GS-9674 shows reduced side effect profile in mice, monkeys and human phase I studies compared to its predecessor Px-102

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Background
FXR agonists have demonstrated very promising clinical results in the treatment of liver disorders. However, FXR agonists have demonstrated improvements in barrier function and this effect is anti-inflammatory and anti-fibrotic. Therefore, this study was designed to investigate the potential of GS-9674 as a FXR agonist.

METHODOLOGY & RESULTS
We initially developed a highly functional, non-estrogen FXR agonist, Px-102, and tested it in preclinical NASH model, and in a single ascending (SAD) and seven-day multiple dose (MAD) phase study. In the SAD study, Px-102 was given to rats at two doses of 0.1-4 mg/kg. FXR agonist was evident from dosedependent increases in plasma FGF-19. The MAD study revealed dose increases associated with the cardio-metabolic parameters. However, ALT and AST levels increased dose-dependently and liver size dropped. In addition, FGF-19 induction was shown to increase plasma FXR levels. The lack of FXR activity in non-hepatic tissues was not observed. These FXR agonist effects prompted us to explore the potential FXR agonist for FXR-mediated changes to be investigated in non-hepatic tissues. Therefore, C635-A1 mice on a high fat diet (HFD) showed similar changes whereas FXR+ mice of the same background showed no Px-102 induced effects. This suggests that FXR agonist is likely to increase ALT increases rather than bolus liver fibrosis. The next candidate, GS-9674, showed no ALT increases and only very modest total cholesterol changes. Comparing the results of fibrosis of GS-9674 in Px-102 in a cholesterol-free HFD rat model of acholesterolemic fibrosis revealed similar efficacy at 30 mg/kg GS-9674 versus 0 mg/kg of Px-102. Moreover, GS-9674 had no effects on HDLC, whereas Px-102 lowered HDLC in a HFD-chow model. Despite similar FGF-19 induction, GS-9674 was tested in a SAD and 21 days MAD human phase I study and displayed dose-dependent induction of FGF-19, whereas cholesterol parameters remained unchanged up to 100 mg/kg.

SUMMARY & CONCLUSION
In this translational effort the human side effects of Px-102 were recapitulated in an appropriate animal model. Using the model as a screen we identified GS-9674 as a potential FXR agonist with minimally tested activity. Subsequent preclinical evaluation in non-human primates and initial clinical studies are indicative of reduced side effects for further clinical development in NASH.