

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



Authors: Kristoffer Voldum-Clausen¹, Jacob Nøhr-Meldgaard¹, Sanne S. Veidal¹, Martin Rønne Madsen¹, Henrik H. Hansen¹, Michael Feigh¹

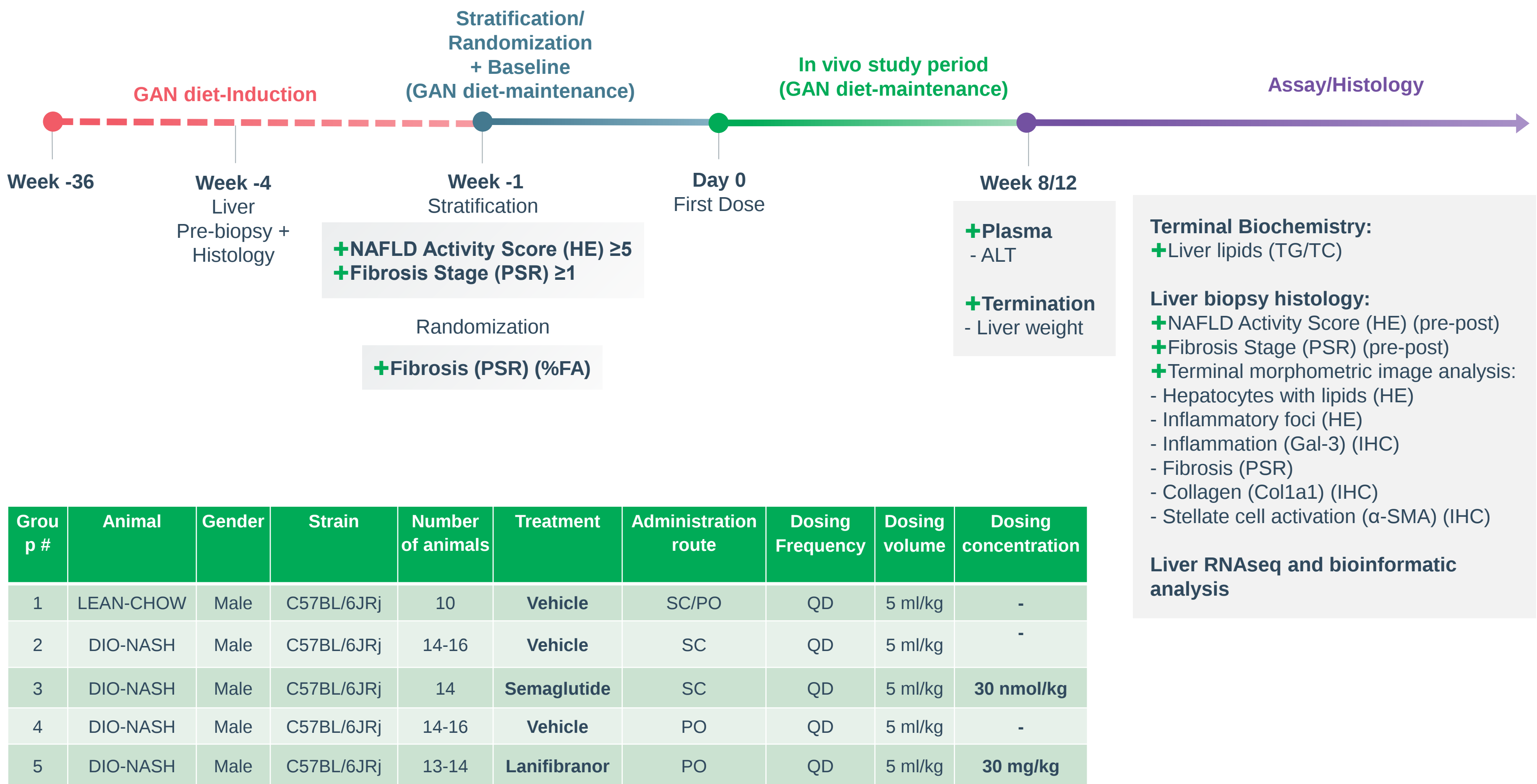
¹Gubra ApS - Hørsholm, Denmark

Corresponding author: Michael Feigh - mfe@Gubra.dk

Background & Aim

Semaglutide (GLP-1 analogue) and lanifibranor (pan-PPAR agonist) have recently been reported to promote NASH resolution (semaglutide, lanifibranor) and improvement in fibrosis stage (lanifibranor) in late-stage clinical trials for NASH. The present study aimed to evaluate the metabolic, biochemical, histological and transcriptomic effects of 8- and 12-weeks treatment with semaglutide and lanifibranor in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of fibrosing NASH.

