

Differential Therapeutic Profile of Efruxifermin in the GAN DIO-MASH and CDAA-HFD Mouse Models of MASH

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Background & Aim

Fibroblast growth factor 21 (FGF21) plays a key role in hepatic lipid metabolism and holds great promise as therapeutic target for metabolic dysfunction-associated steatohepatitis (MASH). Efruxifermin (EFX) is a long-acting FGF21 analogue currently in phase 3 clinical development for pre-cirrhotic (F2-F3) MASH and compensated cirrhosis (F4) due to MASH (SYNCHRONY trials). In this study, we evaluated the therapeutic effects of EFX in two preclinical MASH models, i.e. the biopsy-confirmed Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse and the non-obese choline-deficient L-amino-acid defined high-fat diet (CDAA-HFD) mouse.

Study design

GAN DIO-NASH mouse study (Fig. 1): Male C57BL/6J mice were fed the GAN diet high in fat, fructose, and cholesterol for 36 weeks prior to study initiation. Mice with liver biopsy-confirmed disease (NAFLD Activity Score ≥ 5 ; fibrosis stage F2-F3) were treated with EFX (1.0 mg/kg, SC, n=18) or vehicle (n=17) once weekly for 12 weeks. Age-matched chow-fed mice served as healthy controls (n=10). CDAA-HFD mouse study (Fig. 2): Male C57BL/6J mice were fed a CDAA-HFD for 4 weeks prior to treatment. Mice then received EFX (1.0 mg/kg, SC, n=12) or vehicle (n=12) once weekly for 8 weeks. A baseline group (n=12) was terminated at study start following the initial 4-week CDAA-HFD feeding period.

Conclusion

- + Efruxifermin improves MASH but not fibrosis in GAN DIO-MASH mice
- + Efruxifermin improves fibrosis but not MASH in CDAA-HFD mice
- + Model-specific effects of efruxifermin reflect the distinct disease phenotypes of GAN DIO-MASH and CDAA-HFD mice
- + Longer treatment may be required to demonstrate anti-fibrotic effects of efruxifermin in the GAN DIO-MASH mouse model.



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1 GAN DIO-MASH mouse - Study outline

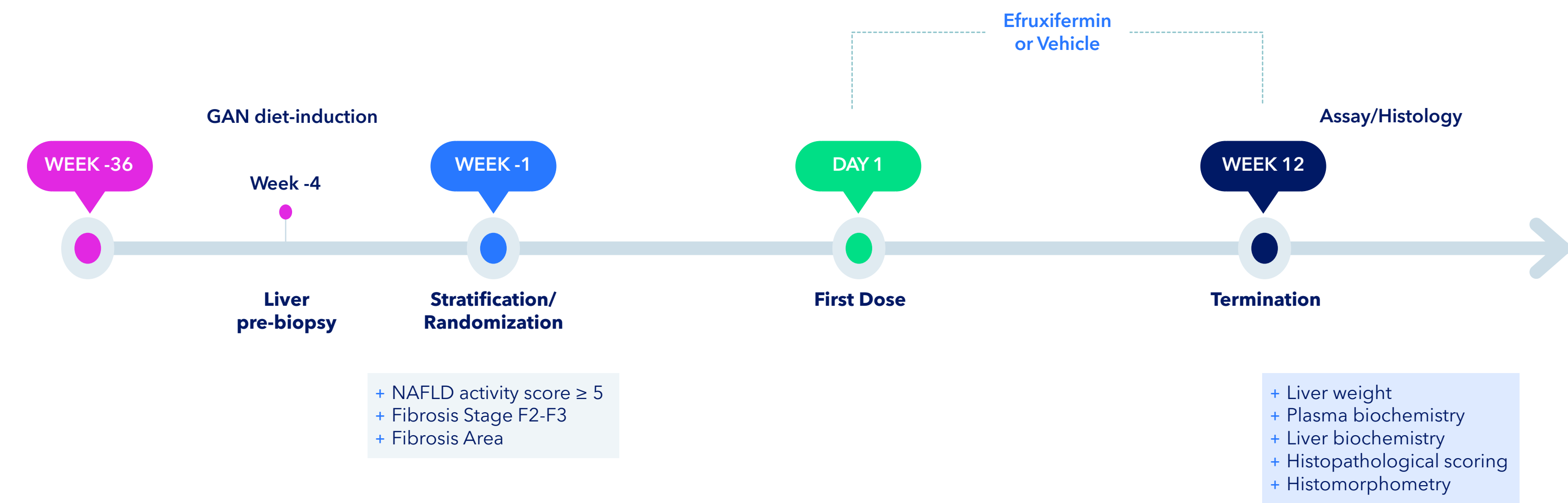


Figure 1. 12-week efruxifermin treatment in GAN DIO-MASH mice.

