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

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Abstract

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.

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_1 4-10 h: mean difference 150 mL, 20%; p=0.026); and significantly increased the minimum FEV $_1$ during LAR (mean difference 180 mL; p=0.014). 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 FE_{NO}. Pharmacokinetic data showed that AQX-1125 was rapidly absorbed with mean $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ values of 1508 ng/mL and 17228 h.ng/mL respectively. AQX-1125 was well tolerated but mild GI side effects (dyspepsia, nausea 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 safe and well tolerated.

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 key role in regulating cell migration and activation
- Targeting SHIP1 is an alternate 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

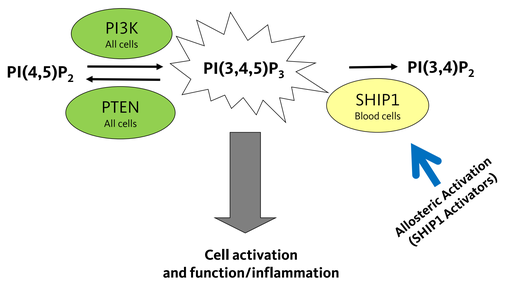

Figure 1. *SHIP1 and PI3K signalling. SHIP1 activators redirect PI3K signalling, PI3K inhibitors block PI3K signalling.*

Background

SHIP1 Activation

AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators[1,2], but has an improved drug scaffold and superior drug-like properties. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain, and are anti-inflammatory in cellular and murine models.

An initial Phase 1 trial was conducted in healthy human subjects to study the safety, tolerability and pharmacokinetics of single ascending doses (17-542 mg), multiple 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 at all doses, exhibited predictable pharmacokinetic behavior and absorbed equally in a fed versus a fasted state.

Study Design

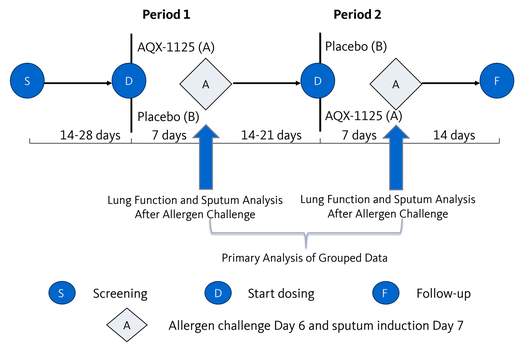

Figure 2. *The effect of AQX-1125 on the late asthmatic response (LAR) was evaluated using a 2-way crossover design with a 14-21 day washout period between treatment periods. In each treatment period either 450 mg AQX-1125 or matching placebo was administered once-daily for 7 days.*

AQX-1125 was evaluated using inhaled allergen challenge in two-way crossover design

Results

Baseline Characteristics	Mean (SD)
Age (yr)	31(9)
BMI (kg/m^2)	24 (2.7)
PC_{20} (mg/mL)	0.906 (1.35)
FEV1 (% predicted)	84 (11)

Table 1. *A total of 22 patients (20 males and 2 females) with a mean age of 31 years were randomized into this study. At baseline, the study population had mean PC_{20} value ≤ 16 mg/mL and FEV_1 ≥ 70 % of predicted indicating mild to moderate asthma. All subjects demonstrated a positive wheal reaction to a specific allergen and a clear early asthmatic response (EAR) and late asthma response (LAR) following an inhaled allergen challenge in the screening period.*

Efficacy Analysis: FEV1 vs. Time profile following inhaled allergen challenge

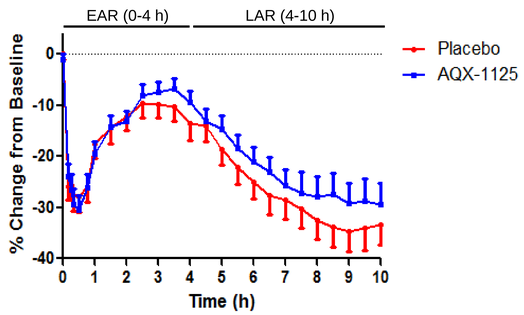

Figure 3. *The effect of AQX-1125 on the % change from baseline FEV_1 following inhaled allergen challenge. Subjects treated with active and placebo demonstrated a similar decline in FEV_1 profile within 4 hours following the inhaled allergen challenge during the early asthmatic response (EAR) with a slight separation starting at 3 h post challenge. Subjects on active treatment demonstrated a reduced late asthmatic response (LAR) indicating an anti-inflammatory mechanism of action. The magnitudes of effects are shown in Table 2.*

AQX-1125 inhibits the late asthma response (LAR) in subjects with asthma

Efficacy Analysis: Primary Endpoint – LAR $AUC_{4\text{-}10}$

Parameter		Unit	Treatment difference (Active-Placebo)	P-value
LAR	$AUC_{4\text{-}10}$	min x L	54.07	0.027
	Min FEV_1	L	0.18	0.014
EAR	$AUC_{0\text{-}4}$	min x L	4.5	0.828
	Min FEV_1	L	0.0	0.990
FE_{NO}	$AUC_{0\text{-}24}$	min x ppb	87.07	0.317
	Max	ppb	11.75	0.193

Table 2. *AQX-1125 significantly reduced the late asthmatic response following inhaled allergen challenge as measured by the baseline-corrected area under the FEV_1 curve from 4 to 10 h (LAR $AUC_{4\text{-}10}$) (primary endpoint). The treatment difference in the LAR $AUC_{4\text{-}10}$ corresponded to a time weighted improvement in FEV_1 of 150 mL. The comparison between treatments was carried out using the analysis of covariance (ANCOVA) with baseline FEV_1 (Day 6, post-saline) as a covariate. The treatment difference in the primary endpoint correlated with a significant increase in the minimum FEV_1 during the LAR. There were no statistical significant effects of AQX-1125 on the early asthmatic response (EAR) or in the fraction of exhaled nitric oxide (FE_{NO}). All analyses were planned.*

