Comparison of M480 and PX-102, two non-bile acid FXR agonists from different chemical scaffolds, in a diet-induced obese mouse model with 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. The semi-synthetic bile acid FXR agonist, obeticholic acid (OCA), has shown clinical efficacy in non-alcoholic steatohepatitis (NASH) in both NASH resolution and fibrosis improvement. However, OCA is also associated with significant pruritus and elevation in LDL cholesterol and these appear to be molecule specific and not a FXR class effect.

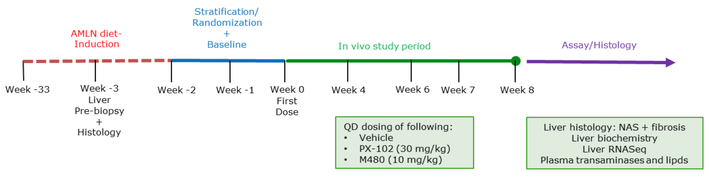
M480 and PX-102 represent non-bile acid/non-steroidal FXR agonists, each based on different chemical scaffolds. The structural classes from which M480 and PX-102 are derived induce different conformations of the FXR receptor as judged by crystallography. M480 has FXR activity both in the ileum and liver as assessed by activation of direct target genes downstream of FXR.

OBJECTIVES

Compare the efficacy of M480 and PX-102, two non-bile acid FXR agonists each derived from a unique chemical scaffold, in an in vivo NASH model.

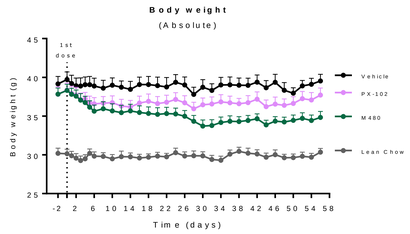
METHODS

Male C57BL/6 mice were fed a diet high in trans-fat, fructose and cholesterol (AMLN diet – D09100301, Research Diet, US). At 29 weeks, livers were biopsied under isoflurane anesthesia and only histologically-confirmed steatotic and fibrotic animals (steatosis score ≥2; Fibrosis Stage ≥1) were included. Animals were stratified based on fibrosis stage into groups (n=10-12) and treated with M480 at 10 mg/kg, PX-102 at 30mg/kg, or vehicle by oral gavage for 8 weeks. At the midpoint of treatment, plasma levels of ALT, AST, total cholesterol (TC), and total triglycerides (TG) were obtained. Following completion of treatment, mice were sacrificed and the liver was assessed histologically for NAFLD activity score (NAS), Galectin 3 staining, as well as fibrosis using morphometric scanning of Col1a1 staining. RNA-Seq analysis was also performed on liver tissue at the completion of the study. For the sequencing analysis, samples were multiplexed and run on an Illumina NextSeq 500 with single-end 75bp reads. An average sequencing depth of 23.9 million reads per sample was obtained.



RESULTS

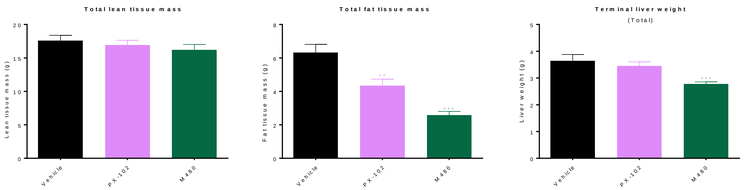
M480 improves body weight, liver weight and fat mass over PX-102



