AQX-1125, A SHIP1 Activator In Clinical Development For Pulmonary Inflammation: Pharmacokinetics, Metabolism And Tolerability In Healthy Human Volunteers

Patrick Tam, Lloyd F. Mackenzie, Judy Toews, Grant R. Stenton, Curtis Harwig, Jeffrey Raymond, Csaba Szabo, Thomas MacRury and David Chernoff

Aquinox Pharmaceuticals Inc., Richmond, BC, Canada

Abstract

Rationale: Pharmacological modulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway is an established approach to controlling inflammatory disorders. SH2-containing inositol-5'-phosphatase 1 (SHIP1) metabolizes PI(3,4,5)P3 to PI(3,4)P2. SHIP1-deficient mice exhibit pulmonary inflammation, characterized by significant granulocyte recruitment into the lung, while pharmacological SHIP1 activation exerts anti-inflammatory effects in preclinical models of lung inflammation. Here we present an overview of the results of a Phase I study with AQX-1125, a small molecule SHIP1 activator, and compare the pharmacokinetic profile of the compound across three species (human, dog and rat).

Methods: AQX-1125 was tested in a three-part Phase I study that included a single ascending dose, a multiple ascending dose and a food effect component in healthy human volunteers. In addition, the pharmacokinetics, *in vitro* metabolism, tissue distribution (quantitative whole-body autoradiography) and excretion of AQX-1125 were investigated in rats and/or dogs. Plasma concentrations were quantified by a validated/qualified HPLC tandem mass spectrometry method.

Results: Oral administration of AQX-1125 in healthy human volunteers (17, 50, 100, 200, 400 and 542 mg doses in single dose, and 100, 250 and 542 mg doses in multiple dose studies with 10-days repeat administration) demonstrated dose-proportional pharmacokinetics over the dose-range tested. AQX-1125 was rapidly absorbed with maximal plasma concentration occurring approximately 1-2 h post-dose. Plasma concentrations declined in a log-linear fashion with a terminal elimination half-life of approximately 20 h. Food had no effect on the absorption of AQX-1125 (200 mg capsule). The drug was well tolerated both in the single ascending dose and the multiple ascending dose Phase 1 trial. The plasma levels obtained in humans exceeded the levels required to achieve *in vivo* efficacy in preclinical models of lung inflammation. PK/ADME studies in the rat and/or dog show high bioavailability, lack of *in vitro* metabolism by liver microsomes, high tissue concentrations in the lung, liver and urinary tract and insignificant drug concentrations in the brain, spinal cord and the eye.

Conclusions: AQX-1125 was well tolerated in healthy human subjects and demonstrated dose-proportional pharmacokinetics with a terminal half-life supportive of once-daily oral administration. AQX-1125 showed no significant *in vitro* metabolism across species and the pharmacokinetics are well correlated between the three species studied. Preclinical data showing efficacy of AQX-1125 in standard pulmonary inflammation models, coupled with the safety, tolerability and pharmacokinetic data in humans, supports moving to proof-of-concept clinical efficacy studies in pulmonary inflammation.

Introduction: Targeting SHIP1

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 restricted to hematopoietic derived cells - limits off-target toxicity
- SHIP1 activation redirects cellular PI3K signaling, rather than preventing it

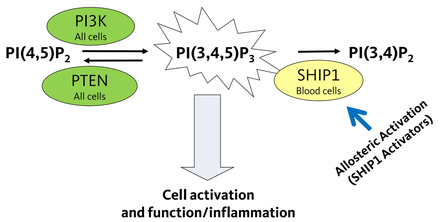


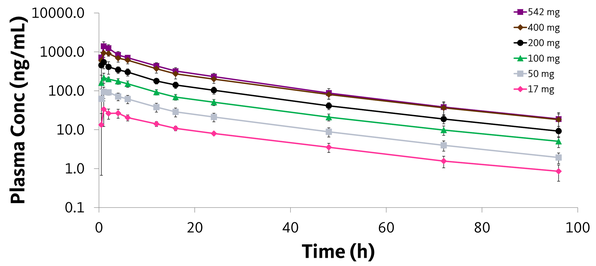
Figure 1. *SHIP1 and PI3K signalling. SHIP1 activators redirect PI3K signalling, PI3K inhibitors block PI3K signalling.*

Phase 1 – Subject Demographics

Table 1. *Subject demographics for FIM study for AQX-1125*

	Phase 1 Study Part		
	SAD	MAD	FE
No. of Subjects (M/F)	16 (10/6)	24 (12/12)	12 (7/5)
Age (yr)	29 (20-45)	28 (21-44)	28 (18-44)
Body Weight (kg)	75.7 (63.8-95.5)	69.6 (50.6-92.3)	72.4 (59.5-87.9)
Mean BMI (kg/m^2)	24.3 (20.2-28.6)	23.3 (20.1-27.2)	24.0 (20.8-72.4)

Phase 1 – Single Dose Pharmacokinetics



PK Parameter	AQX-1125 Dose (mg)					
	17	50	100	200	400	542
C_{max} (ng/mL)	28.5	99.7	231	555	1025	1363
$AUC_{0\text{-}inf}$ (h × ng/mL)	581	1637	4007	8000	15755	18448
$t_{½}$ (h)	22.4	20.7	21.4	20.6	20.6	19.5

Figure 2 and Table 2. *Single dose pharmacokinetics of AQX-1125 following a single oral administration healthy human volunteers. Plasma concentration-time profiles of AQX-1125 in healthy human volunteers (N=5 or 6 per group). Mean values (±SD) are shown.*