3 Efruxifermin improves MASH but not fibrosis in GAN DIO-MASH mice

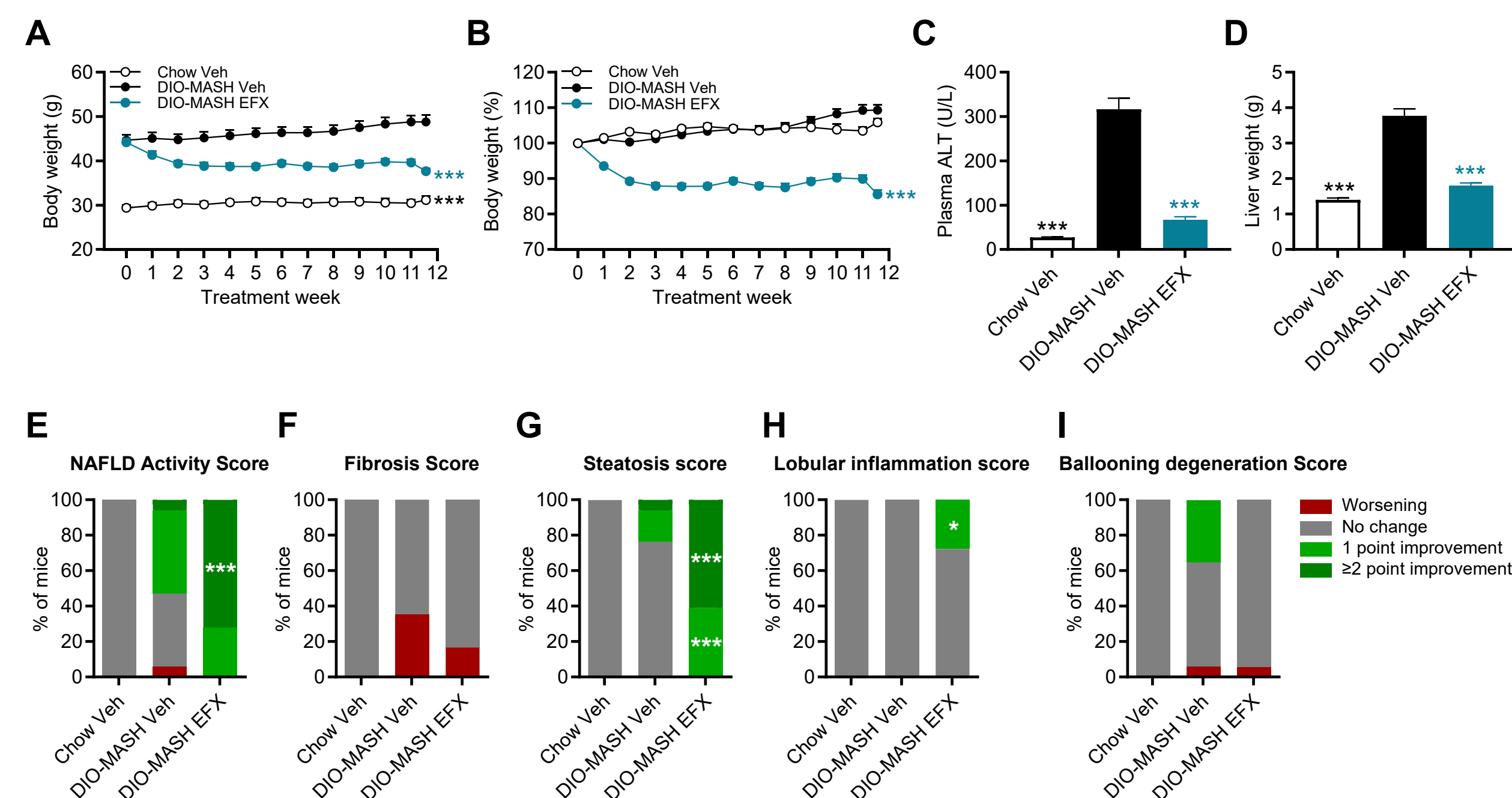


Figure 3. Efruxifermin improves metabolic markers and NAFLD activity score without reducing fibrosis in GAN DIO-MASH mice. (A, B) Body weight (g and % change vs. baseline). ***p<0.001 vs. Vehicle (Dunnett's test two-factor linear model). (C) Plasma alanine transaminase (ALT). (D) Liver weight. ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model). (E-I) NAFLD Activity Score (NAS) and fibrosis score. *p<0.05, **p<0.01, ***p<0.001 vs. Vehicle (one-sided Fisher's exact test with Bonferroni correction). Data are indicated as mean $\pm$ S.E.M.

