Efficacy of the FXR agonist, MET409, in male and female mouse models of NASH and fibrosis

Brandee Wagner[1], Angelica Milik[1] Helen Mondala[1], Steven Govek[1], Johnny Nagasawa[1], Karensa Douglas[1], Kyoung-Jin Lee[1], Alvaro Ortiz[1], Eric Bischoff[1], Dipti Deshpande[2], Gretchen Butler[2], Nikole Siegmund[2], Michael Briggs[2], Ken Song[1], and Nicholas Smith[1]

[1]Metacrine Inc., San Diego, CA USA, [2]Woodland Biosciences, Grafton, MA USA

12780 El Camino Real, Suite 301
San Diego, CA 92130
www.metacrine.com

INTRODUCTION

The farnesoid X receptor (FXR) is a ligand activated transcription factor highly expressed in the liver and intestinal tract. Activating FXR has been shown to be clinically beneficial at reducing steatohepatitis and fibrosis in non-alcoholic steatohepatitis (NASH) patients

AIM

Herein, we assess the efficacy of MET409, a potent non-bile acid FXR agonist, developed from a unique chemical scaffold, in a male NASH mouse model and novel female mouse liver fibrosis model.

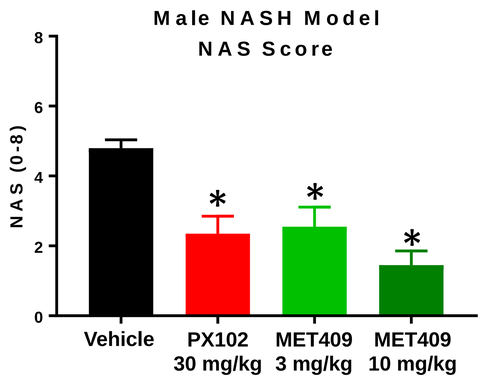
MATERIAL & METHODS

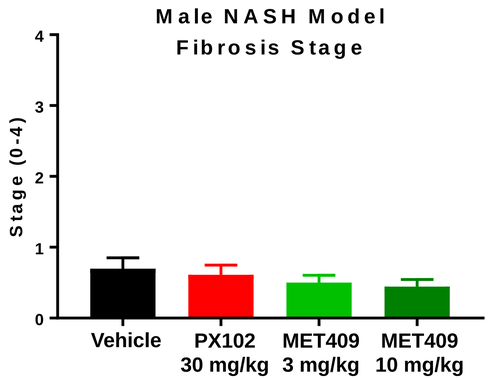
NASH was induced in male and female C57BL/6 mice by inducing hyperglycemia with streptozotocin (STZ) followed by a modified high fat diet (Research Diets D09100301 for males and D02062102 for females). In addition, females were injected twice weekly with thioacetamide (TAA) to increase fibrosis. Male and female mice were treated for 8 or 6 weeks, respectively, with FXR agonists PX-102 (30 mg/kg), MET409 (3 and 10 mg/kg) or vehicle (n=10 per group). At study completion livers, were assessed histologically for steatohepatitis, inflammation, ballooning and fibrosis. In addition, qPCR and biochemical assays were used to examine fibrosis, inflammation and steatosis.

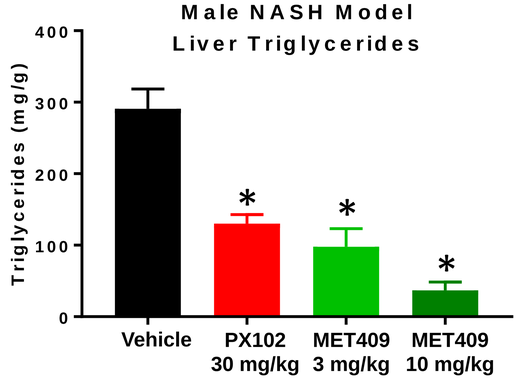
C57 Male STZ + Diet Induced NASH

C57 Female STZ + Diet + TAA Induced Fibrosis

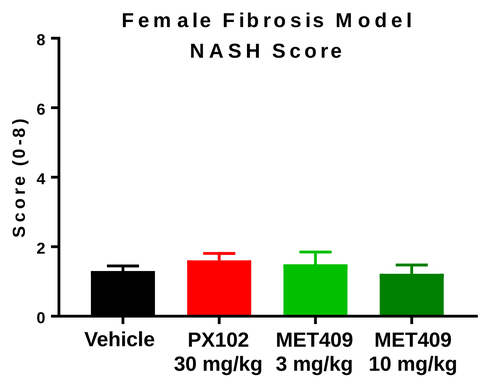
RESULTS

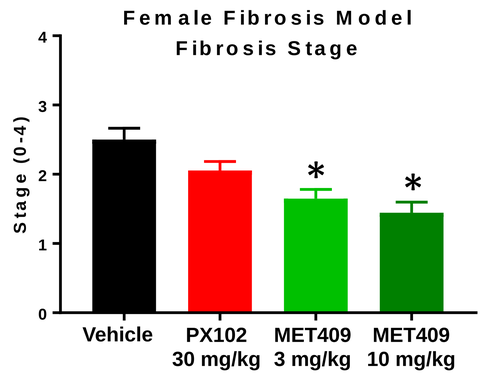






Male NASH Model	Vehicle Mean ± SEM	PX102 30 mg/kg Mean ± SEM	MET409 3 mg/kg Mean ± SEM	MET409 10 mg/kg Mean ± SEM
Steatosis (0-3)	3 ± 0	1.6 ± 0.2 *	1.1 ± 0.2 *	0.5 ± 0.2 *
Ballooning (0-2)	1.7 ± 0.2	0.8 ± 0.2 *	0.7 ±0.2 *	0 ± 0 *
Inflammation (0-3)	0.1 ±0.1	0.2 ± 0.2	0.75 ± 0.4	1.2 ± 0.5
Collagen 1a1 hepatic mRNA (Fold rel. Veh)	1 ± 0.3	0.14 ± 0.04 *	0.17 ± 0.03 *	0.12 ± 0.07 *
TIMP2 hepatic mRNA (Fold rel. Veh)	1 ± 0.2	0.53 ± 0.14 *	0.39 ± 0.08 *	0.31 ± 0.03 *
MMP2 hepatic mRNA (Fold rel. Veh)	0.8 ± 0.3	0.59 ± 0.32	0.12 ± 0.05	0.08 ± 0.04





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

CONCLUSIONS

- MET409 shows dose responsive improvement in male NASH model, primarily decreasing steatosis and hepatocyte ballooning.
- Minimal fibrosis histopathology in male model, however MET409 clearly decreases fibrotic gene signature
- MET409 decrease fibrosis histopathology in female model in absence of NASH

DISCLOSURES

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

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES