**From mice to men - Plasma and fecal bile acid composition as sensitive markers of pharmacological FXR activation: Results from animal and human phase I studies using the potent and selective FXR agonist PX20606**

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**BACKGROUND**

FXR (NURR1) is a bile-acid-activated nuclear receptor which controls several steps in bile acid synthesis and conjugation. Beyond its primary function, FXR exerts strong effects on cholesterol and lipid metabolism, and on liver steatosis, inflammation and fibrosis. Recently, a phase I/II trial using Oleoerucic Acid (OCA) as the first clinical stage FXR agonist has demonstrated improvements in all histopathological parameters underlying Non-alcoholic Steato-hepatitis (NASH). However, OCA demonstrated side effects such as worsening the HHb/LDL ratio or pruritus. This prompted a quest for novel, synthetic and more selective FXR agonists with an improved therapeutic profile. PX20606 is one such an FXR agonist which we developed from early stage drug discovery up to phase I clinical studies. In order to monitor PX20606-mediated FXR activation in these human volunteers, it was essential to qualify pharmacochemical biomarkers from blood or feces that would enable to extrapolate from PX20606 mediated changes in FXR target gene expression in animals to the human situation without the need for isocapnia. Here, we present data on changes in FXR target gene expression along with their corresponding changes in plasma and fecal bile acid profiles, plasma FGF-19 levels from mouse, monkey and human phase I studies.

**MATERIALS & METHODS**

15 days repeated oral dosing study in mice

10 days repeated oral dosing study in normal and hypercholesterolemic rats

10 days repeated oral dosing study in cynomolgus monkey

7 days clinical Phase I randomized placebo controlled study

**RESULTS**

**Bile acid species in plasma**

Expression changes in Cyp7a1 and Cyp27a1 upon FXR agonist treatment suggest changes in bile acid pool composition

**Bile acid species in plasma**

FXR induced changes in Cyp7a1 and Cyp27a1 as well as control over conjugation enzymes (Black, Blue) cause shifts in bile acid post-compartment.

**REFERENCES**

1 Klempn, T Claudel, J Llaur, B. Maier: The feline nurr1 receptor (FXR) as modulator of bile acid metabolism J Vet Endocrinol Disord (5) (2008), pp. 219–226


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