Additive hepatoprotective effects of DA-1241, a novel GPR119 agonist, in combination with semaglutide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background & Aim

The G protein-coupled receptor 119 (GPR119) and glucagon-like peptide-1 receptor (GLP1R) are promising therapeutic targets for metabolic dysfunction-associated steatohepatitis (MASH).

The aim of this study was to evaluate the metabolic, biochemical, histological and transcriptomic effects of DA-1241 (GPR119 agonist, Phase 2a) and semaglutide (GLP-1R agonist) combination therapy in the GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with moderate-severe liver fibrosis.

1 Study outline
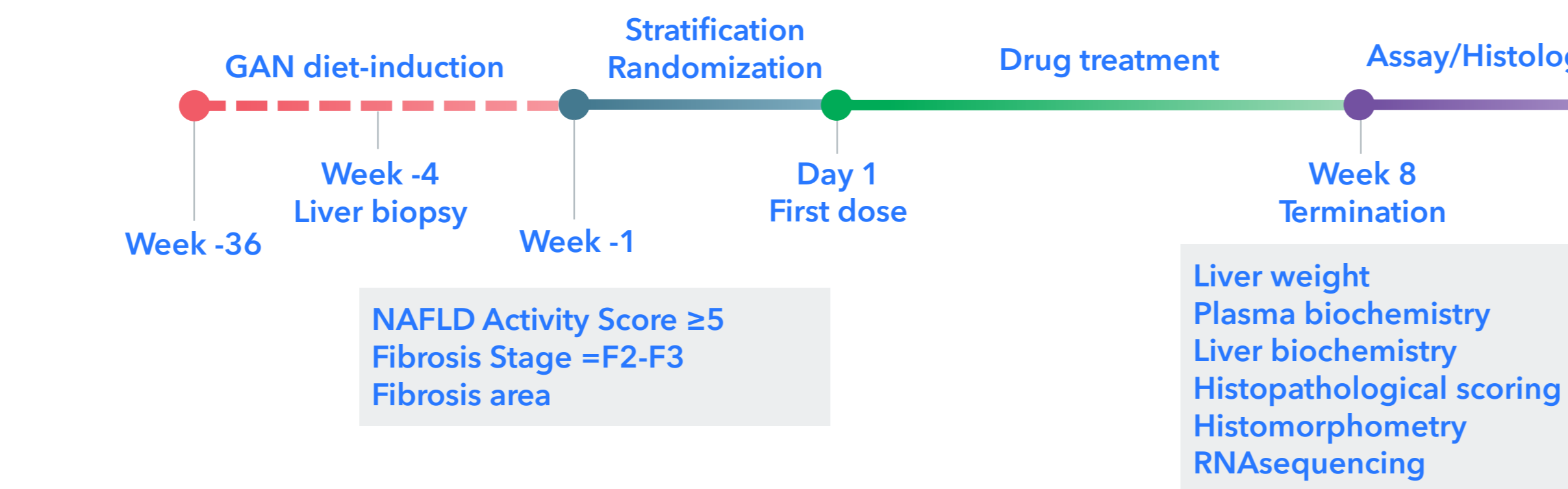
Group	Animal	Gender	Number of animals	Treatment		Administration route	Dosing Frequency	Dosing concentration
1	DIO-MASH	Male	15	Vehicle	Vehicle	PO + SC	QD	NA + NA
2	DIO-MASH	Male	15	DA-1241	Vehicle	PO + SC	QD	100 mg/kg + NA
3	DIO-MASH	Male	15	Vehicle	Semaglutide	PO + SC	QD	NA + 30 nmol/kg
4	DIO-MASH	Male	15	DA-1241	Semaglutide	PO + SC	QD	100 mg/kg + 30 nmol/kg

Figure 1. Study outline. PO; per oral, SC; subcutaneous, QD; Once daily, NA; Not applicable, GAN; Gubra Amylin NASH.

