

Enhancing Effects of Combining Resmetirom and Semaglutide in a Modified AMLN Diet-induced Mouse Model for Metabolic Dysfunction-associated Steatohepatitis (MASH)

Abstract #2883

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Background and Aims:

Both a thyroid hormone receptor (THR)-beta agonist, resmetirom and a glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide were recently approved for treating noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis. However, not all patients respond to resmetirom with MASH resolution. We therefore evaluated, before the indication expansion of semaglutide, whether semaglutide in combination with resmetirom would improve the effects of resmetirom using a modified AMLN diet induced mouse MASH model.

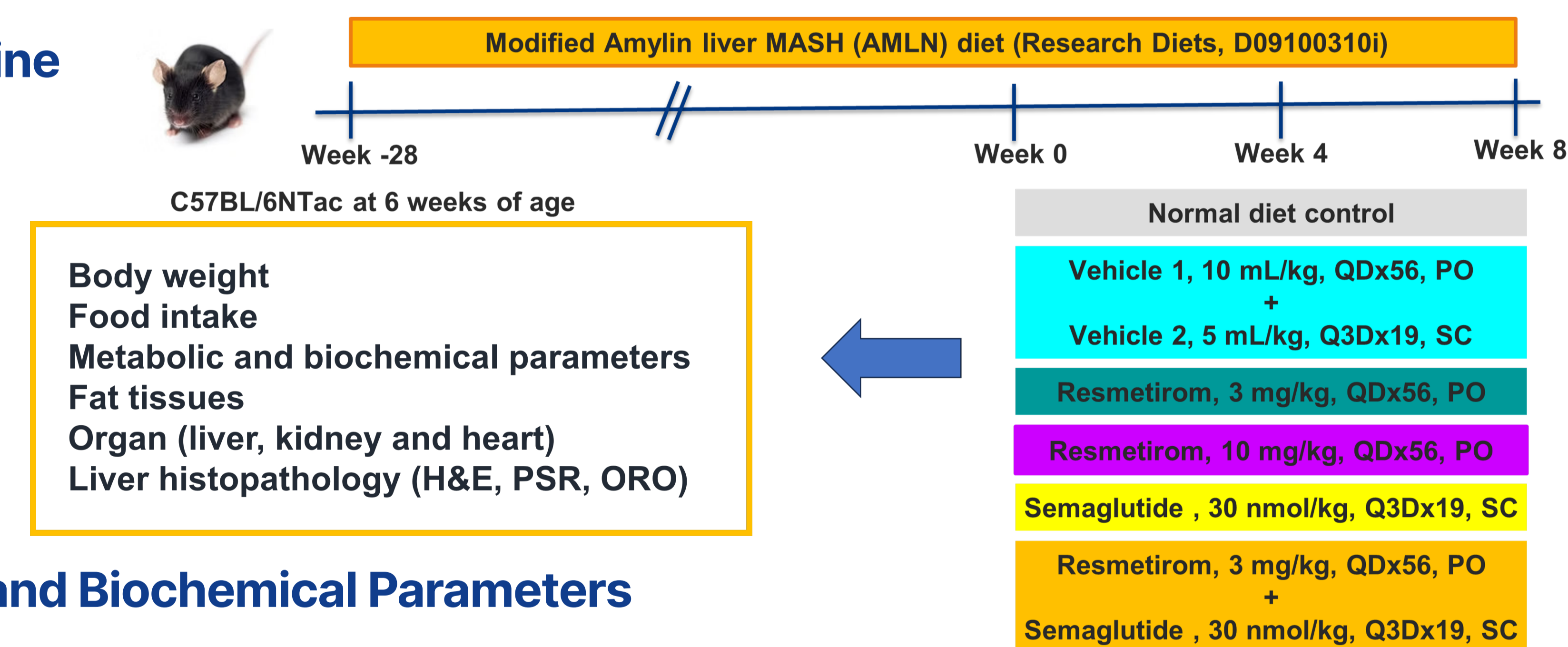
Method:

