

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



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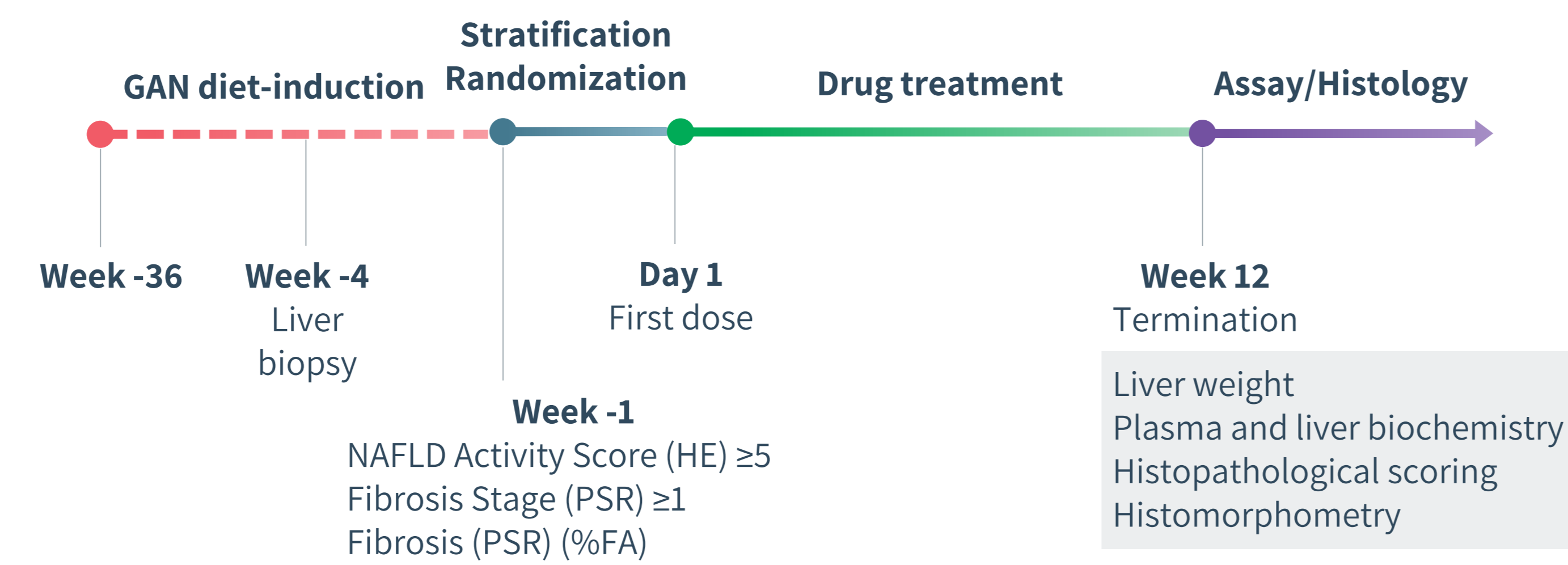
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## BACKGROUND & AIM

