AQX-1125, a Small Molecule SHIP1 Activator, is Effective in a Murine NASH Model

J.L. Cross, C. Harwig, P. Tam, J. Toews and L.F. Mackenzie

Aquinox Pharmaceuticals (Canada) Inc., Vancouver, BC, Canada

ABSTRACT

Non-alcoholic steatohepatitis (NASH) is a progressive liver disease that is characterized by steatosis and liver inflammation leading to fibrosis and culminating in cirrhosis and liver failure. Obesity, hyperlipidemia and diabetes are risk factors for the development of NASH and it represents a rapidly growing concern in developed countries. There are currently no approved therapies for NASH.

The chronic inflammatory component of NASH is a key step towards the pathological development of hepatic fibrosis and it therefore represents a strategic area for intervention to inhibit disease progression. The PI3K pathway plays an important role in driving inflammation and the expression of SHIP1, a negative regulator of this pathway, has been inversely correlated with liver fibrosis in patients with chronic hepatitis C infection[1]. Pharmacological activation of SHIP1 has emerged as a novel approach to regulate inflammation. AQX-1125 is the first clinical-stage, once-daily, oral, SHIP1 activator with demonstrated anti-inflammatory effects in animals and humans[2-3]. We have previously demonstrated positive effects of AQX-1125 in pre-clinical models of lung fibrosis and in inflammatory bowel disease.

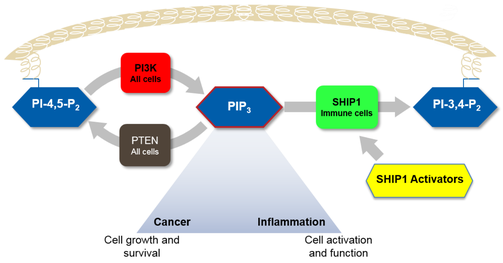
The ability of AQX-1125 (3, 10 or 30 mg/kg/day) to reduce inflammation and fibrosis was assessed in the diabetic mouse model of NASH (STAM™). NASH was induced in mice by a single streptozotocin injection 2 days after birth, followed by a high-fat diet from 4 weeks of age. AQX-1125 was dosed for 3 weeks, starting at 6 weeks of age. At 9 weeks, mice were sacrificed for evaluation of histopathology, non-alcoholic fatty liver disease score (NAS) and fibrosis.

Mice with NASH treated with AQX-1125 at 30 mg/kg showed a significant improvement in their overall NAS, comprised of the histopathological evaluation of steatosis, lobular inflammation and hepatocellular ballooning. AQX-1125 was also able to reduce macrophage infiltration into the liver and decreased the fibrotic area. These data suggest that AQX-1125, a SHIP1 activator, may be beneficial in the treatment of inflammation with associated fibrotic disease.