The primary objective was met with significant improvement in the LAR as measured by the LAR $AUC_{4\text{-}10}$ and the minimum FEV_1

Efficacy Analysis: *Sputum Cell Counts*

Cell Type	Unit	Treatment ratio (Active/Placebo)	P-value
Eosinophils	%	0.53	0.625
Neutrophils	%	0.79	0.185
Macrophages	%	0.43	0.525
Eosinophils	cells/mg	0.32	0.483
Neutrophils	cells/mg	0.73	0.573
Macrophages	cells/mg	0.19	0.388

Table 3. *The effect of AQX-1125 on the differential (%) and absolute sputum cell counts (cells/mg sputum) at 24 h following inhaled allergen challenge. Of the randomized patients, paired sputum samples were available from 11 subjects only. The treatment ratio (active/placebo) for the differential and absolute cell count for eosinophils, neutrophils and macrophages all trended in favour of AQX-1125 treatment vs. placebo. None of the individual effects were considered statistically significant. The comparisons between treatments were carried out using the analysis of variance (ANOVA) for a crossover design on log- transformed values.*

The effect on differential and absolute cell counts all trended in favour of AQX-1125 treatment (vs. placebo) and correlated with the effects on the LAR

Pharmacokinetics

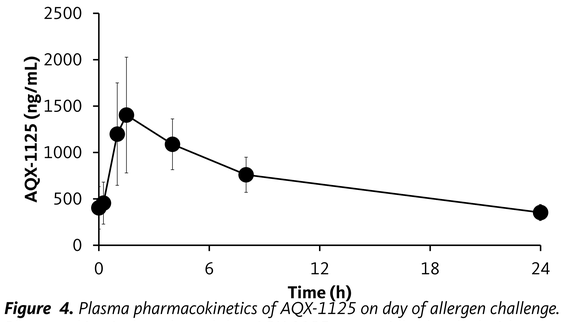

Figure 4. *Plasma pharmacokinetics of AQX-1125 on day of allergen challenge. Pharmacokinetic data showed that AQX-1125 was rapidly absorbed with mean $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ values of 1508 ng/mL and 17228 h.ng/mL respectively.*

Pharmacokinetics of AQX-1125 in subjects with mild to moderate asthma supports a once-daily dosing regimen

Safety

Preferred Term	450 mg Active (N=22) N(%)	450 mg Placebo* (N=21) N(%)
Subjects with any AE	15(68%)	9(43%)
Headache	4(18%)	3(14%)
Dyspepsia	3(14%)	-
Wheezing	3(14%)	-
Rhinitis	1(5%)	2 (9%)
Chest discomfort	2(9%)	1(5%)
Musculoskeletal pain	1(5%)	1(5%)
Back pain	-	2 (9%)
Dyspnoea	-	2 (9%)

Table 4. *Treatment-emergent adverse events by preferred term in >1 subject. The majority of the TEAEs were considered mild with no TEAEs considered severe. The most common TEAE was headache which was reported in 4 subjects on active treatment and in 3 subjects in placebo treatment. Dyspepsia was the most common gastrointestinal AE that was considered related to treatment. Other TEAEs were considered a result of the allergen challenge. *One subject was withdrawn from the study prior to the second treatment period (placebo) due to a positive urine drugs of abuse test.*

The only AQX-1125 related adverse events were considered GI related and were mild and self limited

Clinical Development of AQX-1125

Current Phase II: Studies

- Interstitial Cystitis/Bladder Pain Syndrome "LEADERSHIP" Study
  - Parallel group, randomized, double-blind, placebo-controlled, multicenter study
  - 6 weeks dosing
  - Bladder pain and IC/BPS symptom endpoints
- COPD Exacerbation "FLAGSHIP" Study
  - Parallel group, randomized, double-blind, placebo-controlled, multicenter study
  - 12 weeks dosing
  - Exacerbation rates and COPD symptom endpoints

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

"The Effects of AQX-1125, a Selective Oral SHIP1 Activator on Lipopolysaccharide-Induced Cellular and Biochemical Changes in Sputum From Healthy Volunteers"

and

"Prophylactic or Therapeutic AQX-1125, A Small Molecule SHIP1 Activator, Inhibits Bleomycin-Induced Pulmonary Fibrosis"

Summary

SHIP1 is a novel drug target which controls PI3K-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 PI3K pathway resulting in an inhibition of Akt phosphorylation and reduced chemotaxis. AQX-1125, has high water-solubility, good oral bioavailability, a terminal half-life suited to once per day dosing, minimal metabolism, and distributes to the lung at high concentrations.

Once daily orally administered AQX-1125 inhibited the late asthmatic response in subjects with atopic asthma following inhaled allergen challenge. The magnitude of improvement on FEV_1 was 150 mL during the LAR and a maximum improvement of 180 mL observed at trough FEV_1. The effect on lung function was correlated with nominal reductions in the absolute and differential sputum cell counts for eosinophils, neutrophils and macrophages. Together with the safety and pharmacokinetics, this study demonstrates the required pharmacodynamic effect for the treatment of atopic asthma and further supports the clinical development of AQX-1125 in inflammatory respiratory diseases.

References

1. Helgason *et al.* Targeted disruption of SHIP leads to hemopoietic perturbations, lung pathology, and a shortened life span. *Genes & Dev.* 1998;12:1610-1620.
2. Ong *et al.* Small molecule agonists of SHIP1 inhibit the phosphoinositide 3-kinase pathway in hematopoietic cells. *Blood.* 2007;110:1942-1949.