125 was well tolerated and exhibited predictable pharmacokinetic behavior and absorbed equally in fed vs a fasted state.

**Results**
- AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.

**Methods**
- An initial Phase 1 trial was conducted in healthy human subjects to study the safety, tolerability and pharmacokinetics of AQX-1125. Healthy, non-smoking adults (N=106) were randomized into 5 treatment groups. Subjects were administered ascending doses (100-542 mg for 10 days) and food effects (200 mg) of AQX-1125. The results showed that AQX-1125 was well tolerated and exhibited predictable pharmacokinetic behavior and absorbed equally in fed vs a fasted state.

**Results**
- AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.

**Methods**
- An initial Phase 1 trial was conducted in healthy human subjects to study the safety, tolerability and pharmacokinetics of AQX-1125. Healthy, non-smoking adults (N=106) were randomized into 5 treatment groups. Subjects were administered ascending doses (100-542 mg for 10 days) and food effects (200 mg) of AQX-1125. The results showed that AQX-1125 was well tolerated and exhibited predictable pharmacokinetic behavior and absorbed equally in fed vs a fasted state.

**Results**
- AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.

**Methods**
- An initial Phase 1 trial was conducted in healthy human subjects to study the safety, tolerability and pharmacokinetics of AQX-1125. Healthy, non-smoking adults (N=106) were randomized into 5 treatment groups. Subjects were administered ascending doses (100-542 mg for 10 days) and food effects (200 mg) of AQX-1125. The results showed that AQX-1125 was well tolerated and exhibited predictable pharmacokinetic behavior and absorbed equally in fed vs a fasted state.

**Results**
- AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.

**Methods**
- An initial Phase 1 trial was conducted in healthy human subjects to study the safety, tolerability and pharmacokinetics of AQX-1125. Healthy, non-smoking adults (N=106) were randomized into 5 treatment groups. Subjects were administered ascending doses (100-542 mg for 10 days) and food effects (200 mg) of AQX-1125. The results showed that AQX-1125 was well tolerated and exhibited predictable pharmacokinetic behavior and absorbed equally in fed vs a fasted state.

**Results**
- AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug safety and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain. They are anti-inflammatory in cellular and murine models.