

Metabolic, biochemical and histological effects of elafibranor in a CDAA-HFD-induced non-obese rat model of advanced NASH with progressive fibrosis



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BACKGROUND & AIM

Elafibranor is dual PPAR- α/δ agonist, which has demonstrated hepatoprotective effects in clinical trials and preclinical models of non-alcoholic steatohepatitis (NASH). The present study aimed to evaluate the metabolic, biochemical and histological effects of 8 weeks treatment with elafibranor in a Choline-Deficient L-Amino-Acid defined High-Fat Diet-induced (CDAA-HFD) non-obese Sprague Dawley rat model of advanced NASH with progressive fibrosis development.

1 Study outline

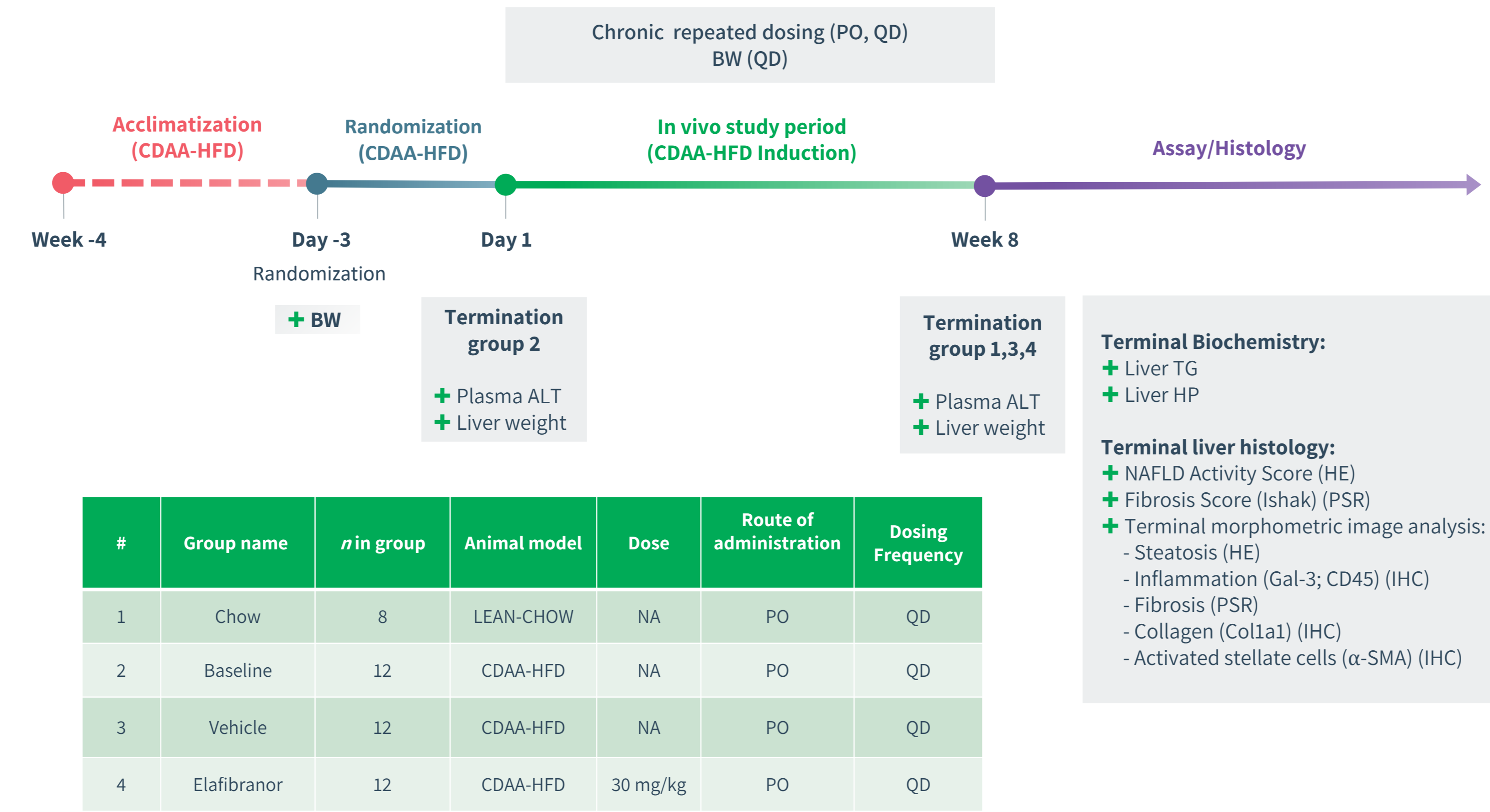


Figure 1. Study outline, groups and intervention. BW: body weight; QD: once daily; QW: once weekly; ALT: alanine aminotransferase; TG: total triglycerides; HP: hydroxyproline; HE: Haematoxylin Eosin; PSR: Picro Sirius Red; IHC: Immunohistochemistry