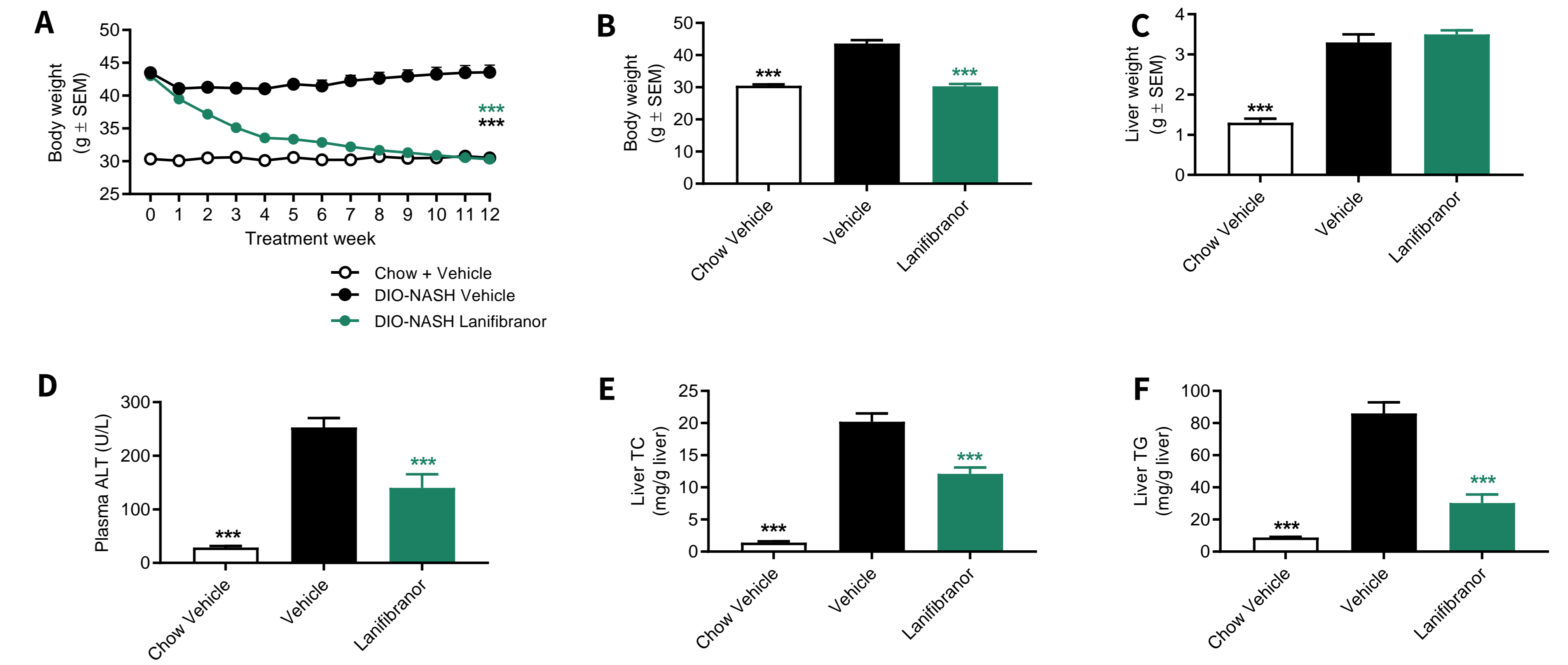
The pan-PPAR agonist Lanifibranor has recently been reported to promote NASH resolution and improvement in fibrosis stage in late-stage phase 2b clinical trial (NATIVE) (Francque et al., NEJM, 2021). The present study aimed to (i) evaluate the metabolic, biochemical and histopathological effects of lanifibranor 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