5 Efruxifermin reduces MASH and fibrogenesis histomorphometrics in GAN DIO-MASH mice

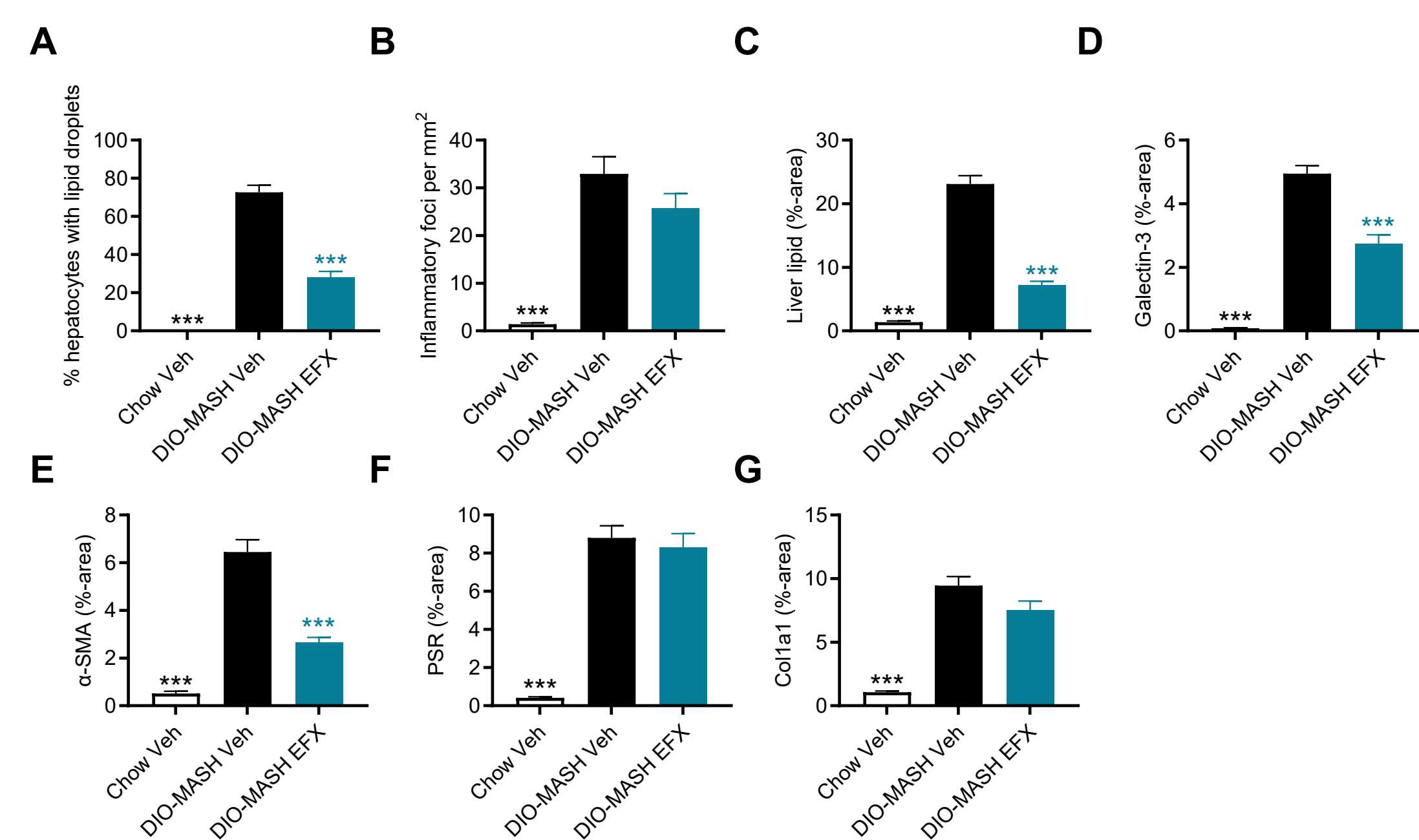


Figure 5. Efruxifermin improves quantitative histological markers of steatosis and inflammation without reducing markers of fibrosis in GAN DIO-MASH mice. (A, B) % hepatocytes with lipid droplets and inflammatory foci density. (C) %-area of liver lipid (HE-staining). (D-E) Galectin-3, α -smooth muscle actin (α -SMA), PSR and collagen-1a1 (Col1a1). Conventional image analysis. Data are expressed relative to parenchymal area after subtraction of the corresponding fat area determined, as determined on adjacent HE-stained sections. ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model). Mean $\pm$ S.E.M.

2 CDAA-HFD mouse - Study outline

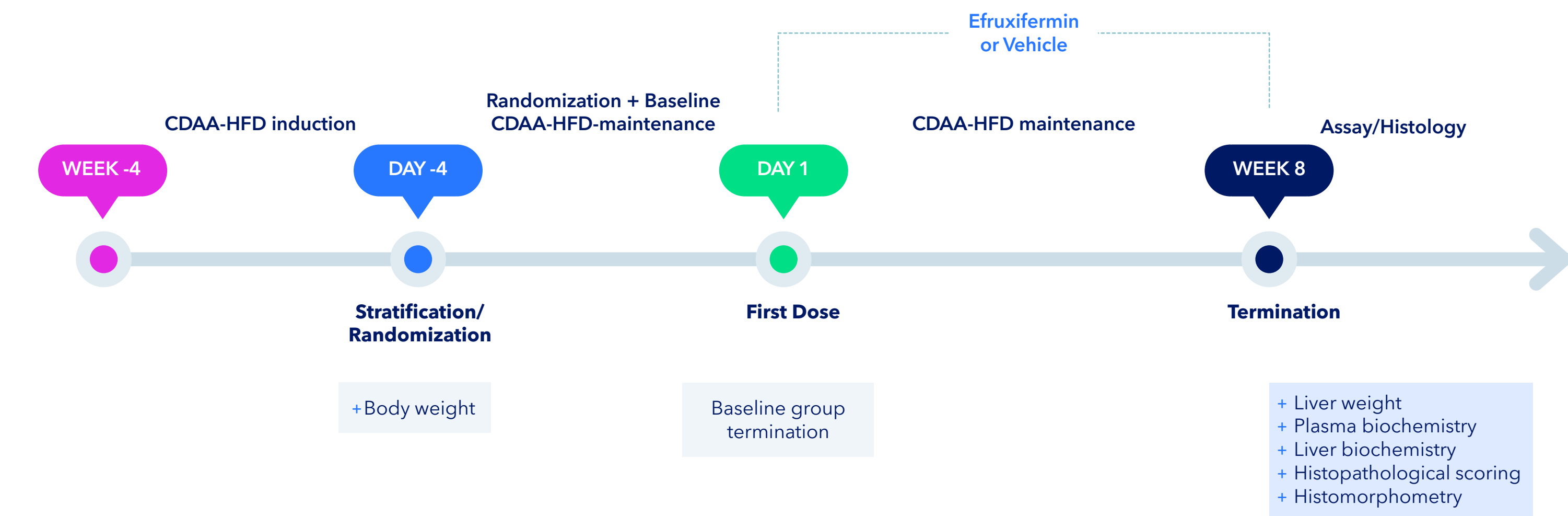


Figure 2. 8-week efruxifermin treatment in CDAA-HFD mice.

