Efficacy of MET409, a potent, novel, non-bile acid FXR agonist, in rodents and cynomolgus monkeys

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INTRODUCTION

The farnesoid X receptor (FXR) is a ligand-activated transcription factor highly expressed in the liver and intestinal tract. OCA, a semi-synthetic bile acid FXR agonist, has shown clinical efficacy in non-alcoholic steatohepatitis (NASH), but is associated with significant pruritus and elevations in LDL cholesterol. MET409 is a potent non-bile acid FXR agonist (EC50 human = 16nM, ECS0 mouse = 2nM) with no cross-reactivity for TGR5, PXR, VDR and PPARα, δ and γ.

METHODS

FXR functional engagement in rodents was determined by measuring FXR target gene expression in C57BL/6 mice (n=8) in the liver and ileum 24hrs after a single oral dosing. MET409 efficacy was tested in C57BL/6 mice in which NASH was induced via a 33-week diet high in trans-fat, fructose and cholesterol (Gubra, Denmark). Following 8 weeks of treatment (QD PO) at 3 and 10 mg/kg (n=12), efficacy was assessed via histological scoring of NASH and fibrosis. MET409 activity was evaluated in male cynomolgus monkeys (n=6) on a normal diet. Serum drug levels, FGF19, and C4 were measured after daily oral dosing for 7 days at 1 and 3 mg/kg.

RESULTS

Acute Gene Regulation in C57BL/6 Mice

Efficacy in Mouse DIO-NASH Model

Pharmacokinetics and Pharmacodynamic Biomarkers in Cynomolgus Monkey – Day 7

CONCLUSIONS

- MET409 is a potent, non-bile acid FXR agonist from a novel chemical scaffold.
- MET409 shows dose responsive gene regulation 24 hours post dose at doses as low as 1 mg/kg in mice.
- MET409 decreases NASH and fibrosis in multiple mouse models (also see poster 2026).
- In Cynomolgus monkey MET409 shows dose proportional PK, sustained exposure and regulates plasma PD biomarkers FGF19 and C4.
- MET409 is a lead candidate for clinical development in hepatobiliary and other diseases.

DISCLOSURES