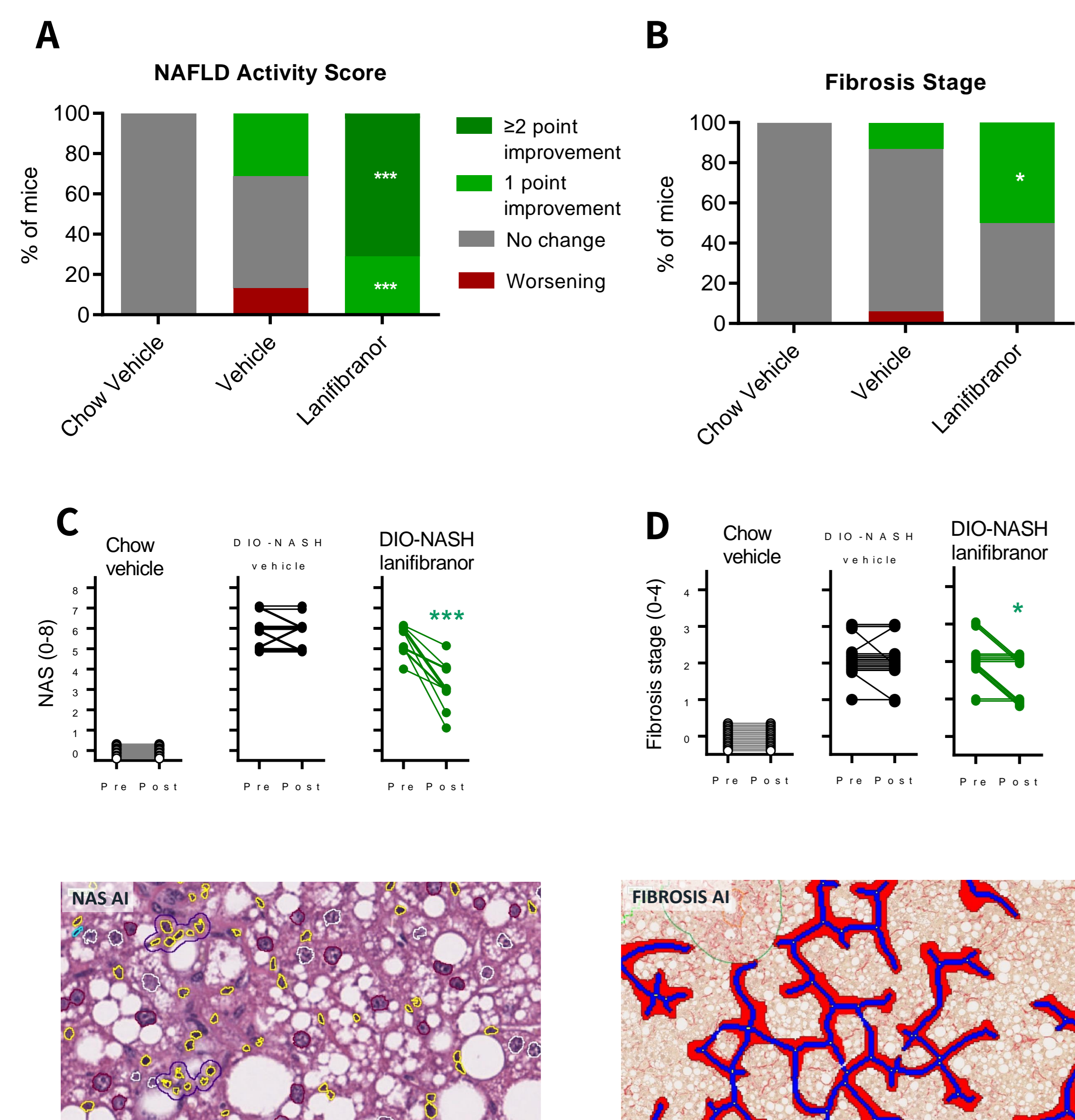
Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dose
1	LEAN-CHOW	Male	10	Vehicle	SC	QD	-
2	DIO-NASH	Male	16	Vehicle	SC	QD	-
3	DIO-NASH	Male	16	Lanifibranor	SC	QD	30mg/kg