Male C57BL/6NTac mice from Taconic Biosciences were fed a modified AMLN diet for 28 weeks and then treated for 8 weeks with either resmetirom alone at 3 and 10 mg/kg given orally every day, semaglutide alone at 30 nmol/kg given subcutaneously every 3 days, or semaglutide in combination with 3 mg/kg resmetirom. Biochemical parameters, glucose and insulin levels were measured at week 0, week 4 and week 8. At termination, liver total cholesterol was quantified, and liver histopathological analyses were performed using hematoxylin and eosin, picrosirius red, and Oil Red O staining.

Results:

Modified AMLN diet feeding induced body weight gain, increased adiposity, and the metabolic, biochemical and histopathological changes characteristic of MASH, including liver injury, steatosis, inflammation and fibrosis. Resmetirom treatment dose-dependently reduced serum and liver total cholesterol (TC), total triglycerides (TG) and low-density lipoprotein as well as liver weight and liver fat accumulation, decreased liver steatosis, inflammation and ballooning in histopathological assessment, and also effectively prevented liver injury. Semaglutide mainly decreased initial food intake (week 4), reduced body and liver weight, lowered serum TC and TG, reduced fat mass and tended to ease liver fat burden. Neither resmetirom nor semaglutide appeared to affect the liver fibrosis levels. Interestingly, semaglutide in combination of lower dose of resmetirom improved its effects and their effects were potentially synergistic; additional studies and analyses are needed to confirm this.

