Metabolic, biochemical, histological, and transcriptomic effects of Firsocostat in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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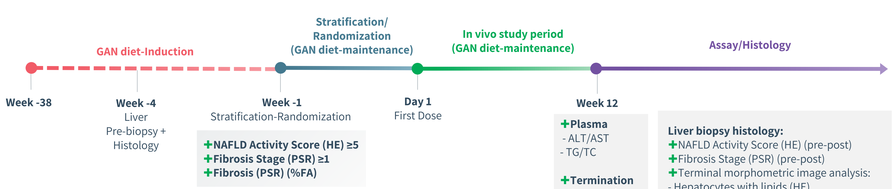
BACKGROUND & AIM

The acetyl-coenzyme A carboxylase (ACC) inhibitor firsocostat has been reported to promote NASH resolution (Loomba et al., Gastro, 2018) in phase 2 clinical trial testing for treatment of NASH.

The present study aimed to evaluate the metabolic, biochemical, histological and transcriptomic effects of 12 weeks of treatment with firsocostat in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of NASH with hepatic fibrosis.

1 Study outline



Group #	Animal	Gender	Strain	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	LEAN-CHOW	Male	C57BL/6JRj	10	**Vehicle**	PO	QD	5 ml/kg	-
2	DIO-NASH	Male	C57BL/6JRj	16	**Vehicle**	PO	QD	5 ml/kg	-
3	DIO-NASH	Male	C57BL/6JRj	16	**Firsocostat**	PO	QD	5 ml/kg	**5 mg/kg**

Figure 1. Study outline, groups and treatments. ALT: alanine aminotransferase; AST: aspartate aminotransferase; TC: total cholesterol; TG: triglycerides; QD: once daily; SC: subcutaneous; HE: Haematoxylin Eosin; PSR: Picro Sirius Red; IHC: Immunohistochemistry.

2 Metabolic and biochemical parameters

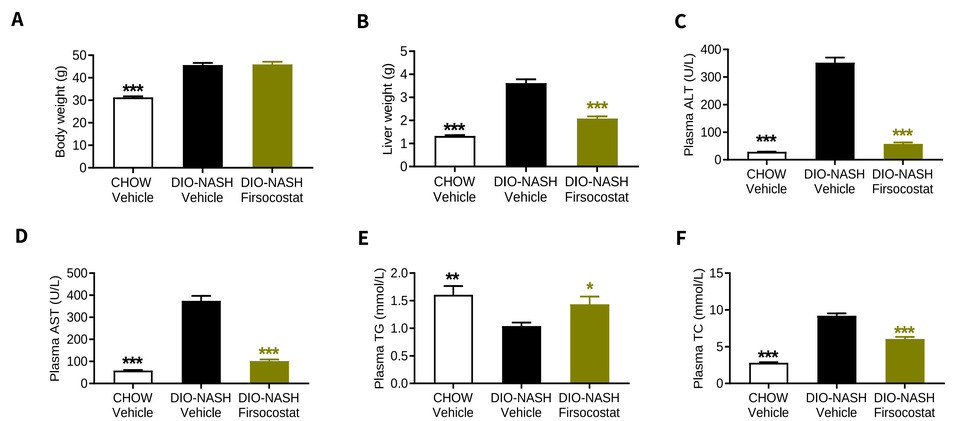


Figure 2. Firsocostat improves hepatomegaly and biochemical parameters in GAN DIO-NASH mice. **(A)** Terminal body weight. **(B)** Terminal liver weight. **(C)** Terminal plasma alanine aminotransferase (ALT). **(D)** Terminal plasma aspartate aminotransferase (AST). **(E)** Terminal plasma triglycerides. **(F)** Terminal plasma total cholesterol. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis stage

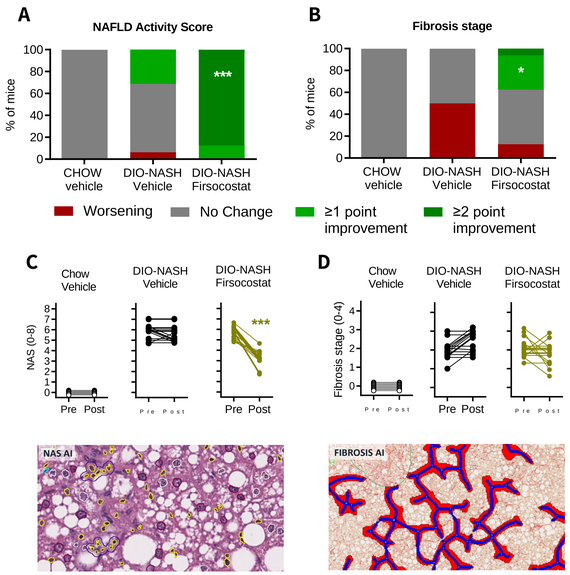


Figure 3. Firsocostat improves NAFLD Activity Score and fibrosis stage in GAN DIO-NASH mice.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C, D)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