## 2 Metabolic and biochemical parameters



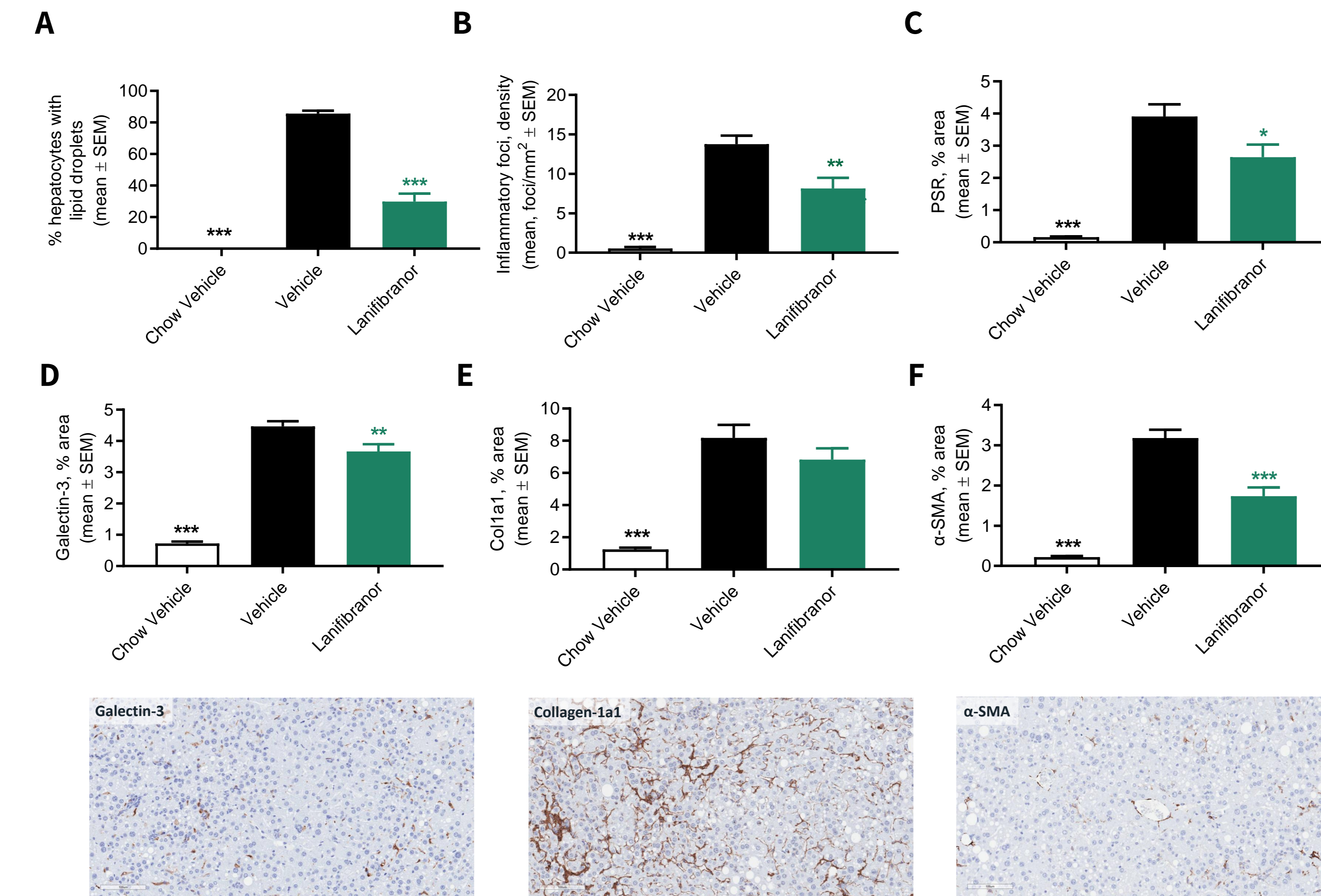
**Figure 1. Lanifibranor improves metabolic and biochemical parameters in GAN DIO-NASH mice.** (A) Absolute body weight during study period. (B) Terminal body weight. (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver total cholesterol. (F) Terminal liver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