Study Outline



Metabolic and Biochemical Parameters

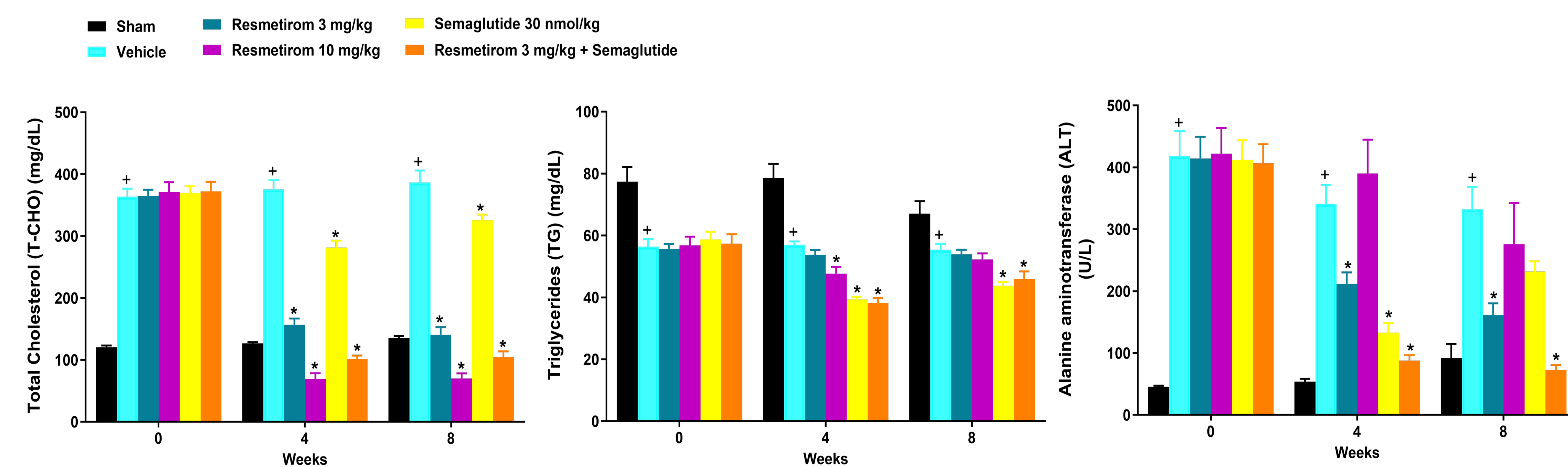


Figure 1: Resmetirom and semaglutide intervention improved serum T-CHO, TG and ALT levels in modified AMLN diet-induced MASH in C57BL/6 mice. Male C57BL/6 mice were fed a modified Amylin liver MASH (AMLN) diet (Research Diets D09100310i with 40 kcal% fat, 20 kcal% fructose and 2% cholesterol) or normal diet starting at 6 weeks of age for 28 weeks. Resmetirom at 3 or 10 mg/kg was given orally QD for 56 days, semaglutide at 30 nmol/kg was given subcutaneously (SC) once every 3 days for a total 19 injections or semaglutide in combination with 3 mg/kg resmetirom. Serum total Cholesterol (T-CHO), triglycerides (TG) and alanine aminotransferase (ALT) levels were determined for evaluation of obesity and hepatic impairment by automated biochemical analyzer on Weeks 0, 4 and 8. $\dagger p < 0.05$, vs sham; $* p < 0.05$, vs vehicle control; two-way ANOVA followed by Bonferroni test. Error bars represent SEM values.

Fat Pad Mass and Liver Weight Changes

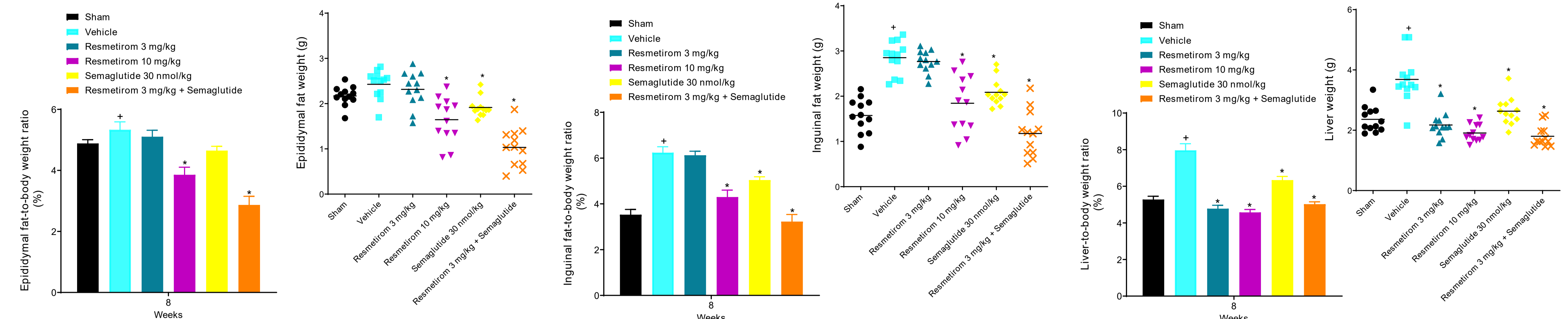


Figure 2: Resmetirom and semaglutide improved fat pad mass and liver weight in modified AMLN diet-induced MASH in C57BL/6 mice. At the end of study (Week 8), epididymal fat pad, inguinal fat pad and liver for each animal were harvested and weighed. Tissue-to-body weight ratio was calculated for each animal according to the formula: tissue (g)/BW x 100. $\dagger p < 0.05$, vs sham; $* p < 0.05$, vs vehicle control; one-way ANOVA followed by Dunnett's test. Error bars represent SEM values.