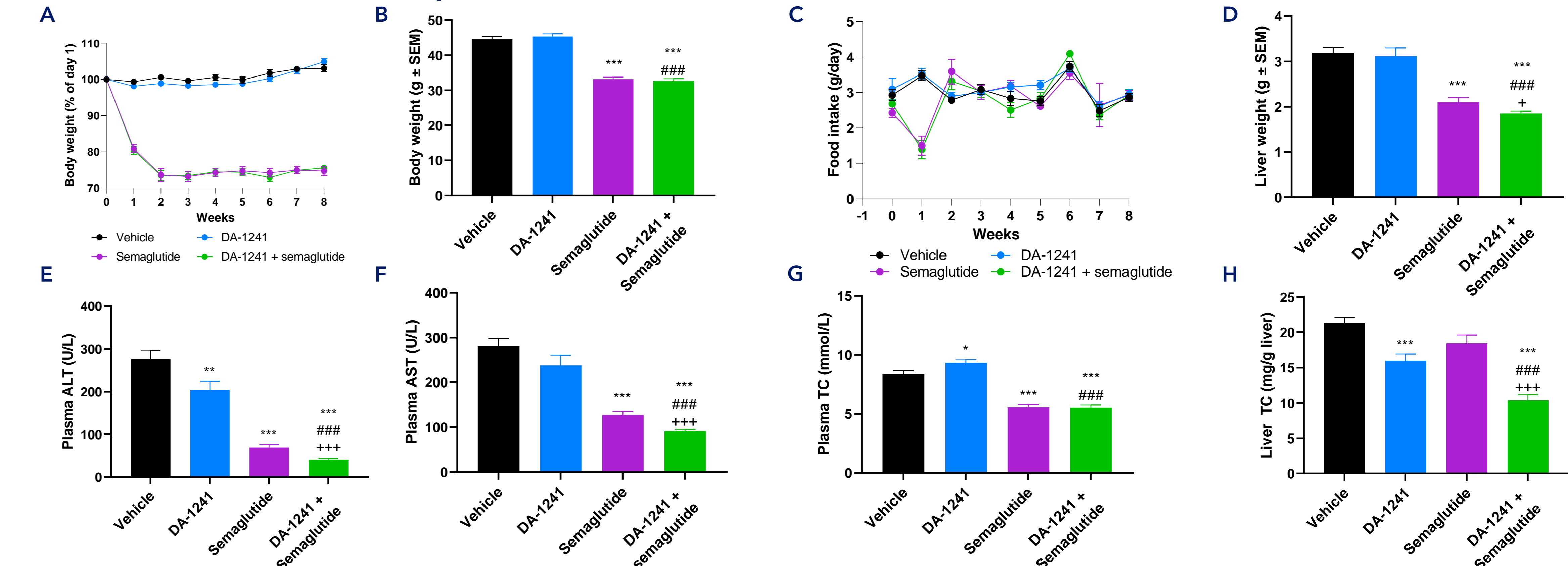## 2 Metabolic and biochemical parameters

Figure 2. Metabolic and biochemical effects of DA-1241 and semaglutide as mono- and combination therapy. (A) Relative body weight during study period. (B) Terminal body weight. (C) Food intake. (D) Liver weight. (E) Terminal plasma alanine aminotransferase (ALT). (F) Terminal plasma aspartate aminotransferase (AST). (G) Plasma total cholesterol (TC) (H) Terminal liver total cholesterol. *p<0.05, ***p<0.001 compared to vehicle control, ###p<0.001 compared to DA-1241, and +p<0.05, +++p<0.001 compared to Semaglutide (Dunnett's test one-factor linear model).

