AQX-1125, a SHIP1 activator in clinical development for pulmonary inflammation: Pharmacokinetics, metabolism and tolerability in healthy humans volunteers

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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. 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.

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