The pharmacokinetics of AQX-1125 support a once-daily dose regimen

Phase 1 – Steady State Achieved Following Once Daily Administration

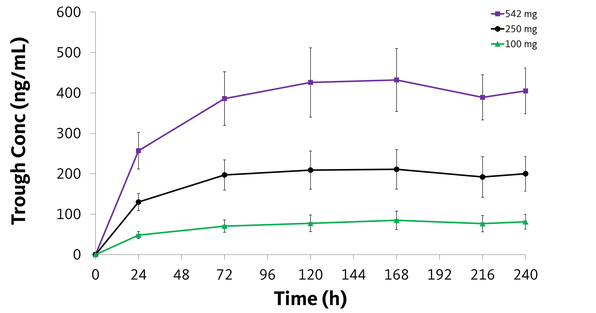


Figure 3. *Steady state plasma concentration achieved following repeated daily oral administration of AQX-1125.*

Steady state trough concentrations were achieved following approximately 5-7 days of once-daily dosing

Phase 1 – AQX-1125 Demonstrates Dose Proportional Dose-Exposure Relationship

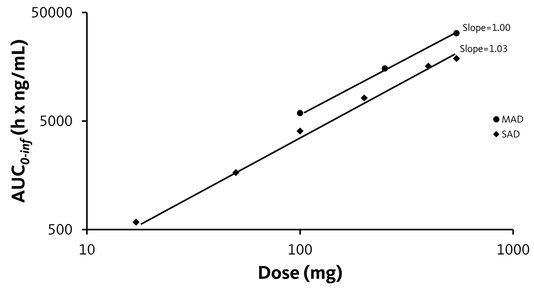


Figure 4 . *Proportional AQX-1125 dose-exposure relationship.*

Mean $AUC_{0\text{-}inf}$ values increased in a dose-proportional manner

Phase 1 – Food Effect on PK

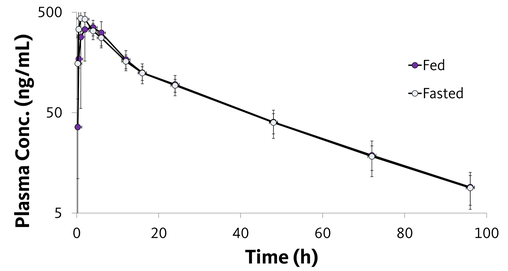


Figure 5. *The effect of food on the pharmacokinetics of 200 mg AQX-1125 capsules.*

The 90% CI limits for the geometric mean ratio (Fed/Fasted) for $AUC_{0\text{-}inf}$ (0.94-1.04) indicate the extent of drug absorption was not altered by food

Safety and Tolerability of AQX-1125

- No severe adverse events
- No clinically significant effects on vital signs and physical examinations
- No changes or trends of clinical significance to ECG parameters
- No clinically important trends in clinical laboratory investigations

Single and multiple doses up to 542 mg for 10 consecutive days were safe and well-tolerated

Distribution, Metabolism and Excretion of ^{14}C-AQX-1125

Table 3. *In vitro metabolism of ^{14}C-AQX-1125 in human hepatocytes*

Conc (µM)	Time (min)	% Radioactivity				
		Parent AQX-1125	Peaks			
			P1	P2	P3	P4
10	0	99.6	-	0.42	-	-
10	240	98.2	-	0.44	1.4	-
100	0	99.5	-	0.52	-	-
100	240	96.9	0.55	0.55	1.0	0.14

AQX-1125 was minimally metabolized in human hepatocytes

Distribution, Metabolism and Excretion of ^{14}C-AQX-1125

Table 2. *Interspecies comparison of the metabolism of AQX-1125*

Species/Gender	% Recovery Compared to Time Zero			
	Phase I, Metabolism		Phase II, Glucuronidation	
	60 min	120 min	30 min	60 min
Rat/Male	103	102	100	107
Rat/Female	105	105	96	105
Dog/Male	103	104	105	103
Dog/Female	98	99	102	106
Human/Mixed Gender	102	99	90	103

AQX-1125 was metabolically stable to Phase I and Phase II metabolism when incubated with hepatic microsomes prepared from the rat, dog and human

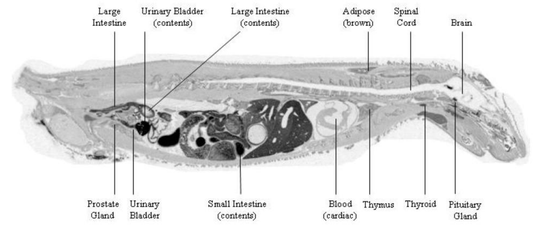


Figure 6. *Distribution and excretion of ^{14}C-AQX-1125 in the rat.*

Distribution and Excretion: most extensive in the lung, tissues of drug excretion and least extensive in the brain, spinal and the eye

Ongoing Clinical Development of AQX-1125

Phase 2A Trials

- Inhaled Allergen Challenge (Asthma POC)
  - Randomized, placebo-controlled, double-blind, 2-way cross-over study in 22 mild to moderate asthmatics, 7 days dosing
  - Lung function, sputum leukocytes and cytokine endpoints
  - Safety and pharmacokinetics
- Inhaled LPS Challenge (COPD POC)
  - Randomized, placebo-controlled, double-blind, 2-way cross-over study with 7 days dosing of placebo and active treatments.
  - Sputum leukocytes and cytokine endpoints
  - Safety and pharmacokinetics

Summary

- AQX-1125 is safe up to 542 mg for 10 days
- AQX-1125 is well absorbed and the pharmacokinetics supports once-daily regimen
- Dose proportional exposure demonstrated
- Absorption of drug is not affected by food
- Drug is metabolically stable, extensively distributed to the lung and excreted via hepatobiliary and renal systems
- Currently under investigation in Proof-of-Concept for asthma and COPD indications