Metabolic, biochemical and histological effects of elafibranor in a CDAA-HFD-induced non-obese rat model of advanced NASH with progressive fibrosis

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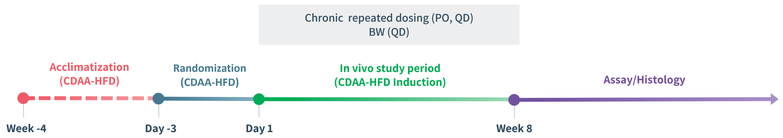
BACKGROUND & AIM

Elafibranor is dual PPAR-α/δ agonist, which has demonstrated hepatoprotective effects in clinical trials and preclinical models of non-alcoholic steatohepatitis (NASH).

The present study aimed to evaluate the metabolic, biochemical and histological effects of 8 weeks treatment with elafibranor in a Choline-Deficient l-Amino-Acid defined High-Fat Diet-induced (CDAA-HFD) non-obese Sprague Dawley rat model of advanced NASH with progressive fibrosis development.

1 Study outline



#	Group name	*n* in group	Animal model	Dose	Route of administration	Dosing Frequency
1	Chow	8	LEAN-CHOW	NA	PO	QD
2	Baseline	12	CDAA-HFD	NA	PO	QD
3	Vehicle	12	CDAA-HFD	NA	PO	QD
4	Elafibranor	12	CDAA-HFD	30 mg/kg	PO	QD

Figure 1. Study outline, groups and intervention.
BW: body weight; QD: once daily; QW: once weekly; ALT: alanine aminotransferase; TG: total triglycerides; HP: hydroxyproline ; HE: Haematoxylin Eosin; PSR: Picro Sirius Red; IHC: Immunohistochemistry

2 Metabolic and biochemical parameters

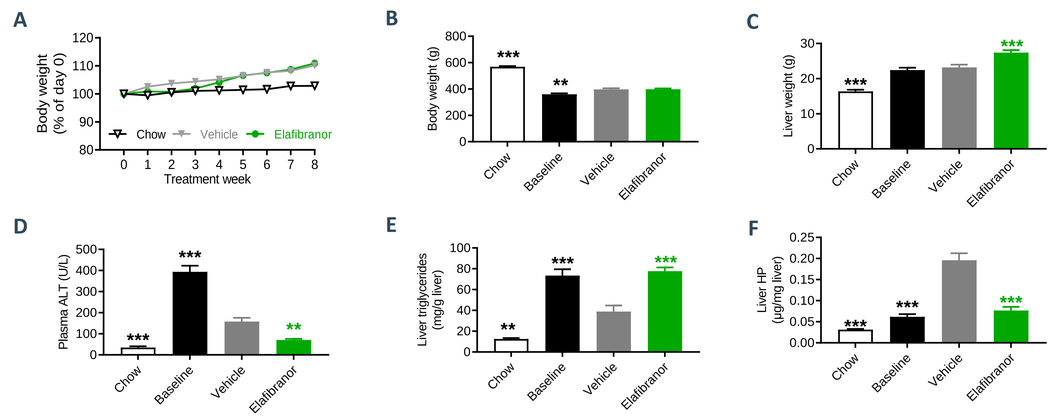


Figure 2. Elafibranor effects on body weight, liver weight and biochemical parameters in the CDAA-HFD rat model. (A) Body weight change relative to baseline (day 0). **(B)** Terminal body weight (g). **(C)** Terminal liver weight. **(D)** Terminal plasma alanine aminotransferase (ALT). **(E)** Terminal liver triglycerides. **(F)** Terminal liver hydroxyproline (HP). **p<0.01, ***p<0.001 compared to corresponding Vehicle (Dunnett's test one-factor linear model).