## 3 NAFLD Activity Score and Fibrosis stage



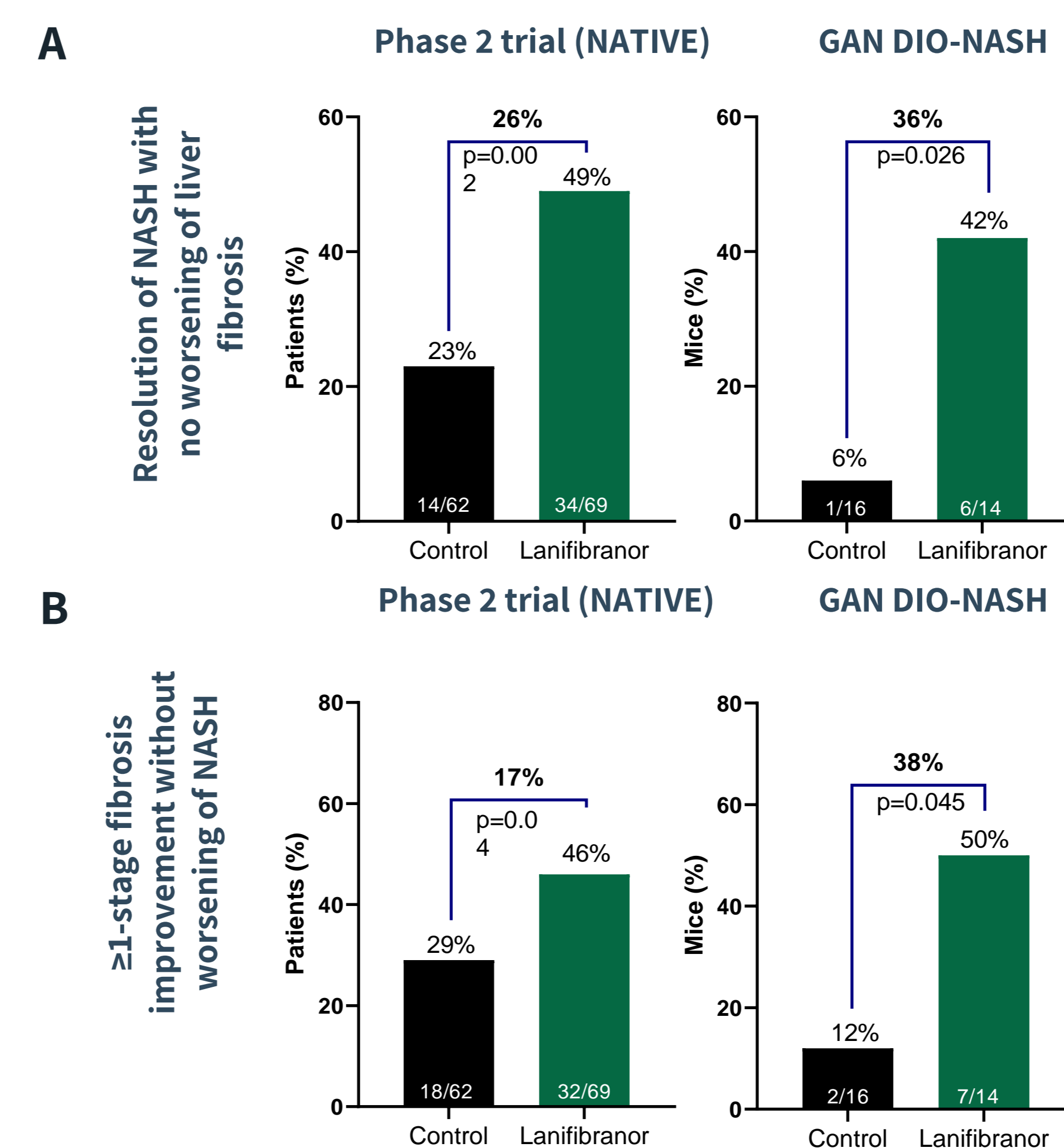
**Figure 2. Lanifibranor improves NAFLD Activity Score and Fibrosis Stage in GAN DIO-NASH mice.** Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C, D) Comparison 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.** Histo-morphometric 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  $\pm$  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  $\leq 1$ ; 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. NEJM 2021). (B)  $\geq 1$ -stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-2 trial data (NATIVE trial; Francque et al. NEJM 2021).

## CONCLUSION

- + Lanifibranor reduces body weight, plasma ALT and liver TC and TG content.
- + Lanifibranor demonstrates  $\geq 2$ -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.