

# Metabolic, biochemical, histopathological, and transcriptomic effects of resmetirom (MGL-3196) in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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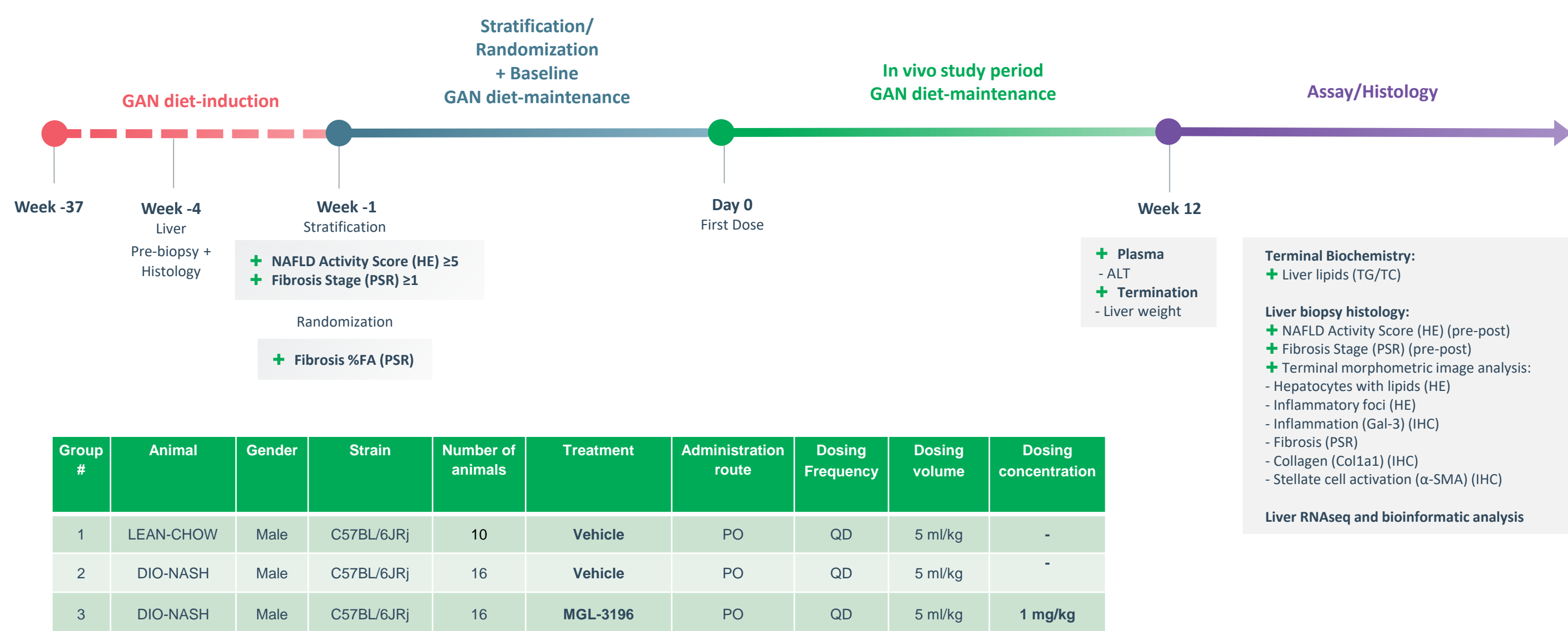
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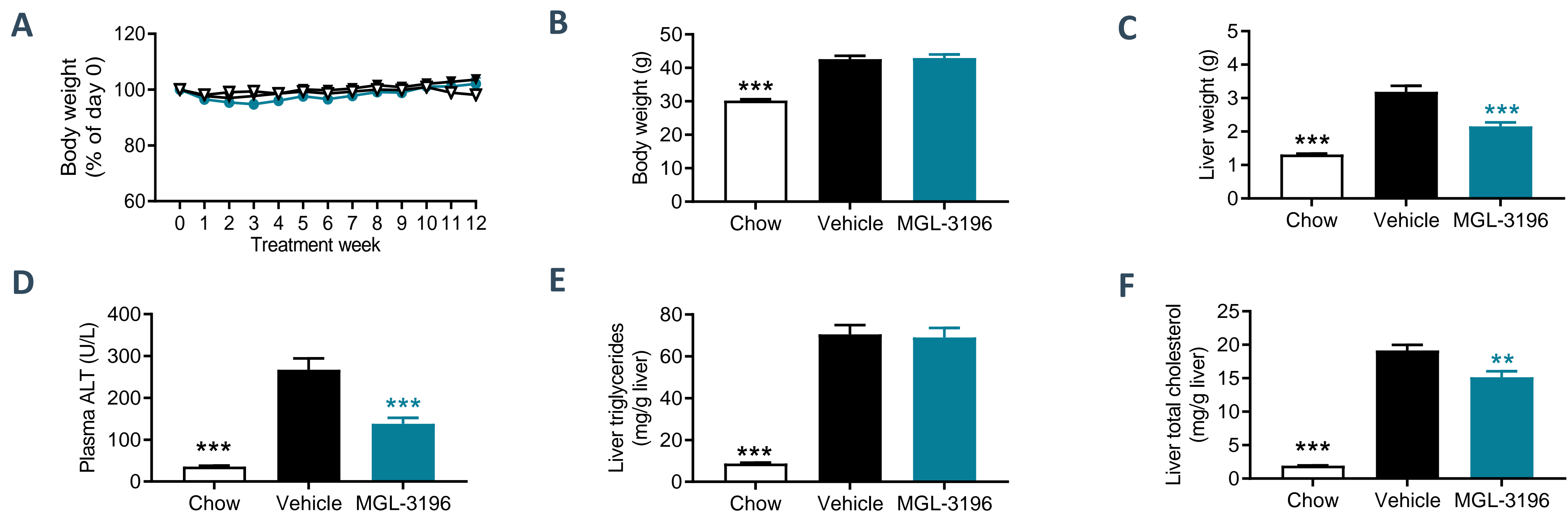
## Background & Aim