Histopathology Analysis

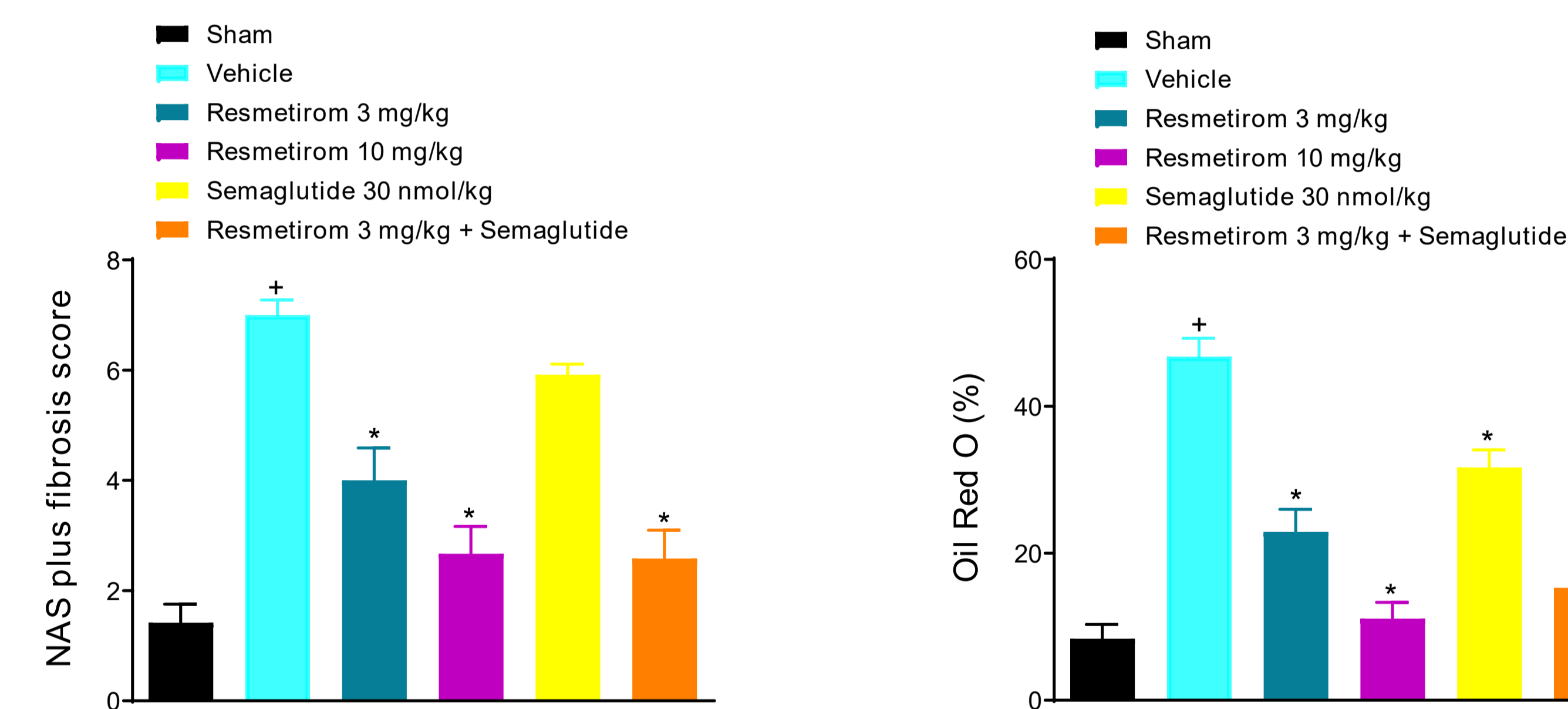


Figure 3: Resmetirom and semaglutide improved liver histopathological scores in modified AMLN diet-induced MASH in C57BL/6 mice. Liver tissue samples from each mouse were fixed in 10% phosphate-buffered formalin and then embedded in paraffin blocks. Five-micrometer tissue sections were cut and stained with Hematoxylin and Eosin (H&E) for histological analysis (NAS scoring) under light microscope. Briefly, the NAS score, including fibrosis, was aggregated from 4 semi-quantitative sub-scores: steatosis (0-3), lobular inflammation (0-2), hepatocellular ballooning (0-2), and fibrosis (0, 1a, 1b, 1c, 2, 3, 4). The % of the Oil-Red O-stained area was also analyzed with ImageJ software. $\dagger p < 0.05$, vs sham; $* p < 0.05$, vs vehicle control; one-way ANOVA followed by Dunnett's test. Error bars represent SEM values.