3 Histopathological NAFLD Activity Score and Fibrosis Score

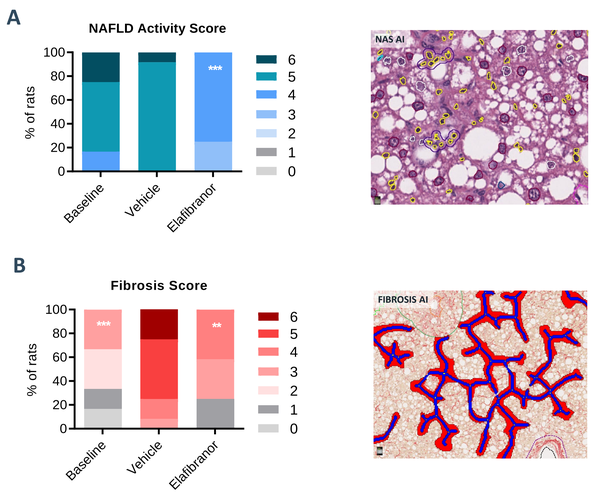


Figure 3. Elafibranor improves liver histopathological scores in the CDAA-HFD rat model.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS) with representative HE photomicrographs used for GHOST evaluation. **(B)** Fibrosis Score (Ishak) Representative PSR photomicrographs used for GHOST evaluation. ***p<0.001 compared to Vehicle (One-sided Fisher's exact test with Bonferroni correction).

4 Histological quantitative markers of steatosis, inflammation and fibrosis.

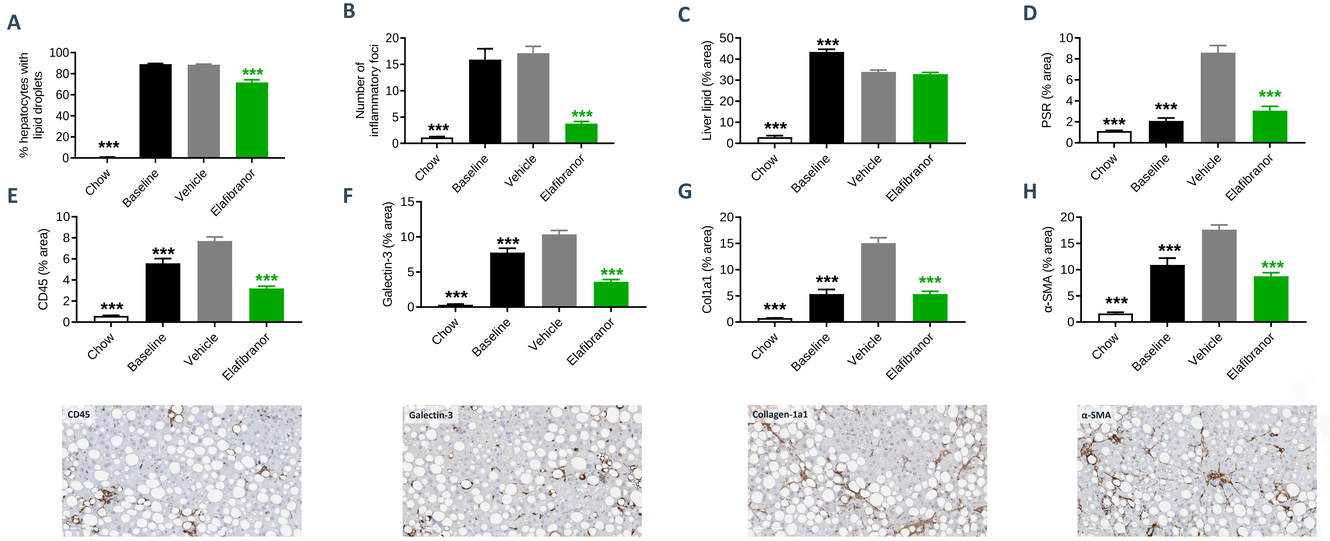


Figure 4. Elafibranor improves quantitative liver histological markers for fibrosis in the CDAA-HFD rat model.
Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-H). **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % liver area with lipids. **(D)** % area of PSR. **(E)** % area of CD45 **(F)** % area of galectin-3. **(G)** % area of collagen-1a1. **(H)** % area of alpha-smooth muscle actin (α-SMA) as marker for stellate cell activation. Mean ± SEM., ***p<0.001 compared to Vehicle (Dunnett's test one-factor linear model). Bottom panels: Representative CD45, galectin-3, collagen 1a1 and α-SMA photomicrographs for elafibranor treatment group (scale bar, 100 µm).

CONCLUSION

+ Elafibranor has no effect on body weight, but increases liver weight in conjunction with decreased plasma ALT and liver HP levels, while preserves liver TG.
+ Elafibranor improves NAFLD Activity Score and Fibrosis Score.
+ Elafibranor reduces histological markers for liver inflammation, fibrosis and stellate cell activation.
+ These findings highlight the CDAA-HFD non-obese rat model of advanced NASH for exploration of drug efficacy for progressive fibrosis.

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