2 Metabolic and biochemical parameters

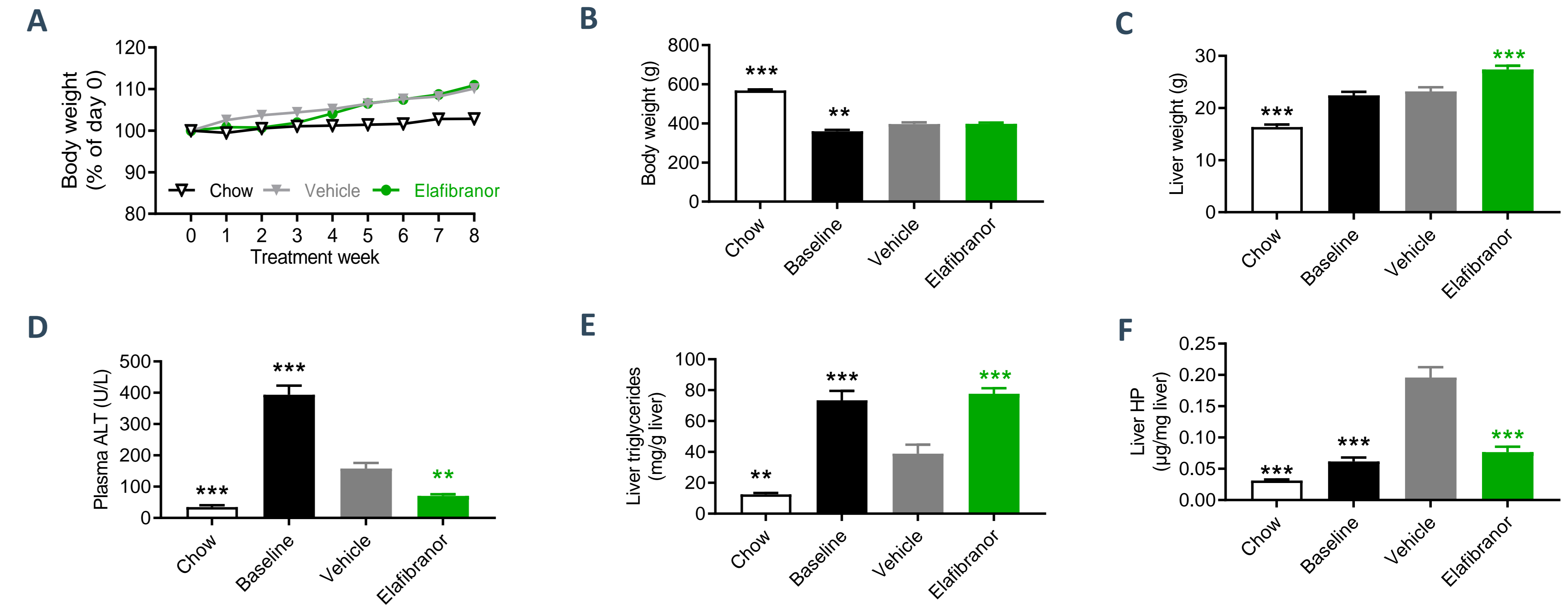


Figure 2. Elafibranor effects on body weight, liver weight and biochemical parameters in the CDAA-HFD rat model. (A) Body weight change relative to baseline (day 0). (B) Terminal body weight (g). (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver triglycerides. (F) Terminal liver hydroxyproline (HP). **p<0.01, ***p<0.001 compared to corresponding Vehicle (Dunnett's test one-factor linear model).