Body Weight Changes

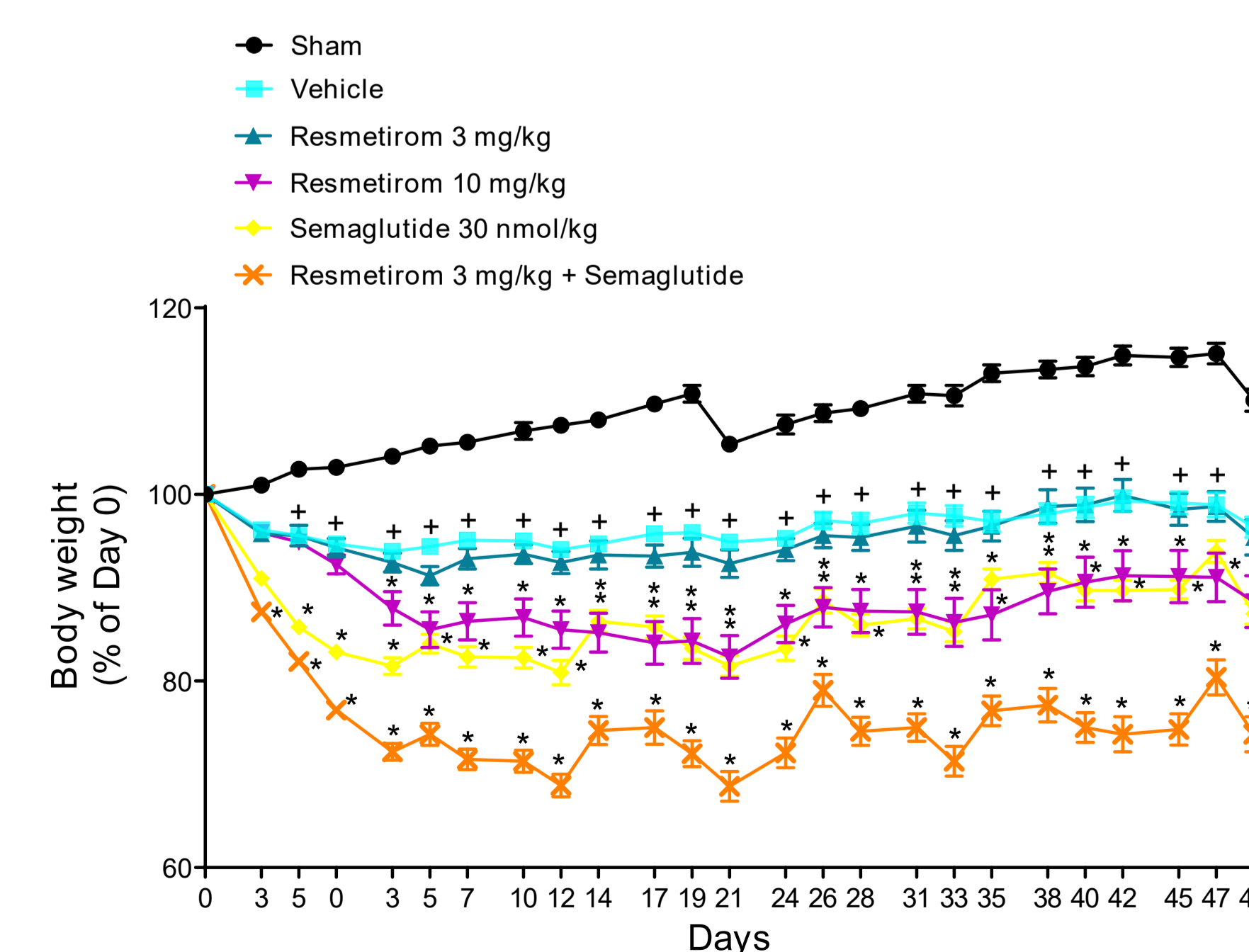