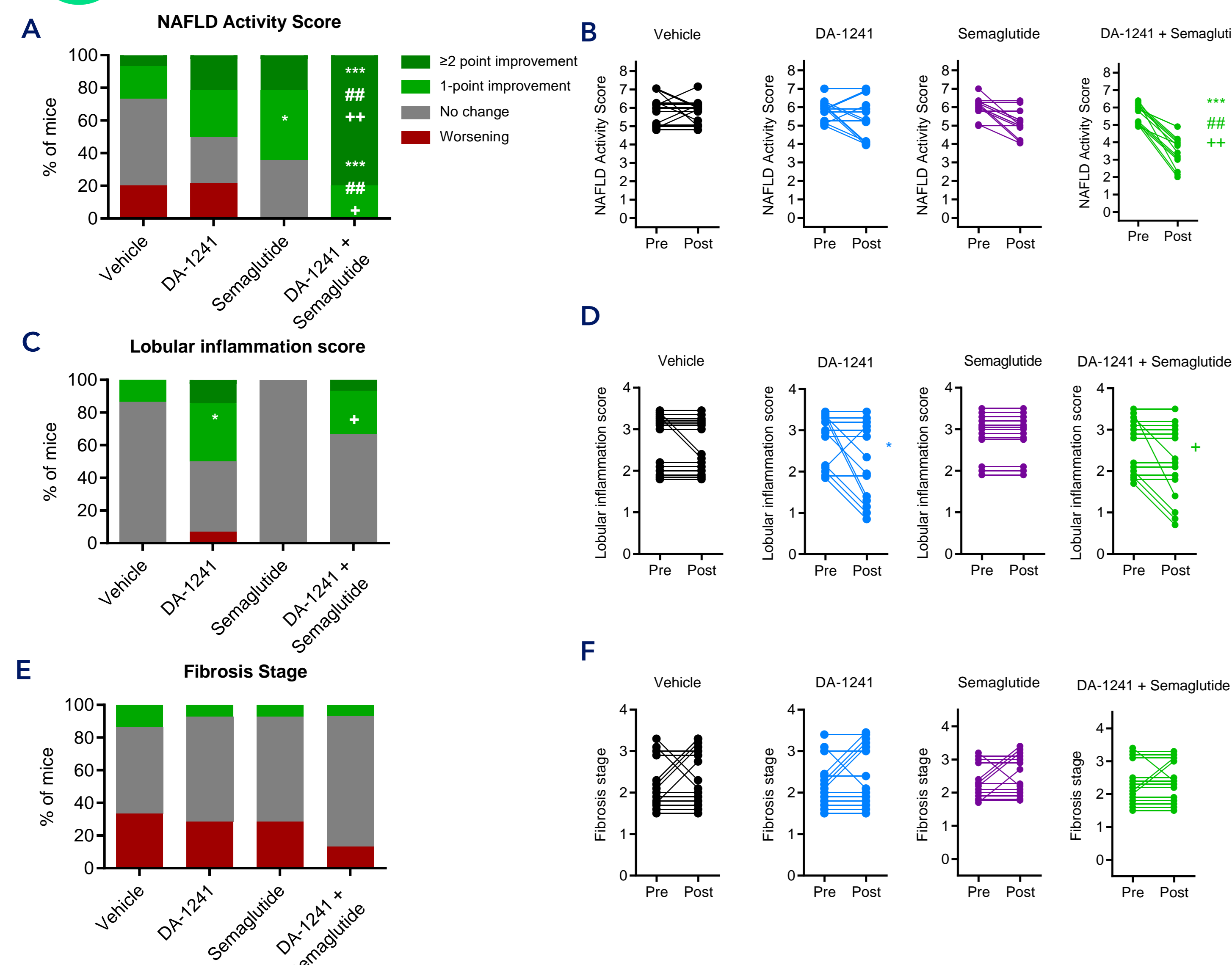## 3 NAFLD Activity Score and Fibrosis Stage

Figure 3. Synergistic therapeutic effects of DA-1241 and semaglutide on NAFLD Activity Score in GAN DIO-MASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Individual pre-post NAS. (C) Lobular inflammation score. (D) Individual pre-post lobular inflammation score. (E) Fibrosis stage. (F) Individual pre-post fibrosis stage. *p<0.05, ***p<0.001, ##p<0.01 compared to DA-1241, and +p<0.05, +++p<0.01 compared to Semaglutide (Dunnett's test one-factor linear model). compared to corresponding vehicle control (One-sided Fisher's exact test).

