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

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INTRODUCTION

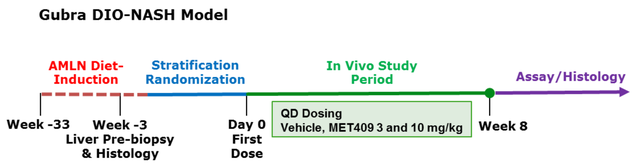
The farnesoid X receptor (FXR) is a ligand activated transcription factor highly expressed in the liver and intestinal tract. OCA, a semi-synthetic bile acid FXR agonist, has shown clinical efficacy in non-alcoholic steatohepatitis (NASH), but is associated with significant pruritus and elevations in LDL cholesterol. MET409 is a a potent non-bile acid FXR agonist (EC_{50} human = 16nM, EC50 mouse = 2nM) with no cross-reactivity for TGR5, PXR, VDR and PPARα, δ and γ.

AIM

The aim of this study was to evaluate MET409, a non-bile acid FXR agonist, from a novel chemical scaffold, for efficacy in a pre-clinical mouse NASH model and activity in cynomolgus monkeys.

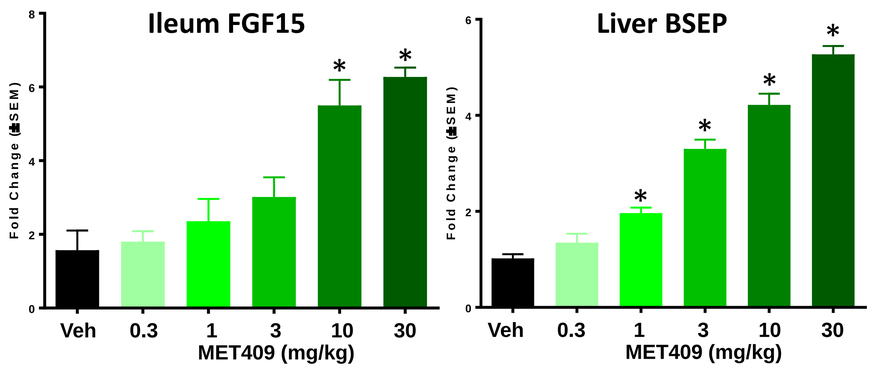
METHODS

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 orally dosing for 7 days at 1 and 3 mg/kg.

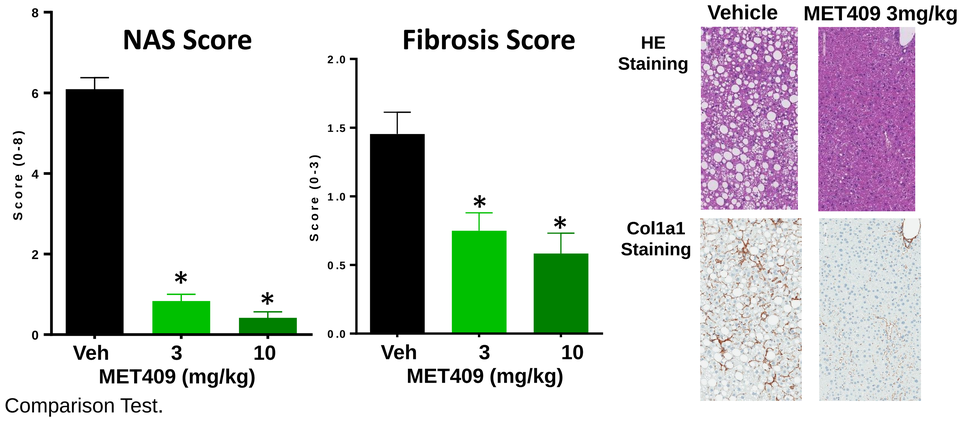


RESULTS

Acute Gene Regulation in C57BL/6 Mice

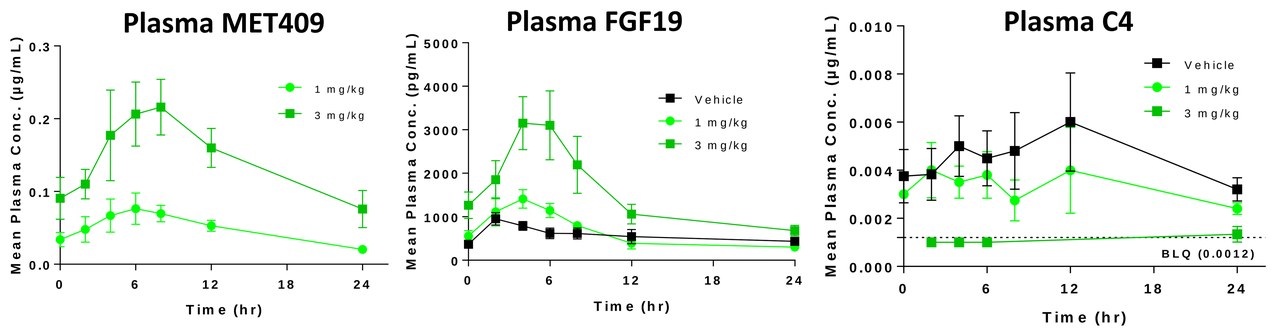


Efficacy in Mouse DIO-NASH Model



Data expressed as mean ± SEM *: P<0.05 vs. Vehicle One-way ANOVA with Dunnett's Multiple Comparison Test.

Pharmacokinetics and Pharmacodynamic Biomarkers in Cynomolgus Monkey – Day 7



		Vehicle Mean ± SD	MET409 1 mg/kg Mean ± SD	MET409 3 mg/kg Mean ± SD
MET409	AUC_{24} (µg.hr/ml)	--	1.17 ± 0.20	3.44 ± 0.37
	Cmax (µg/ml)	--	0.08 ± 0.02	0.23 ± 0.04
FGF19	AUC_{24} (pg.hr/ml)	13,901 ± 5,900	15,208 ± 6,689	36,216 ± 15,053
	Cmax (pg/ml)	1,039 ± 328	1,542 ± 628	3,957 ± 1,654
C4	AUC_{24} (µg.hr/ml)	0.103 ± 0.076	0.064 ± 0.050	BLQ (<0.029)
	Cmax (µg/ml)	0.006 ± 0.005	0.005 ± 0.003	BLQ (<0.0012)

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

B.W., S.G., J.N., K.D., H.D., A.M., K.L., A.O., J.Q., N.L., E.B., K.S. and N.S. are employees and equity holders in Metacrine Inc.

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