Study outline



Improvement in metabolic and biochemical parameters

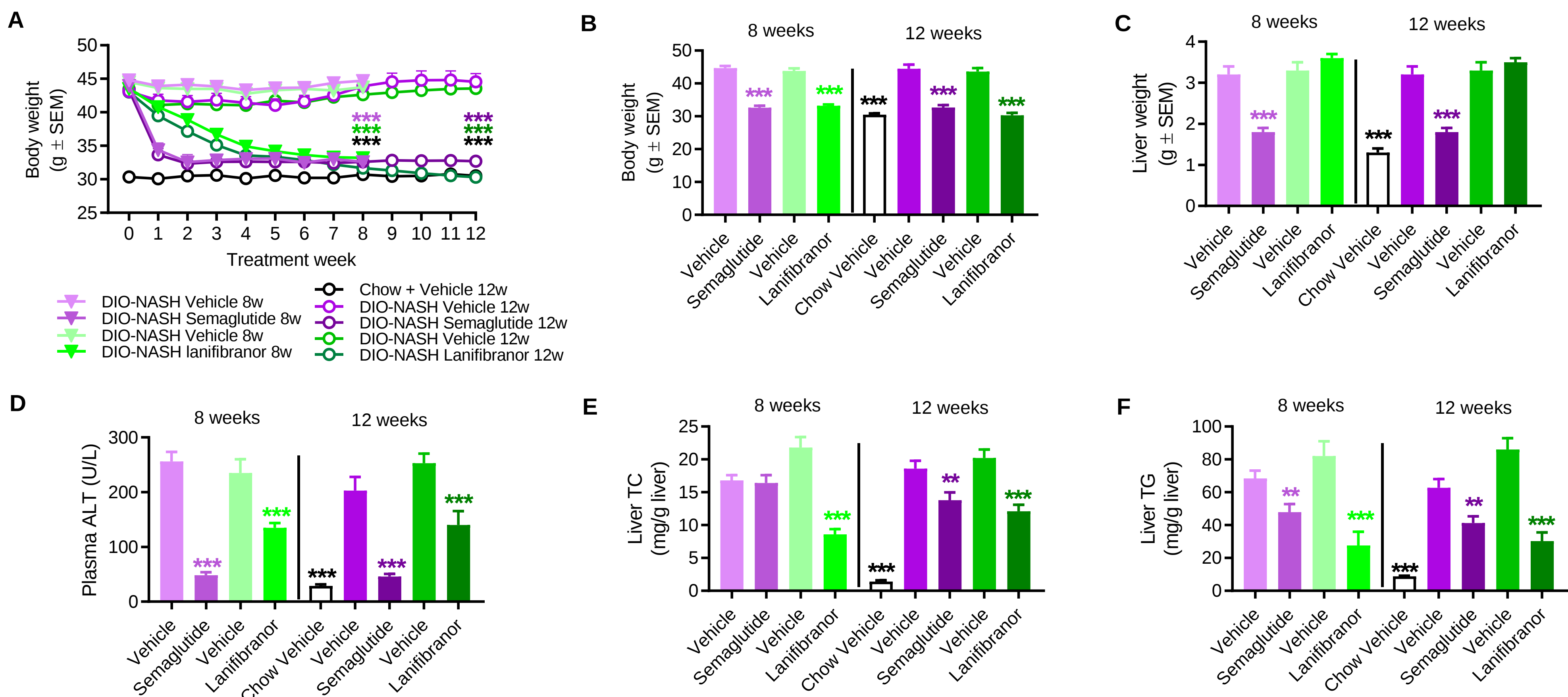


Figure 1. Semaglutide and lanifibranor improves metabolic and biochemical parameters in GAN DIO-NASH mice. (A) Body weight change relative to baseline (day 0). (B) Terminal body weight (g). (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver total cholesterol. (F) Terminal liver triglycerides. **p<0.01, ***p<0.001 compared to corresponding DIO-NASH vehicle control (Dunnett's test one-factor linear model).