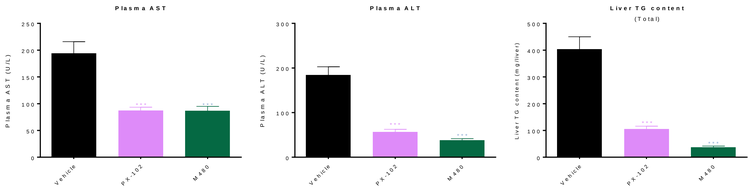
Food intake similar between groups

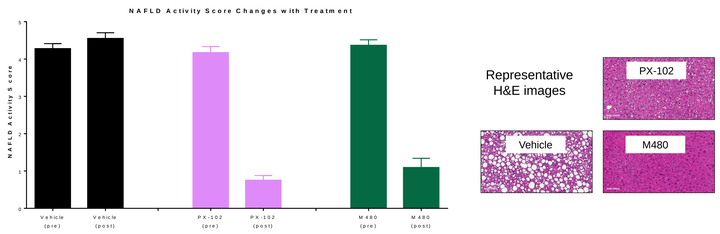
Day	Vehicle	PX-102	M480
5	3.0	2.2	1.9
12	3.0	3.0	3.3
19	3.1	2.9	3.3
26	2.8	3.0	3.5
33	3.0	3.3	3.9
40	3.2	2.9	3.0
47	2.3	3.0	3.7
54	3.0	3.1	3.4

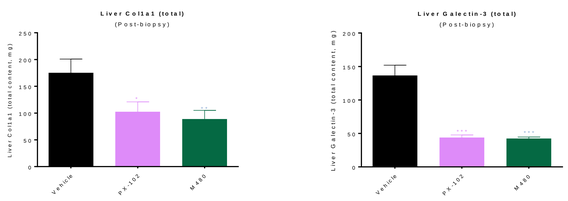
**Average 24hr food intake at specified day*



M480 and PX-102 both demonstrate robust efficacy in NASH

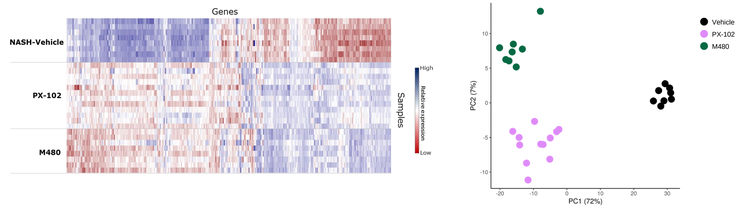




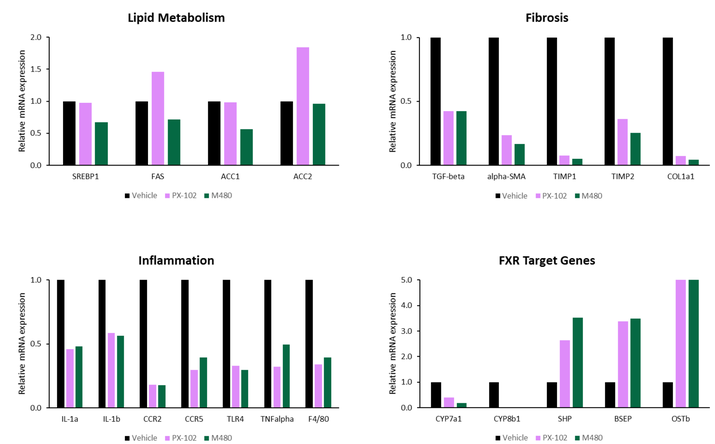


RNASeq Analysis of Liver at Treatment Completion – M480 vs PX-102

M480 and PX-102 lead to different gene expression signatures. PCA plot of 500 most differentially expressed genes shows distinct clustering of M480 vs PX-102.



M480 and PX-102 both beneficially regulate key fibrosis, inflammation and FXR target genes
M480 has beneficial effects on key enzymes with fatty acid metabolism as compared to PX-102



CONCLUSIONS

M480 and PX-102 are non-bile acid FXR agonists that show significant histological and biochemical improvements in a diet-induced mouse model of biopsy-confirmed NASH when administered therapeutically. RNA-Seq identified potentially relevant differences in gene regulation between M480 and PX-102 which are derived from different chemical scaffolds.

DISCLOSURE

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

M.F., K.R., N.V. are employees of Gubra

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