3 Histopathological NAFLD Activity Score and Fibrosis Score

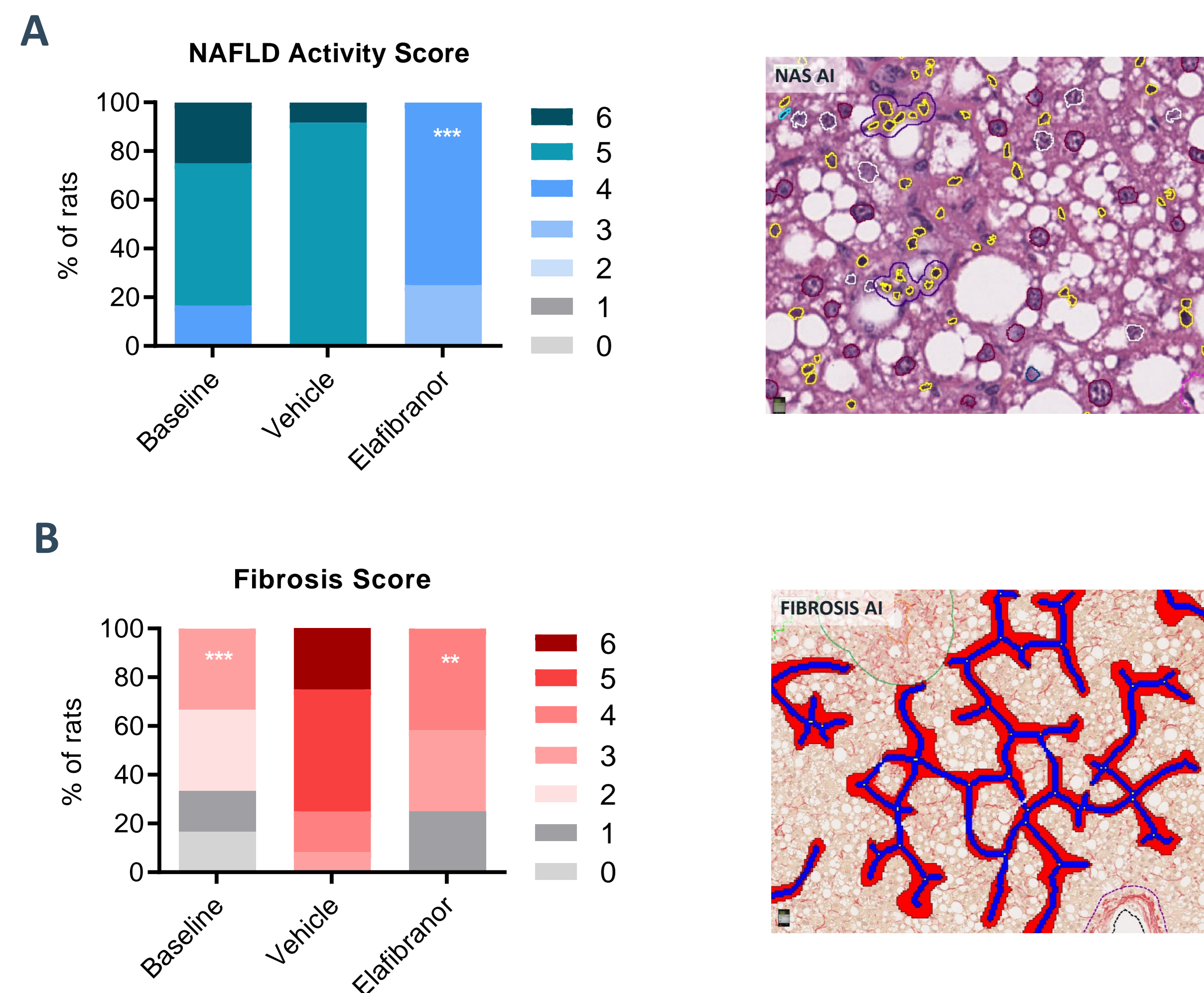


Figure 3. Elafibranor improves liver histopathological scores in the CDAA-HFD rat model. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS) with representative HE photomicrographs used for GHOST evaluation. (B) Fibrosis Score (Ishak) Representative PSR photomicrographs used for GHOST evaluation. ***p<0.001 compared to Vehicle (One-sided Fisher's exact test with Bonferroni correction).