Improvement in NAFLD Activity Score and Fibrosis Stage

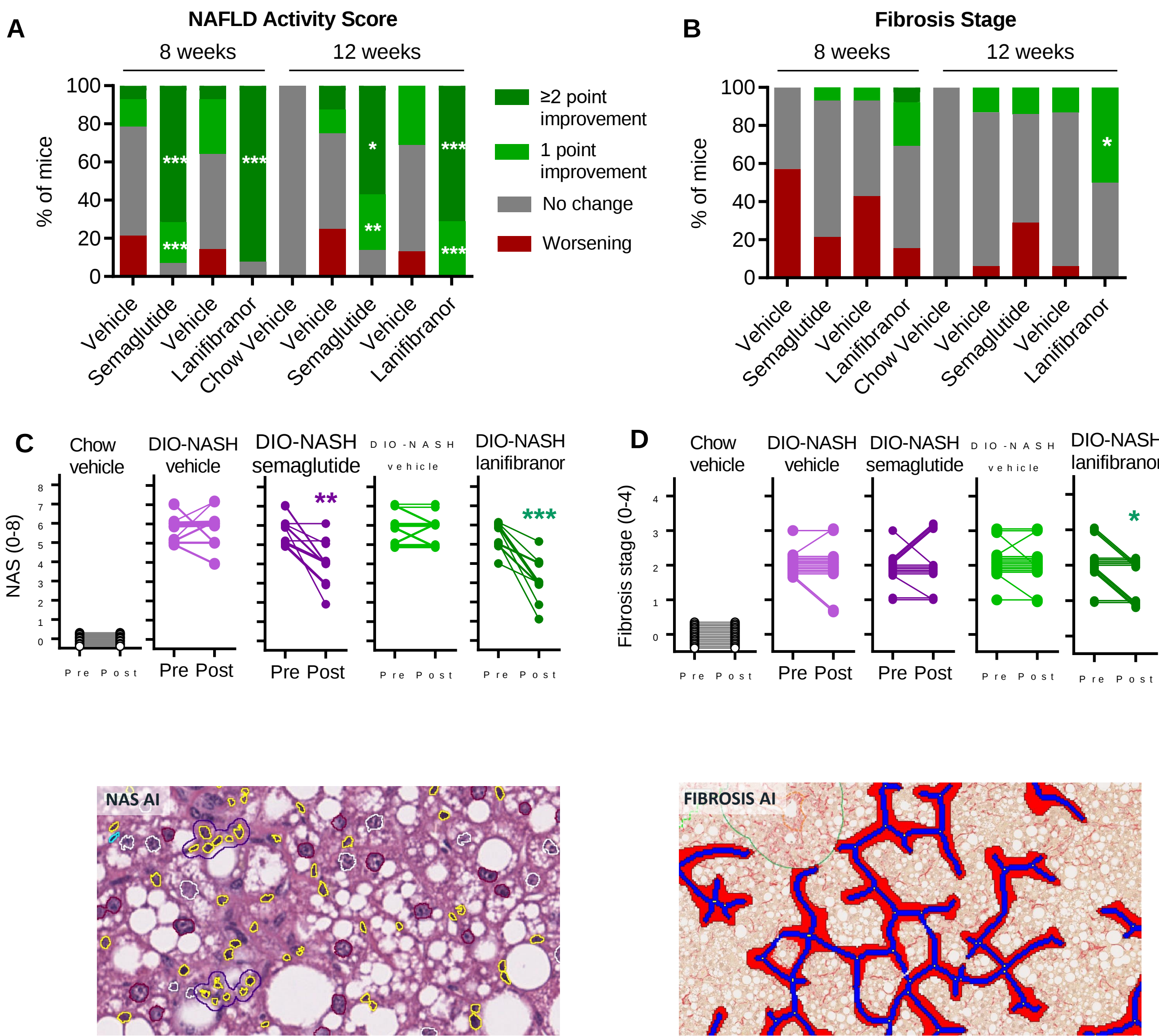


Figure 2. Semaglutide and lanifibranor improves liver histopathological scores in GAN DIO-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C) Comparison of individual pre-post NAS after 12 weeks. (D) Comparison of individual pre-post Fibrosis stage after 12 weeks. *p<0.05, **p<0.01, ***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.

