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

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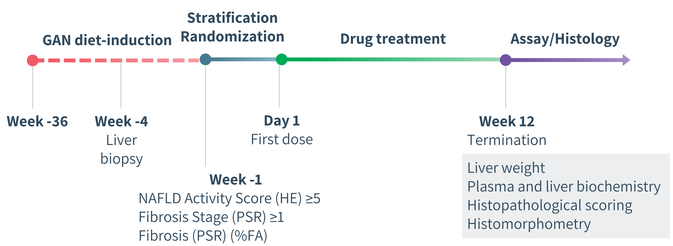
BACKGROUND & AIM

The pan-PPAR agonist Lanifibranor has recently been reported to promote NASH resolution and improvement in fibrosis stage in late-stage phase 2b clinical trial (NATIVE)((Francque et al., NEJM, 2021). The present study aimed to *(i)* evaluate the metabolic, biochemical and histopathological effects of lanifibranor treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and *(ii)* compare to primary outcomes in the NATIVE-NASH trial.

1 Study outline



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

2 Metabolic and biochemical parameters

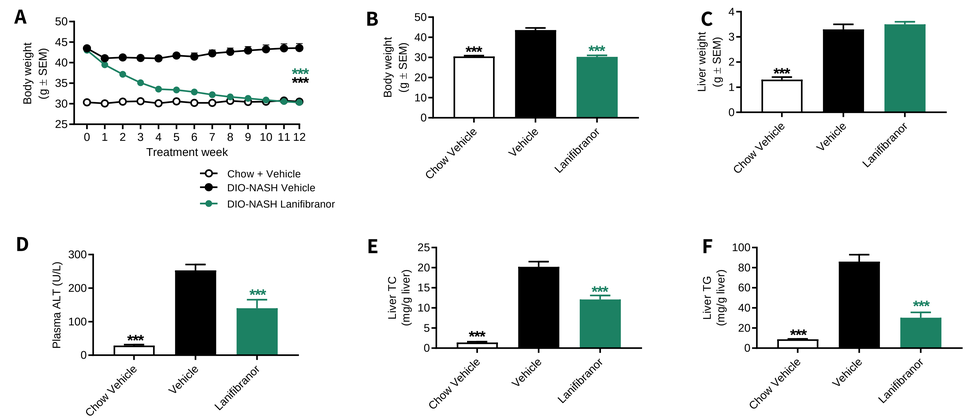


Figure 1. Lanifibranor improves metabolic and biochemical parameters in GAN DIO-NASH mice. **(A)** Absolute body weight during study period. **(B)** Terminal body weight. **(C)** Terminal liver weight. **(D)** Terminal plasma alanine aminotransferase (ALT). **(E)** Terminal liver total cholesterol. **(F)** 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

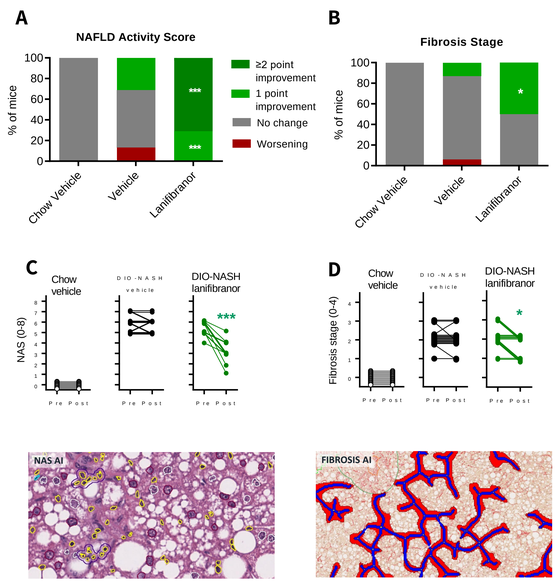


Figure 2. Lanifibranor improves NAFLD Activity Score and Fibrosis Stage in GAN DIO-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C, D)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. *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

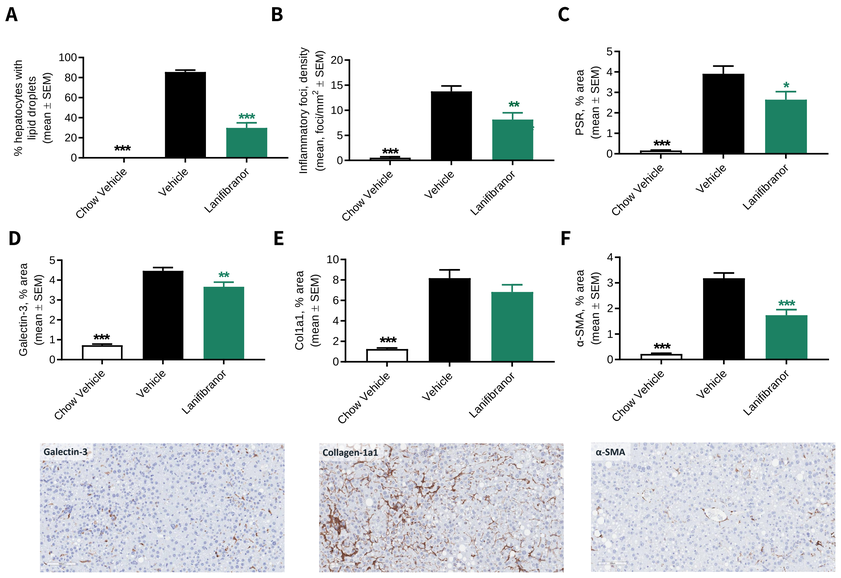


Figure 3. Lanifibranor decreases histological markers for steatosis, inflammation and fibrogenesis in GAN DIO-NASH mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F).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

5 Clinical translatability

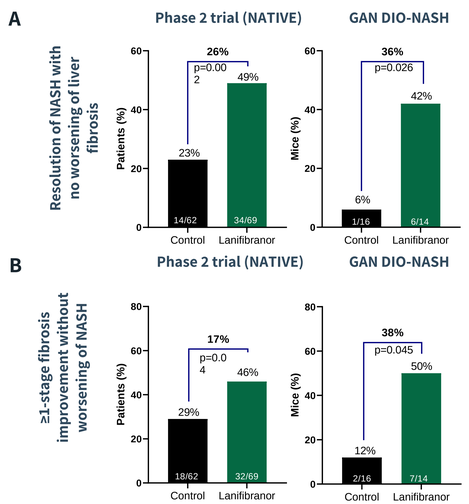


Figure 4. Lanifibranor (pan-PPAR agonist) promotes NASH resolution and improves fibrosis stage in both GAN DIO-NASH mice and NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for lanifibranor in GAN DIO-NASH mice compared to clinical phase-2 trial data (NATIVE trial; Francque *et al.* NJEM 2021). **(D)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-2 trial data (NATIVE trial; Francque *et al.* NJEM 2021).

CONCLUSION

+ Lanifibranor reduces body weight, plasma ALT and liver TC and TG content.
+ Lanifibranor demonstrates ≥2-point significant improvement in NAFLD Activity Score.
+ Lanifibranor demonstrates 1-point significant improvement in Fibrosis Stage.
+ Lanifibranor reduces quantitative histological markers of steatosis, inflammation and fibrogenesis.
+ Lanifibranor demonstrates comparable efficacy on primary histopathological endpoints in NASH patients and GAN DIO-NASH mice.
+ These data agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model.

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