Resmetirom (MGL-3196), a selective THR- $\beta$  agonist, has been recently been reported to improve liver histological outcomes in a clinical trial for non-alcoholic steatohepatitis (NASH). The present study aimed to evaluate the metabolic, biochemical, histopathological and transcriptomic effects of resmetirom treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH.

## Study outline

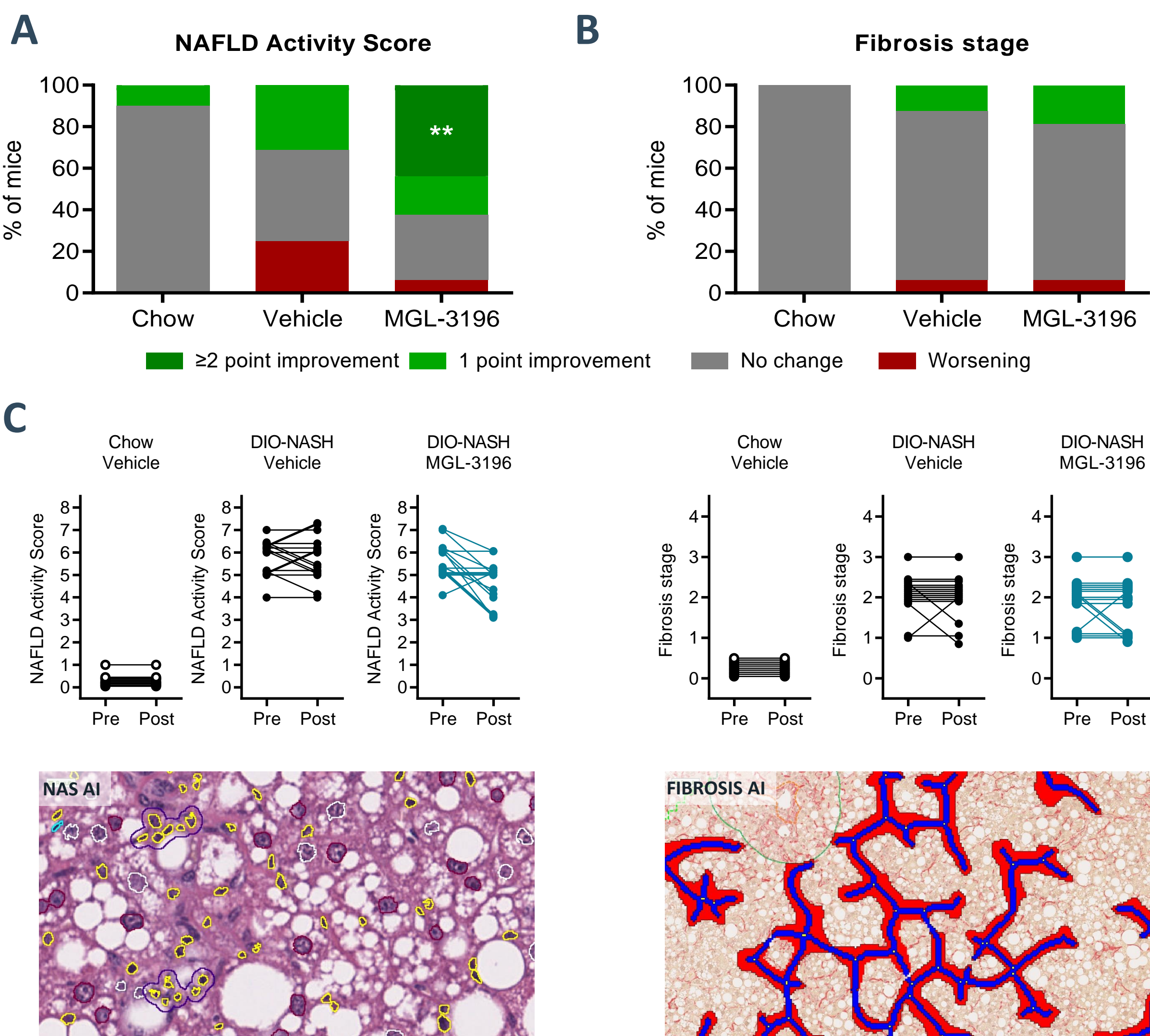


## Improvement in metabolic and biochemical parameters



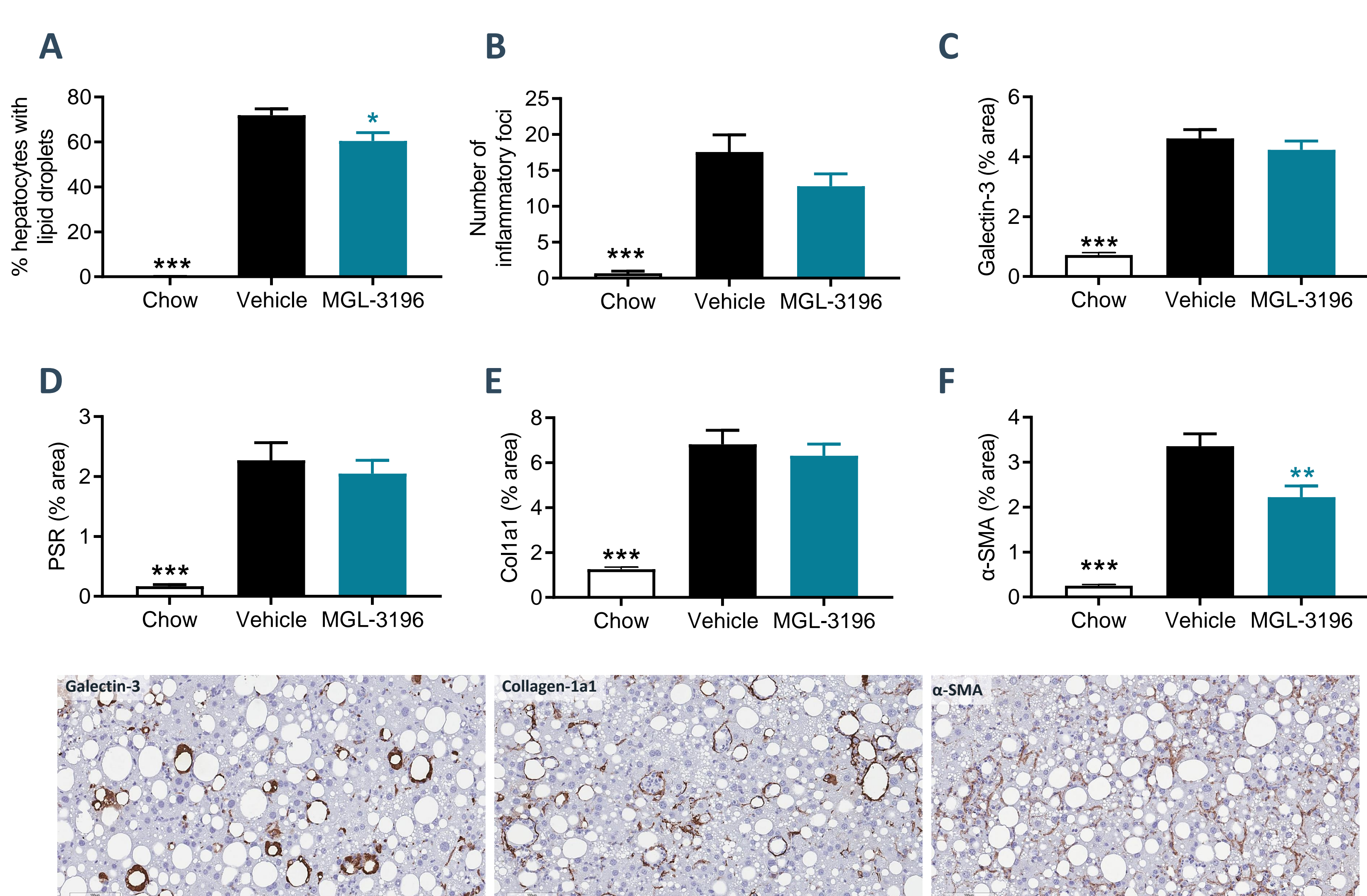
**Figure 1. Resmetirom (MGL-3196) improves hepatomegaly and biochemical parameters in GAN DIO-NASH mice.** (A) Terminal body weight (g). (B) Terminal liver weight. (C) Terminal plasma alanine aminotransferase (ALT). (D) Terminal plasma aspartate aminotransferase (AST). (E) Terminal plasma triglycerides. (F) Terminal plasma total cholesterol. (G) Terminal liver total cholesterol. (H) 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