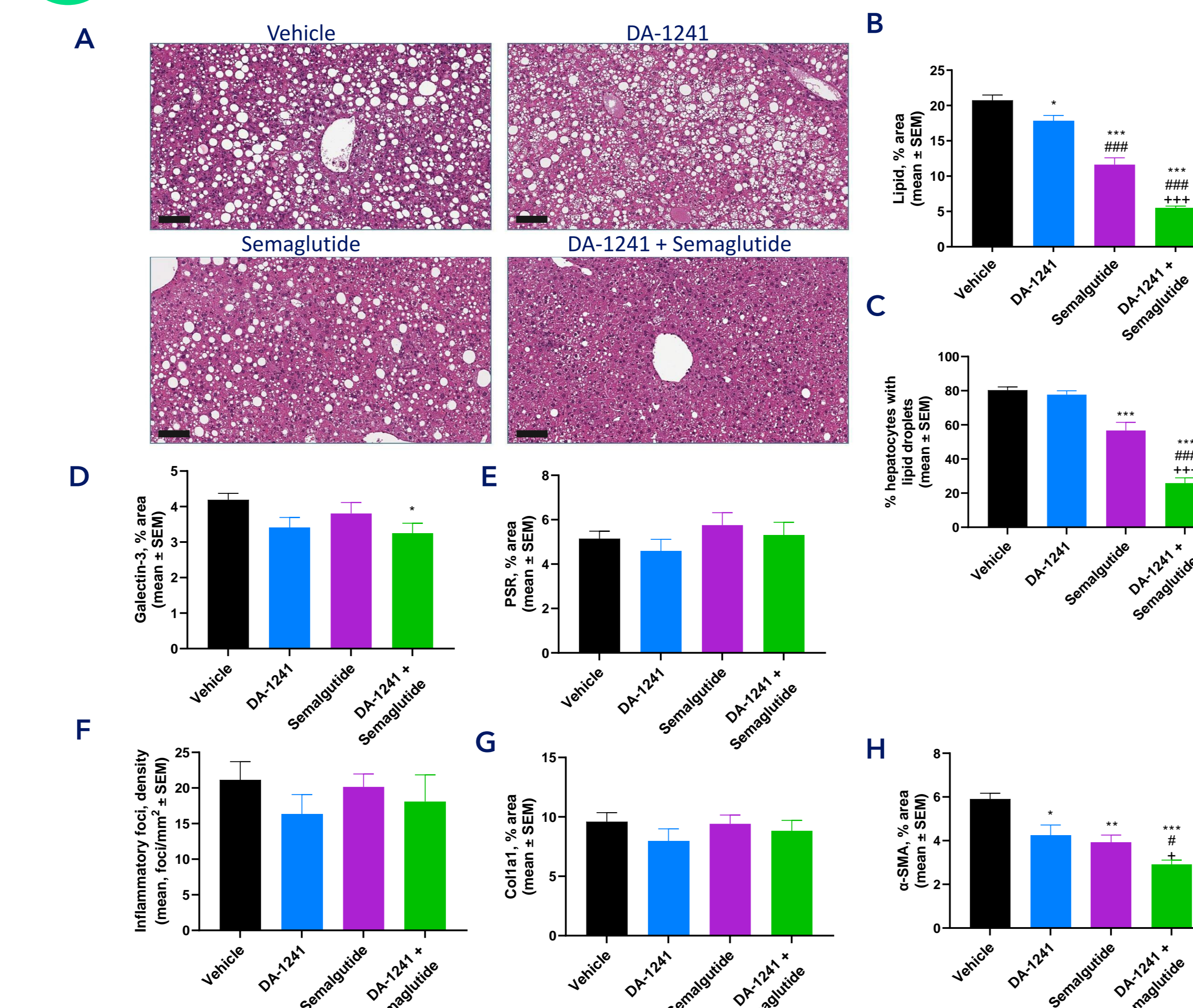## 4 Histological markers of steatosis, inflammation and fibrosis

