Preclinical efficacy and clinical translatability of Elafibranor in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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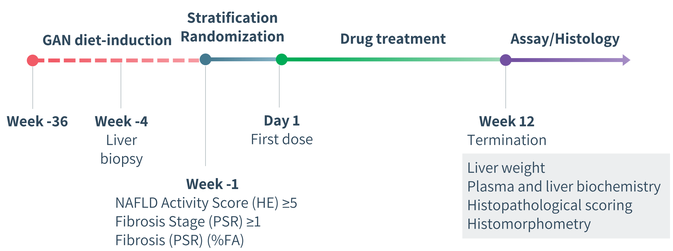
BACKGROUND & AIM

The PPAR-α/δ agonist elafibranor has recently been clinically evaluated in the phase 3 study RESOLVE-IT trial in NASH patients with liver fibrosis. The present study aimed to (i) evaluate the metabolic, biochemical and histopathological effects of Elafibranor treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and (ii) compare to primary outcomes in the RESOLVE-IT NASH trial.

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dose
1	LEAN-CHOW	Male	10	**Vehicle**	PO	QD	-
2	DIO-NASH	Male	16	**Vehicle**	PO	QD	-
3	DIO-NASH	Male	17	**Elafibranor**	PO	QD	30mg/kg

2 Metabolic and biochemical parameters

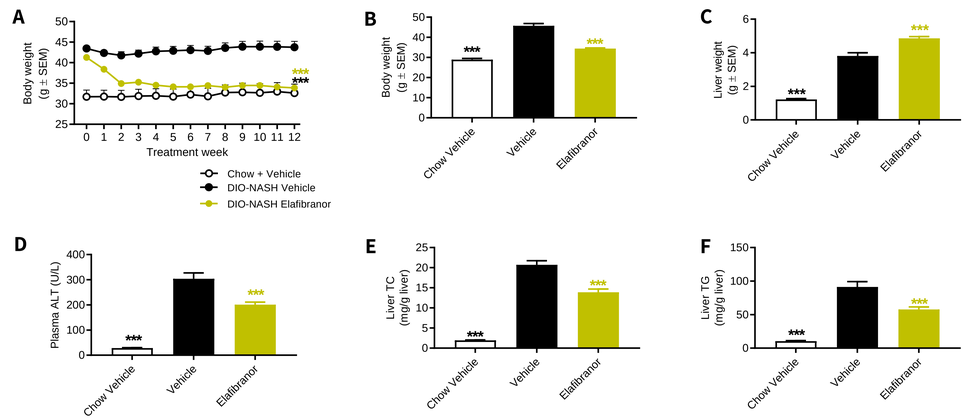


Figure 1. Elafibranor improves metabolic and biochemical parameters in GAN DIO-NASH mice. **(A)** Absolute body weight during study period. **(B)** Terminal body weight. **(C)** Terminal liver weight. **(D)** Terminal plasma alanine aminotransferase (ALT). **(E)** Terminal liver total cholesterol. **(F)** Terminal liver triglycerides. ***p<0.001 compared to corresponding vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis stage

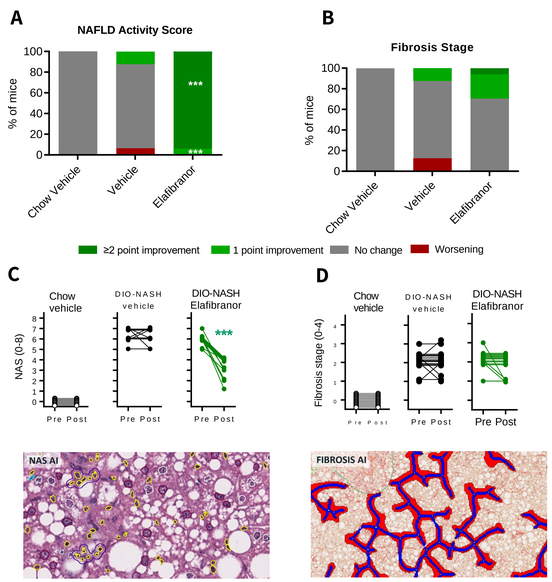


Figure 2. Elafibranor improves NAFLD Activity Score in GAN DIO-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C, D)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. *p<0.05, ***p<0.001 to corresponding DIO-NASH vehicle group (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: representative HE and PSR photomicrographs used for GHOST evaluation.