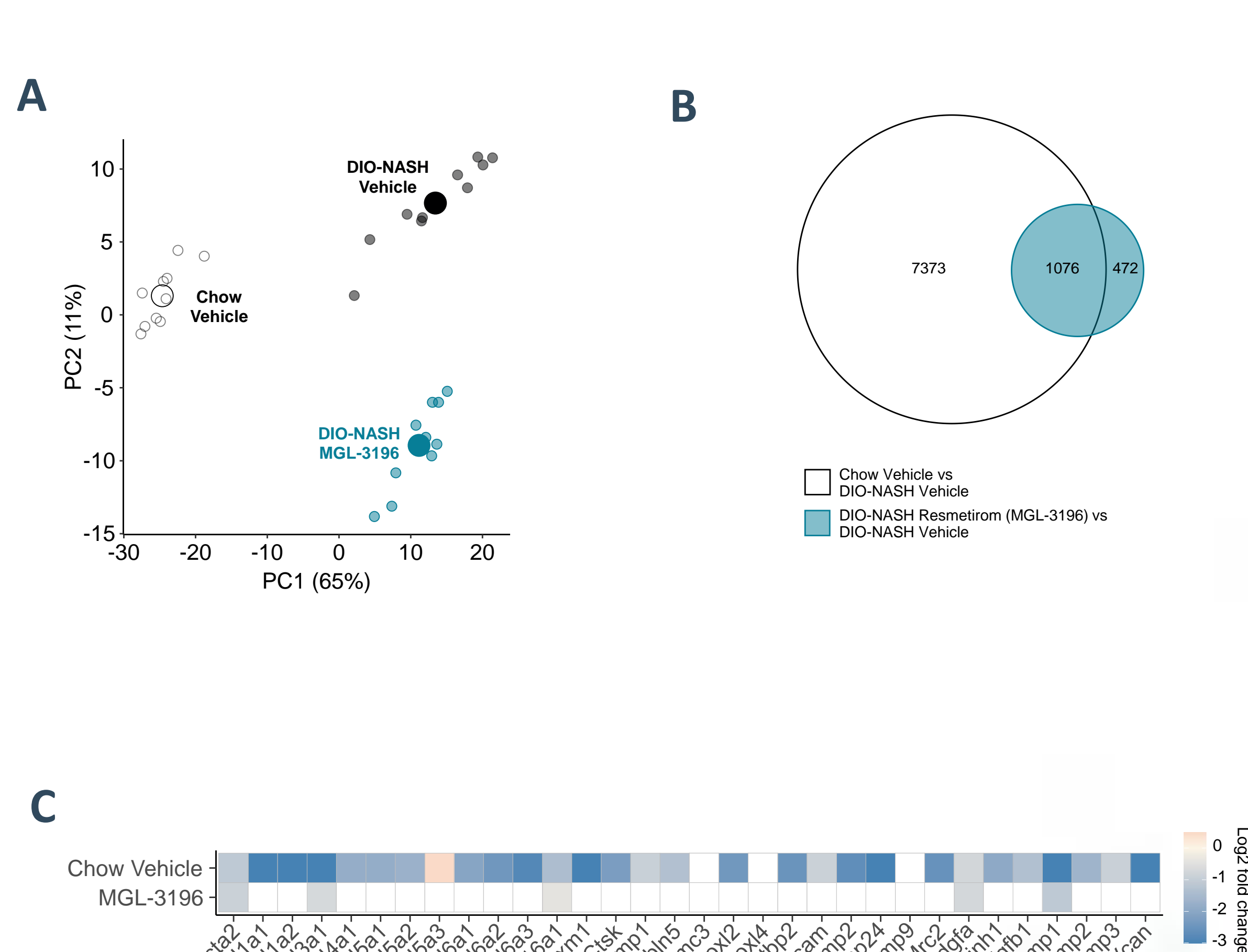
**Figure 2. Resmetirom (MGL-3196) improves liver histopathological scores in GAN DIO-NASH mice.** Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C) Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. \*\*p<0.01 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 and stellate cell activation



**Figure 3. Resmetirom (MGL-3196) 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 ( $\alpha$ -SMA) as marker for stellate cell activation. Mean  $\pm$  SEM. \*p<0.05, \*\*\*p<0.001 to corresponding DIO-NASH vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and  $\alpha$ -SMA photomicrographs (scale bar, 100  $\mu$ m).

## Hepatic transcriptomic profile for fibrosis



**Figure 4. Resmetirom (MGL-3196) unaffected 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) candidate genes (log2-fold change compared to DIO-NASH vehicle mice). Blue colour gradients indicate significantly (p<0.05) down-regulated gene expression. White boxes indicate genes not significantly regulated (p>0.05) compared to DIO-NASH vehicle mice.

## CONCLUSION

- + Resmetirom (MGL-3196) reduces hepatomegaly, plasma ALT and liver total cholesterol.
- + Resmetirom promotes  $\geq 2$ -point significant improvement in NAFLD Activity Score.
- + Fibrosis stage was unaffected by Resmetirom.
- + Resmetirom reduces quantitative histological markers of steatosis and stellate cell activation.
- + Resmetirom demonstrated minor effects on fibrosis-associated gene expression
- + These findings agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model