Improvement in quantitative histology of steatosis, inflammation and fibrosis

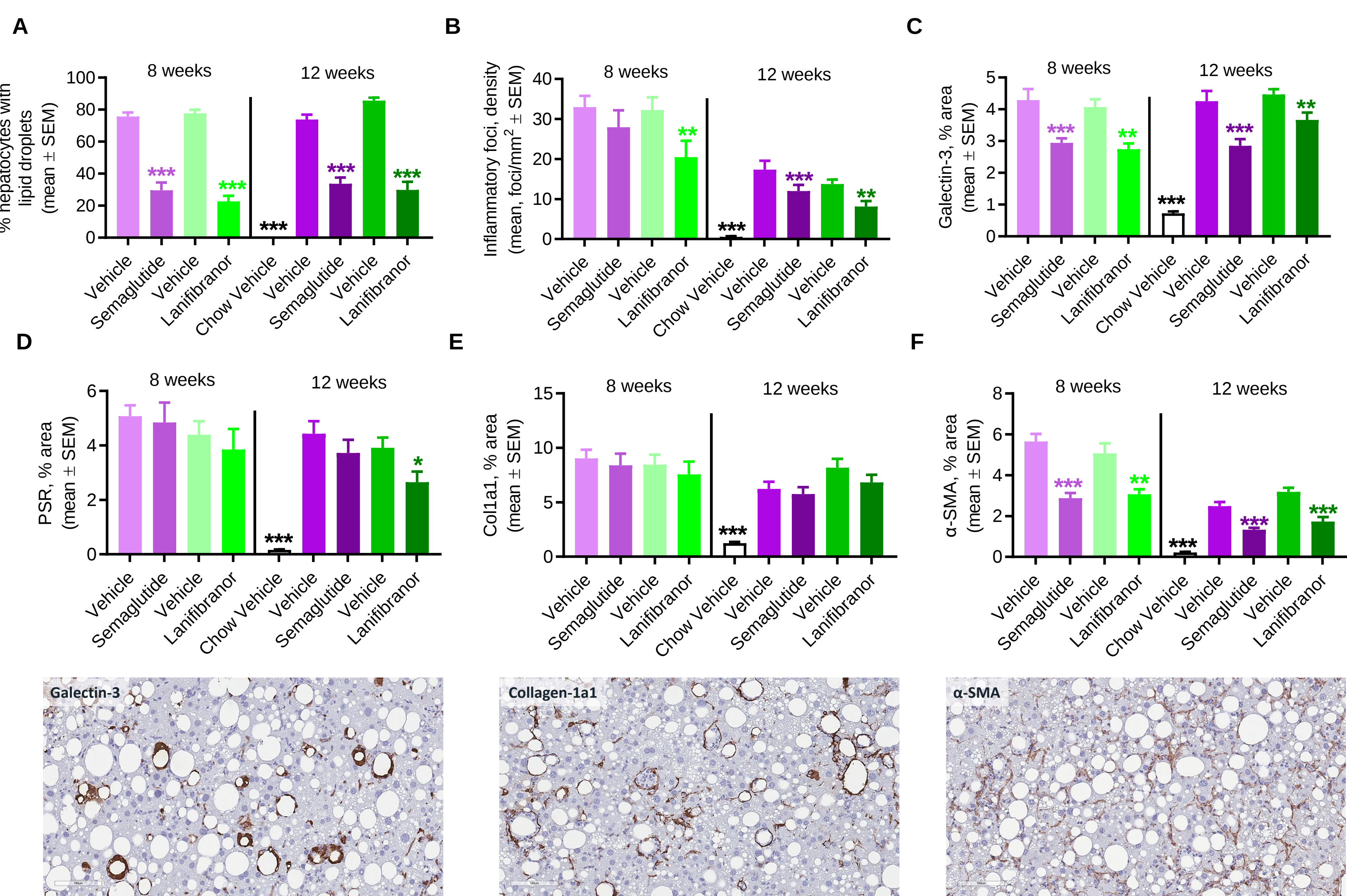


Figure 3. Semaglutide and lanifibranor improves quantitative liver histological markers in GAN DIO-NASH mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area of galectin-3. (D) % area of PSR. (E) % area of collagen-1a1. (F) % area of alpha-smooth muscle actin (α -SMA). Mean $\pm$ SEM. **p<0.01, ***p<0.001 to corresponding DIO-NASH vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and α -SMA photomicrographs (scale bar, 100 μ m).