4 Efruxifermin improves fibrosis but not MASH in CDAA-HFD mice

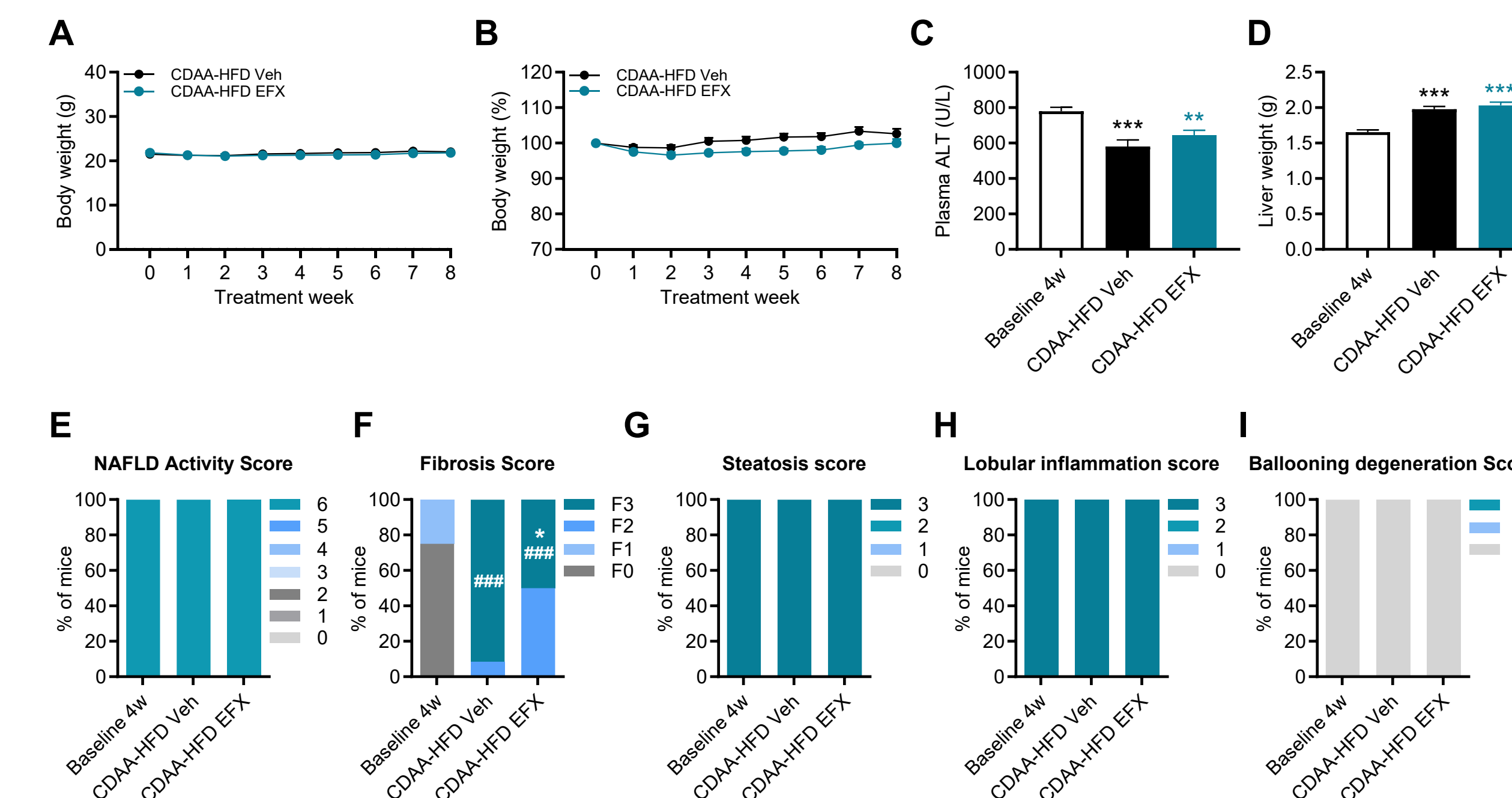


Figure 4. Efruxifermin improves fibrosis score without improving metabolic markers and NAFLD activity score in CDAA-HFD mice. (A, B) Body weight (g and % change vs. baseline). (C) Plasma alanine transaminase (ALT). (D) Liver weight. **p<0.01, ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model). (E, F) NAFLD Activity Score (NAS) and fibrosis score. *p<0.05 vs. Vehicle; ###p<0.001 vs. Baseline 4w (one-sided Fisher's exact test with Bonferroni correction). Data are indicated as mean $\pm$ S.E.M.

