MET409, a potent, non-bile acid sustained FXR agonist, shows rapid disease reversal in a diet-induced obese mouse model of biopsy-confirmed NASH

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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 dose limiting pruritus and LDL increase.

AIMS

The aims of this study were to examine the efficacy time course of MET409, a potent, non-bile acid *sustained* FXR agonist, in a pre-clinical mouse NASH model and compare that activity to a *transient* FXR agonist M1166.

MATERIAL & METHODS

FXR transient or sustained activity was determined by measuring hepatic and intestinal FXR target gene expression in lean C67BL/6 mice, 4 and 24 hrs after a 10 mg/kg dose. For assessment of anti-NASH efficacy, male C57BL/6 mice fed AMLN diet high in trans-fat, fructose and cholesterol for 34 wks. Only DIO-NASH mice with biopsy-confirmed steatosis (score ≥2) and fibrosis (score ≥1) were included. Efficacy was assessed via histological assessment of NAFLD Activity Score (NAS) and Fibrosis Stage after 2, 4 or 8 wks of treatment with *sustained* agonist MET409 (10 mg/kg, p.o.) or 8 wks with the *transient* FXR agonist M1166 (10 and 30 mg/kg, p.o.).

CONCLUSIONS

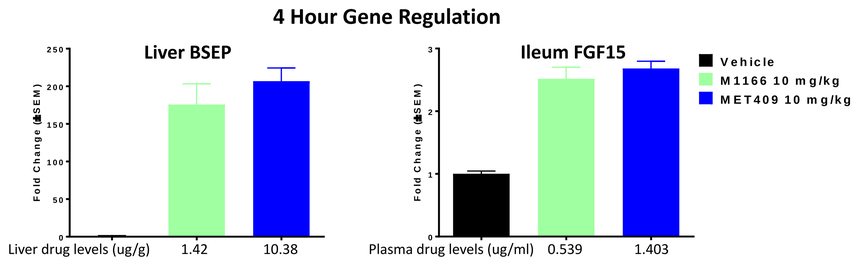
MET409 is a potent, systemic, *sustained* FXR agonist that demonstrates rapid efficacy in DIO-NASH mice. Efficacy achieved with 2 wks of MET409 was superior to 8 wks treatment with an equally potent *transient* FXR agonist. MET409 significantly improved fibrosis, while the *transient* FXR agonist showed no effect. MET409 is a promising drug candidate for rapid improvement in liver health by reducing NASH and fibrosis.

RESULTS

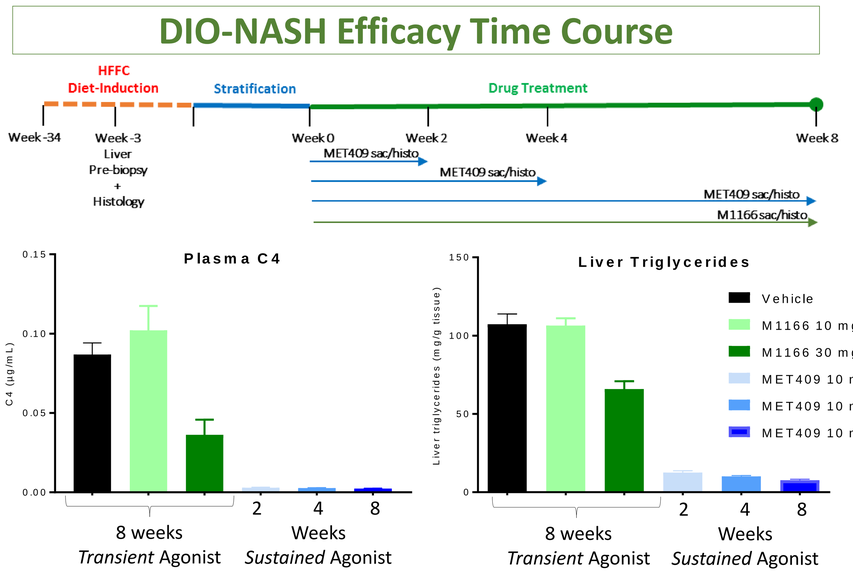
In Vitro Potency

	Mouse EC50 (nM)	Human EC50 (nM)
MET409	2nM	16nM
M1166	5nM	24nM

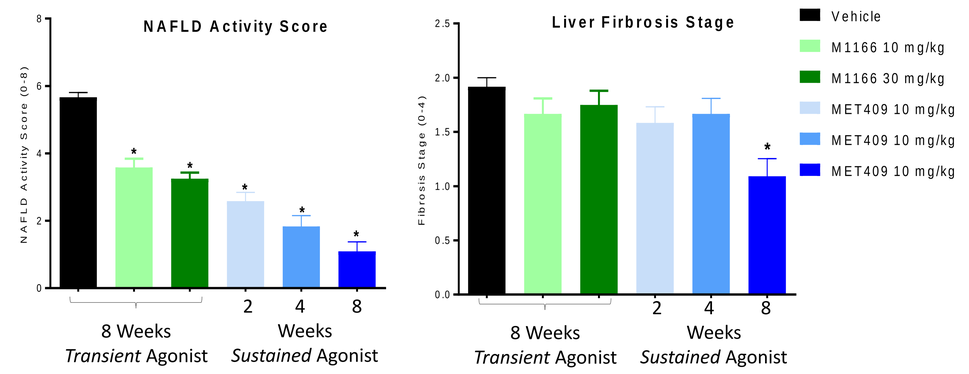
Mouse Single Dose PK/PD Analysis



DIO-NASH Efficacy Time Course

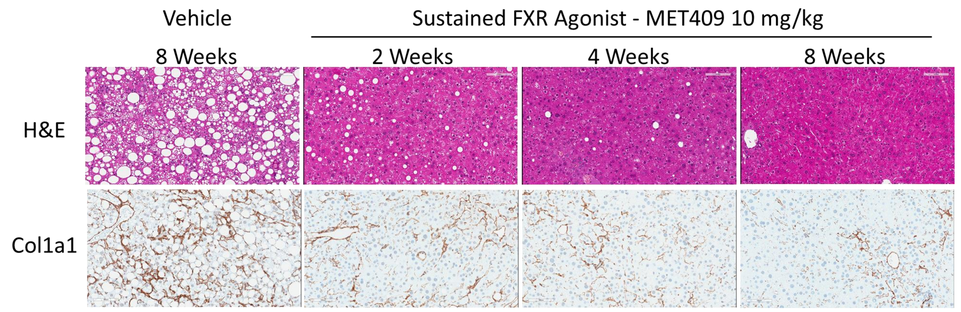


DIO-NASH Efficacy Time Course



Terminal Plasma Clinical Chemistry and Histopathology Scores
Mean (* p<0.05 One-Way ANOVA)

		Transient Agonist M1166		*Sustained* Agonist MET409			
	Vehicle (8wks)	10 mg/kg (8wks)	30 mg/kg (8wks)	10 mg/kg (2wks)	10 mg/kg (4wks)	10 mg/kg (8wks)	Pre-dosing
ALT (U/L)	204	206	247	41*	40*	32*	n/a
AST (U/L)	233	206	291	79*	74*	68*	n/a
Steatosis	3.0	2.7	1.9*	1.3*	0.7*	0.3*	3.0
Inflammation	1.8	0.9*	1.3	1.3	1.2*	0.8*	1.7
Ballooning	0.8	0*	0*	0*	0*	0*	0.3
%Col1a1	8.4	6.1	7.2	6.7	7.8	5.4*	12.5



DISCLOSURES

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

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