4 Histological quantitative markers of steatosis, inflammation and fibrogenesis

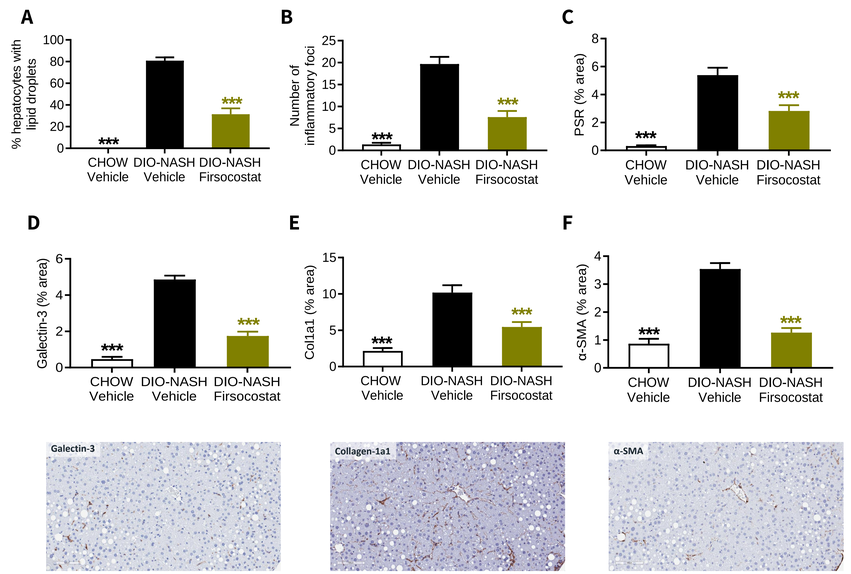


Figure 4. Firsocostat decreases histological markers for steatosis, inflammation and fibrogenesis in GAN DIO-NASH mice.
Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area of PSR. **(D)** % area of galectin-3. **(E)** % area of collagen-1a1. **(F)** % area of alpha-smooth muscle actin (α-SMA) as marker for stellate cell activation. Mean ± SEM. ***p<0.001 to corresponding vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and α-SMA photomicrographs for firsocostat treatment group (scale bar, 100 µm).

5 Transcriptomic profile for fibrosis and inflammation

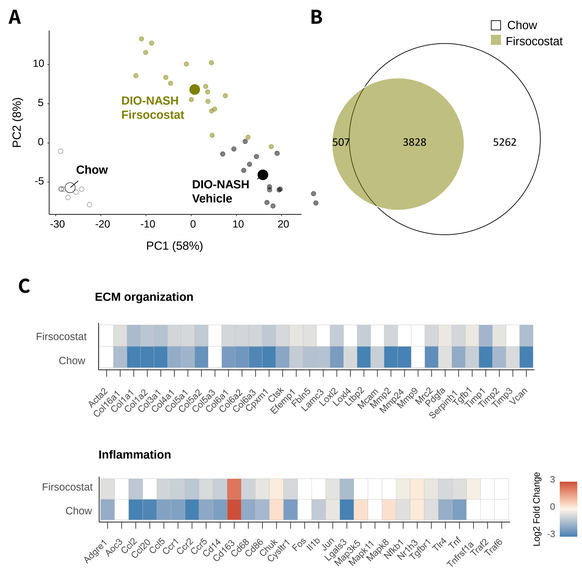


Figure 5. Firsocostat suppresses fibrosis-and inflammation-associated genes in GAN DIO-NASH mice.
(A) Principal component analysis (PCA) of samples based on top 500 most variable gene expression levels. **(B)** Differentially expressed genes. **(C)** Regulation of hepatic extracellular matrix (ECM) and inflammation candidate genes (log2-fold change compared to corresponding DIO-NASH vehicle control mice). Blue and red colour gradients indicate significantly (p<0.05) down-regulated and up-regulated gene expression, respectively. White boxes indicate genes not significantly regulated (p>0.05).

CONCLUSION

- Firsocostat reduces hepatomegaly, plasma liver enzymes, albeit induces hypertriglyceridemia.
- Firsocostat demonstrates ≥2-point significant improvement in NAFLD Activity Score.
- Firsocostat demonstrates 1-point significant improvement in Fibrosis Stage.
- Firsocostat reduces quantitative histological markers of steatosis, inflammation and fibrogenesis.
- Firsocostat suppresses fibrosis and inflammation-associated genes.
- These data agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model.

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