BACKGROUND

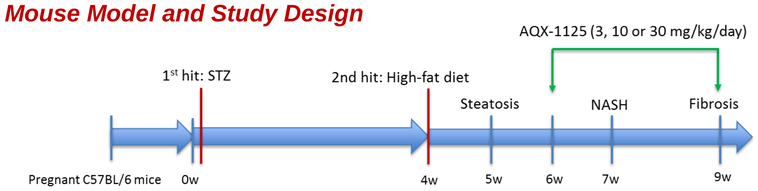
Targeting SHIP1

- PI3K/SHIP1 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



STUDY DESIGN

Mouse Model and Study Design

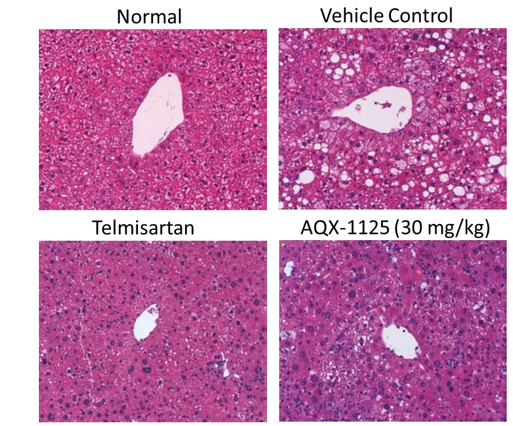


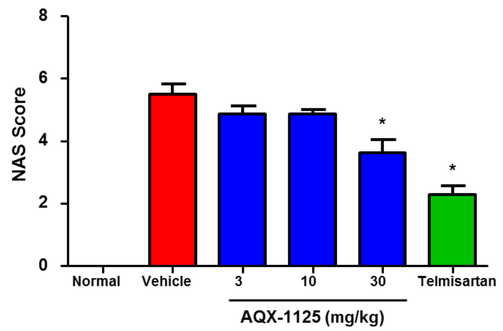
AQX-1125 was assessed in the diabetic mouse model of NASH developed by the Stelic Institute & Co., Inc., Japan. C57BL/6 mice were injected two days after birth with a single dose of streptozotocin and fed a high-fat diet from 4 weeks onwards.

AQX-1125 was administered by liquid gavage at 3, 10 or 30 mg/kg/day starting at Week 6. At Week 9, the effect of AQX-1125 was evaluated by histopathology for features of inflammation, steatosis and fibrosis. The positive control, Telmisartan was dosed at 10 mg/kg/day from Week 6-9.

RESULTS

AQX-1125 Improves NASH Liver Histopathology and Overall NAS Score

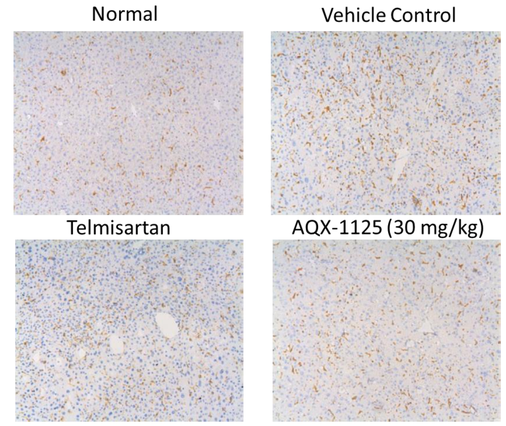




Liver sections from NASH mice treated with AQX-1125 at 30 mg/kg/day for 3 weeks show a noticeable histopathological improvement and a statistically significant improvement in overall NAS score. A representative H&E stained section is shown (top) and NAS results are expressed graphically (bottom) as the mean ± SEM (n=7-8), * $p < 0.01$ vs. vehicle.

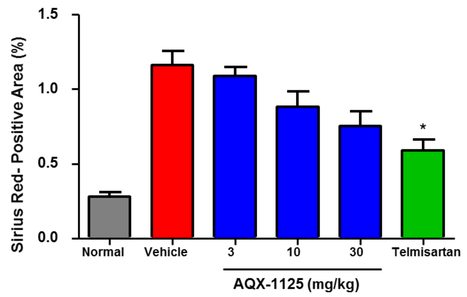
RESULTS

AQX-1125 Reduces Macrophage Infiltration



AQX-1125 reduced the number of macrophages in the livers of NASH mice. A representative F4/80-stained section is shown above.

AQX-1125 Reduces Fibrosis



AQX-1125 showed a dose-dependent trend towards reducing the fibrotic area in the livers of NASH mice. Results are expressed as the mean ± SEM (n=6-8).

SUMMARY

In summary, AQX-1125, a SHIP1 activator, at 30 mg/kg, significantly inhibited the overall NAS score, reduced macrophage infiltration into the livers of NASH mice and trended towards a reduction in fibrotic area.

REFERENCES

1. Katsounas *et al., 2011; J Infect Dis.*, **204:** 1181-5.
2. Stenton *et al., 2013; Br J Pharmacol.*, **168:** 1519-29.
3. Leaker *et al., 2014; Clin Exp Allergy.*, **44:** 1146-53.

FOR ADDITIONAL INFORMATION

Please contact: Brendan Payne
Senior Manager, Investor Relations
Email: bpayne@aqxpharma.com
Phone: 604-629-9223 x 109