4 Quantitative histological markers of steatosis, inflammation and fibrosis

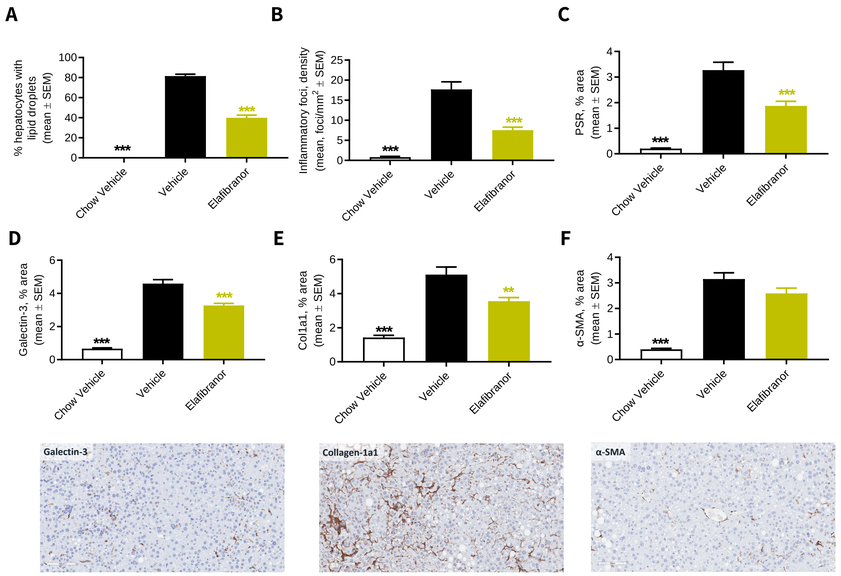


Figure 3. Elafibranor decreases histological markers for steatosis, inflammation and fibrosis in GAN DIO-NASH mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % 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<0.05, **p<0.01, ***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 elafibranor treatment group (scale bar, 100 µm).

5 Clinical translatability

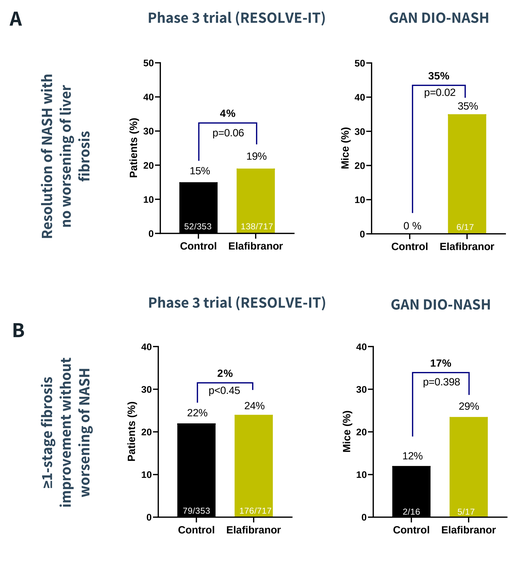


Figure 4. Elafibranor exerts differential effects for NASH resolution and resembling effects on fibrosis improvement in GAN DIO-NASH mice versus NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for elafibranor in GAN DIO-NASH mice compared to clinical phase-3 trial data (RESOLVE-IT). **(D)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-3 trial data (RESOLVE-IT).

CONCLUSION

+ Elafibranor reduces body weight, plasma ALT and liver TC and TG content.
+ Elafibranor demonstrates ≥2-point significant improvement in NAFLD Activity Score.
+ Elafibranor did not improve Fibrosis Stage.
+ Elafibranor reduces quantitative histological markers of steatosis, inflammation and fibrosis.
+ Elafibranor improves primary outcomes for NASH resolution in GAN DIO-NASH mice, but not NASH patients.
+ Elafibranor do not improve primary outcome for fibrosis stage in both GAN DIO-NASH mice and in NASH patients.
+ Level of efficacy for elafibranor treatment on histopathological scoring in GAN DIO-NASH mice resembles fibrosis outcomes in the RESOLVE-IT phase-3 trial in NASH patients with liver fibrosis.

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