4 Histological quantitative markers of steatosis, inflammation and fibrosis.

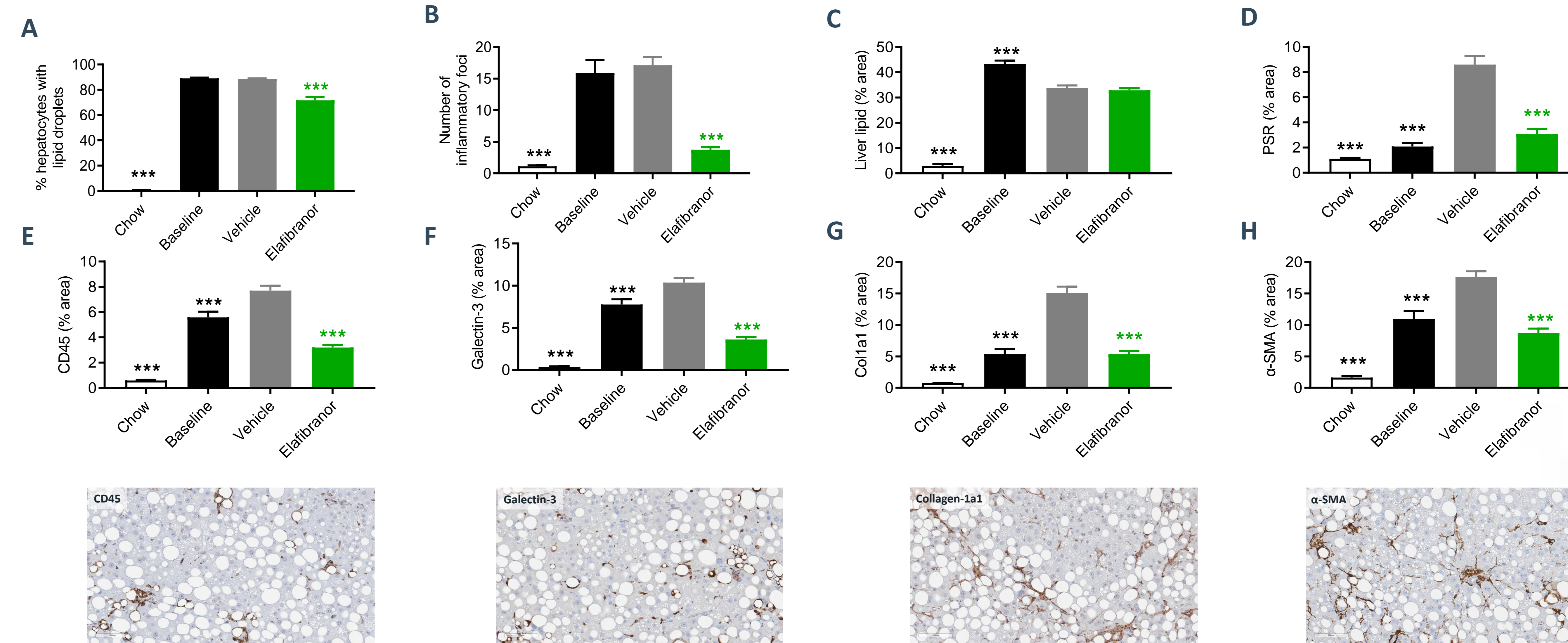


Figure 4. Elafibranor improves quantitative liver histological markers for fibrosis in the CDAA-HFD rat model. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-H). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % liver area with lipids. (D) % area of PSR. (E) % area of CD45 (F) % area of galectin-3. (G) % area of collagen-1a1. (H) % area of alpha-smooth muscle actin (α -SMA) as marker for stellate cell activation. Mean \pm SEM, ***p<0.001 compared to Vehicle (Dunnett's test one-factor linear model). Bottom panels: Representative CD45, galectin-3, collagen 1a1 and α -SMA photomicrographs for elafibranor treatment group (scale bar, 100 μ m).

CONCLUSION

- + Elafibranor has no effect on body weight, but increases liver weight in conjunction with decreased plasma ALT and liver HP levels, while preserves liver TG.
- + Elafibranor improves NAFLD Activity Score and Fibrosis Score.
- + Elafibranor reduces histological markers for liver inflammation, fibrosis and stellate cell activation.
- + These findings highlight the CDAA-HFD non-obese rat model of advanced NASH for exploration of drug efficacy for progressive fibrosis.