Improvement in transcriptomic profile for fibrosis

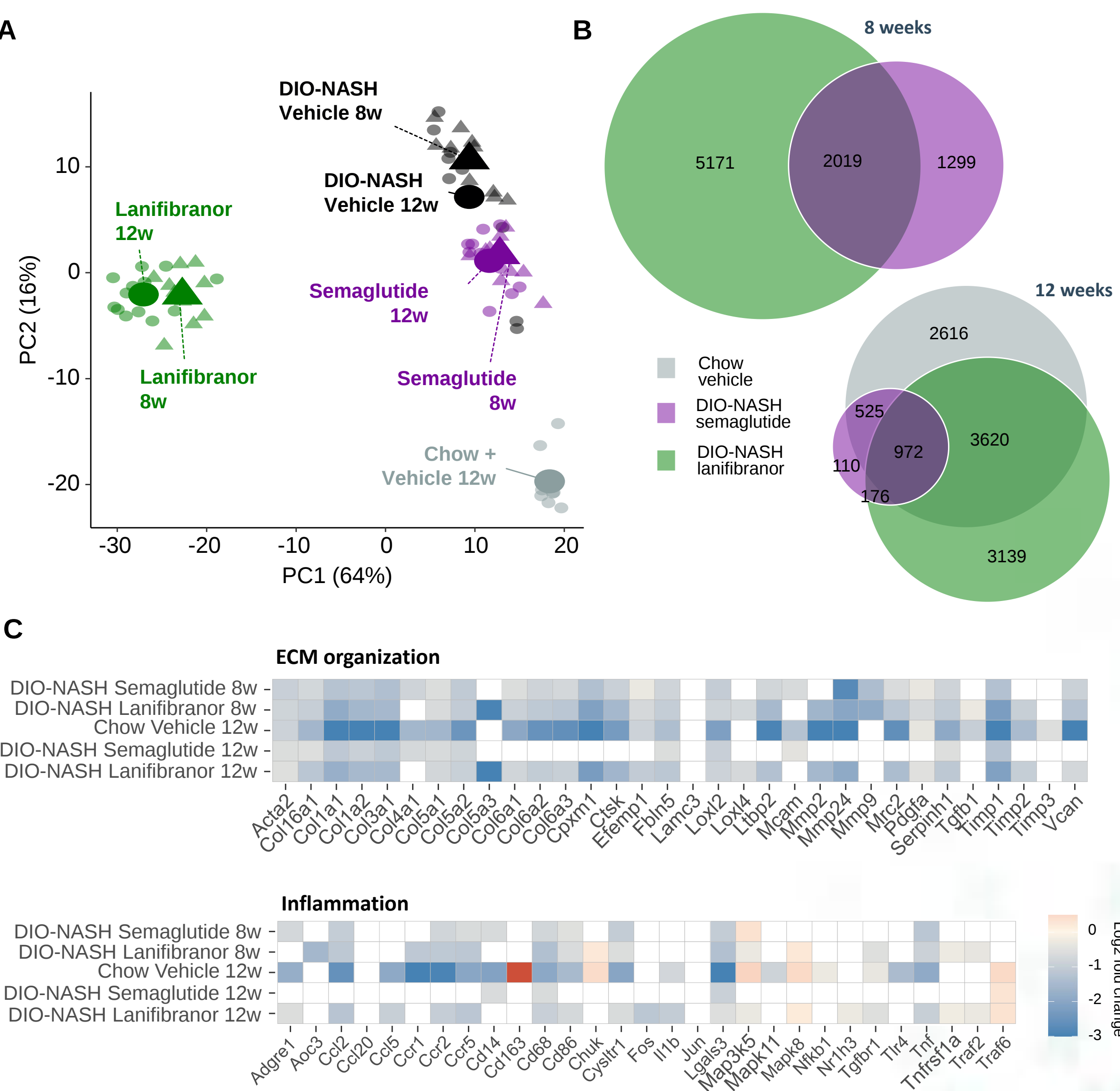


Figure 4. Semaglutide and lanifibranor suppress fibrosis-associated genes in GAN DIO-NASH mice. (A) Principal component analysis (PCA) of samples based on top 500 most variable gene expression levels. (B) Venn diagram depicting shared and separate differentially expressed genes in treatment groups. (C) Regulation of hepatic extracellular matrix (ECM) and inflammation candidate genes. Blue and red colour gradients indicate significantly (p<0.05) down-regulated and up-regulated gene expression, respectively. White boxes indicate genes not regulated (p>0.05) compared to DIO-NASH vehicle mice.

CONCLUSION

- + Semaglutide and lanifibranor reduce body weight, plasma liver ALT and liver lipids.
- + Semaglutide and lanifibranor demonstrate ≥ 2 -point significant improvement in NAFLD Activity Score.
- + Semaglutide and lanifibranor reduce quantitative histological markers of steatosis, inflammation and stellate cell activation.
- + Lanifibranor demonstrate 1-point significant improvement in Fibrosis Stage.
- + Lanifibranor reduce quantitative histological marker of fibrosis.
- + Semaglutide and lanifibranor demonstrate transcriptomic effects on fibrosis-associated genes.
- + These findings agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model.