6 Efruxifermin reduces inflammatory foci and fibrosis histomorphometrics in CDAA-HFD mice

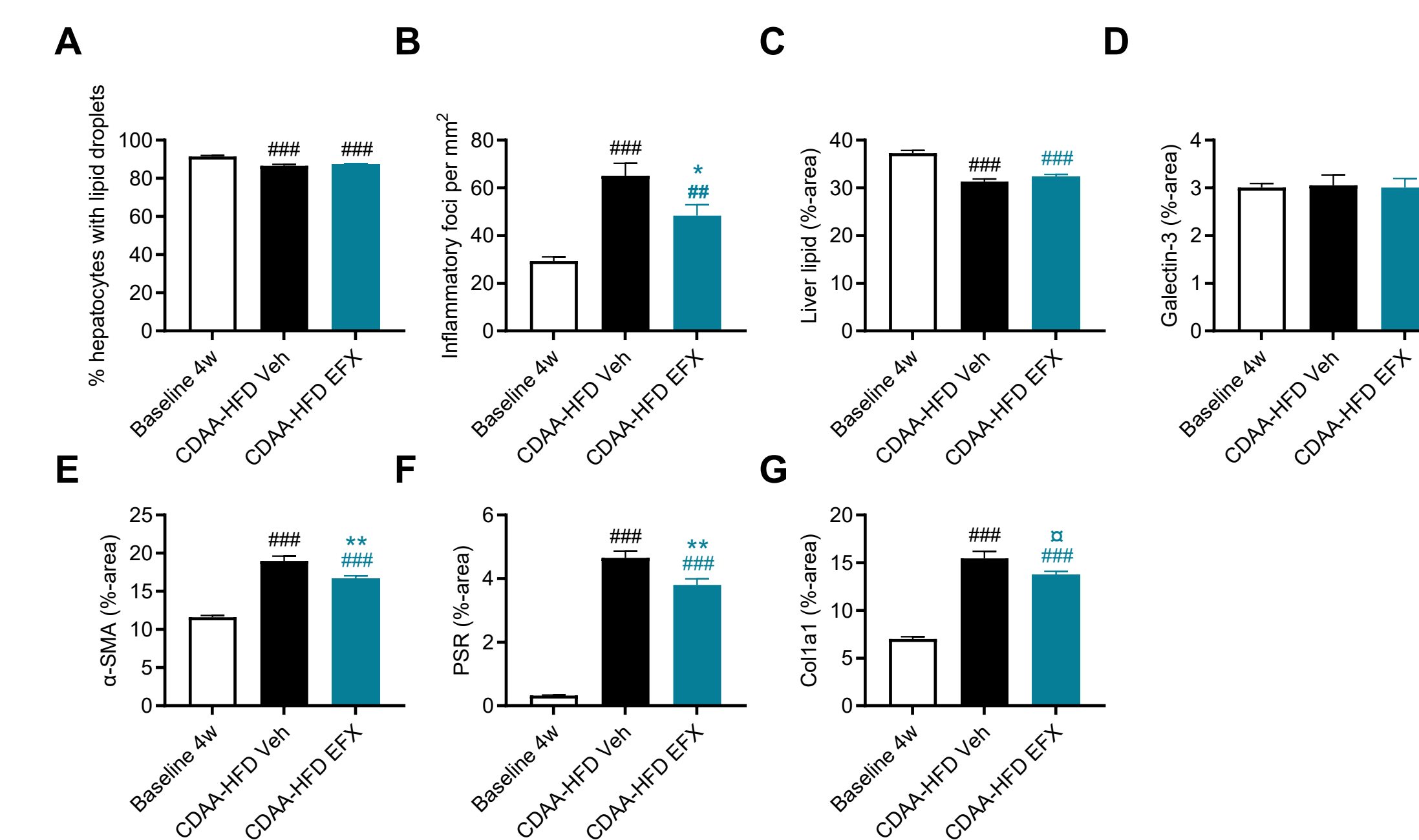


Figure 6. Efruxifermin reduces inflammatory foci density and fibrosis histomorphometrics in CDAA-HFD mice. (A, B) % hepatocytes with lipid droplets and inflammatory foci density. (C) %-area of liver lipid (HE-staining). (D-E) Galectin-3, α -smooth muscle actin (α -SMA), PSR and collagen-1a1 (Col1a1). Conventional image analysis. Data are expressed relative to parenchymal area after subtraction of the corresponding fat area determined, as determined on adjacent HE-stained sections. *p<0.05, **p<0.01, ***p<0.001 vs. Vehicle; ###p<0.001 vs. Baseline 4w (Dunnett's test one-factor linear model). Mean $\pm$ S.E.M.