Figure 4. Synergistic therapeutic effects of DA-1241 and semaglutide on quantitative histological endpoints. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-C) and conventional IHC image analysis (panels D-H). (A) Representative photomicrographs of H&E staining (scale bar, 100 μm). (B) % area of liver lipids. (C) % hepatocytes with lipid droplets. (D) % area of galectin-3. (E) % area of PSR. (F) Number of inflammatory foci. (G) % area of collagen-1a1 (H) % area of alpha-smooth muscle actin (α-SMA, marker of stellate cell activation). Mean ± SEM. *p<0.05, ***p<0.001 to corresponding vehicle group, #p<0.05, ###p<0.001 compared to DA-1241, and +p<0.05, +++p<0.001 compared to Semaglutide (Dunnett's test one-factor linear model). Bottom panels:
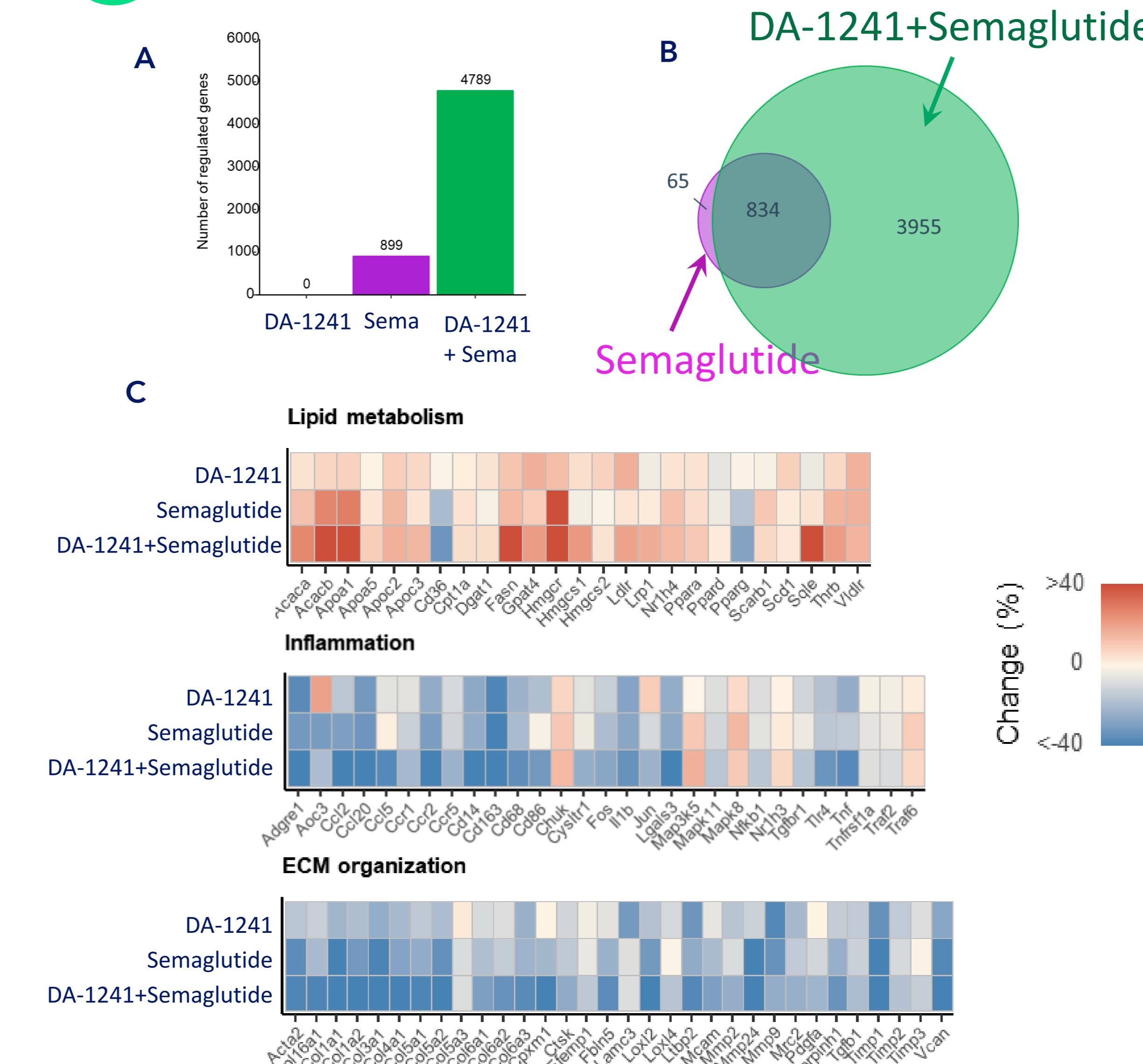
5 Liver transcriptome analysis

Figure 5. Combination therapy with DA-1241 and semaglutide improves hepatic transcriptome profile. (A) Total number of differentially expressed genes. (B) Venn diagram on overlapping gene expression signatures. (C) Expression regulation of hepatic lipid metabolism, inflammation and extracellular matrix (ECM). Red and blue colours indicate up- and down-regulation respectively, shown as % change, when compared to Vehicle.

Conclusion

+ DA-1241 + semaglutide exhibited only body weight loss caused by semaglutide.

+ Combination therapy further improves NAS compared to monotherapy. Driven by anti-inflammatory effects were likely attributed to DA-1241 treatment.

+ Benefits on NAS is supported by quantitative histological markers.

+ Combination therapy improves hepatic gene expression markers of lipid metabolism, inflammation and fibrogenesis.

+ DA-1241 and semaglutide show no effect on fibrosis score after 8-week treatment.

+ Combined GPR119 and GLP1R agonist treatment shows promise in MASH.