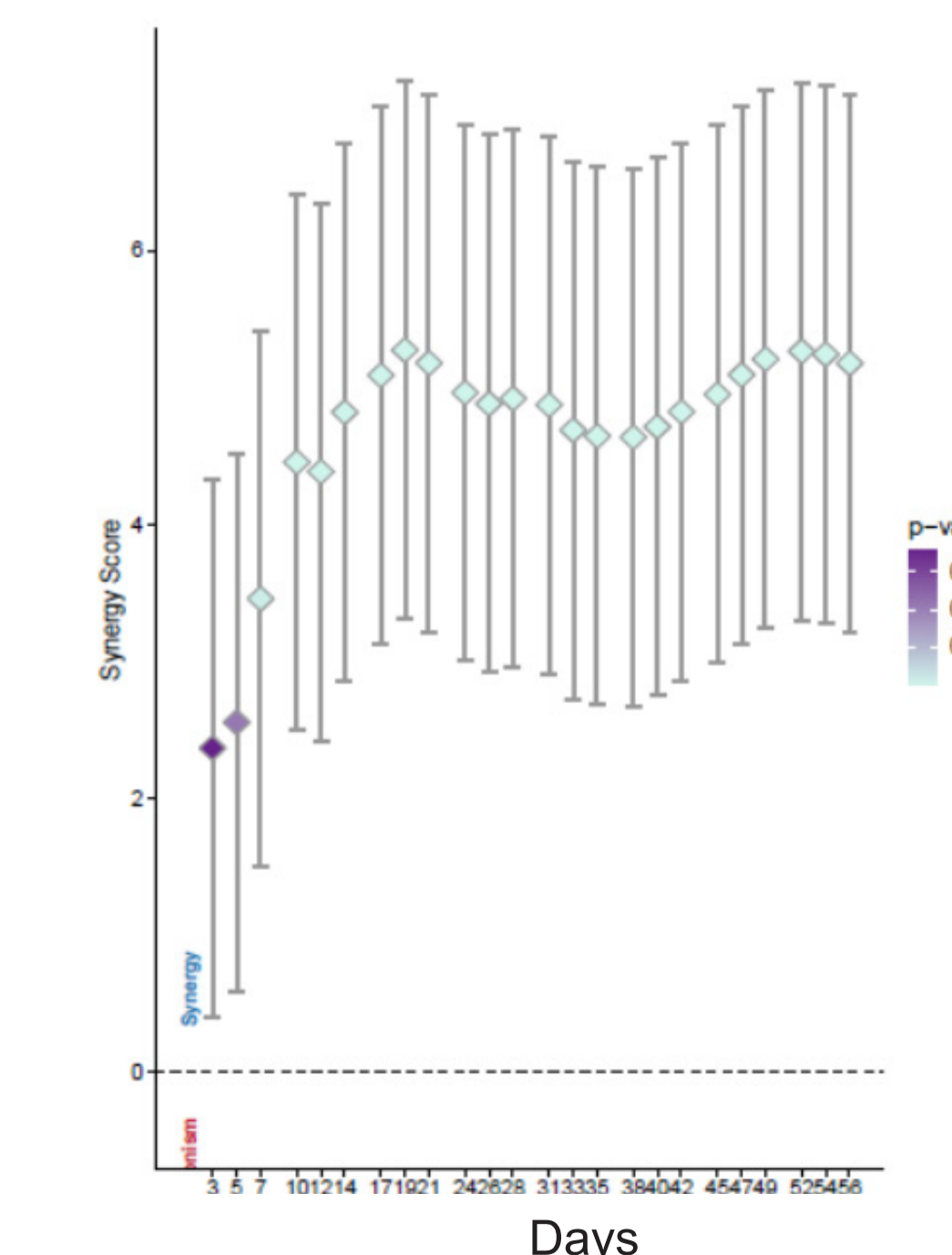
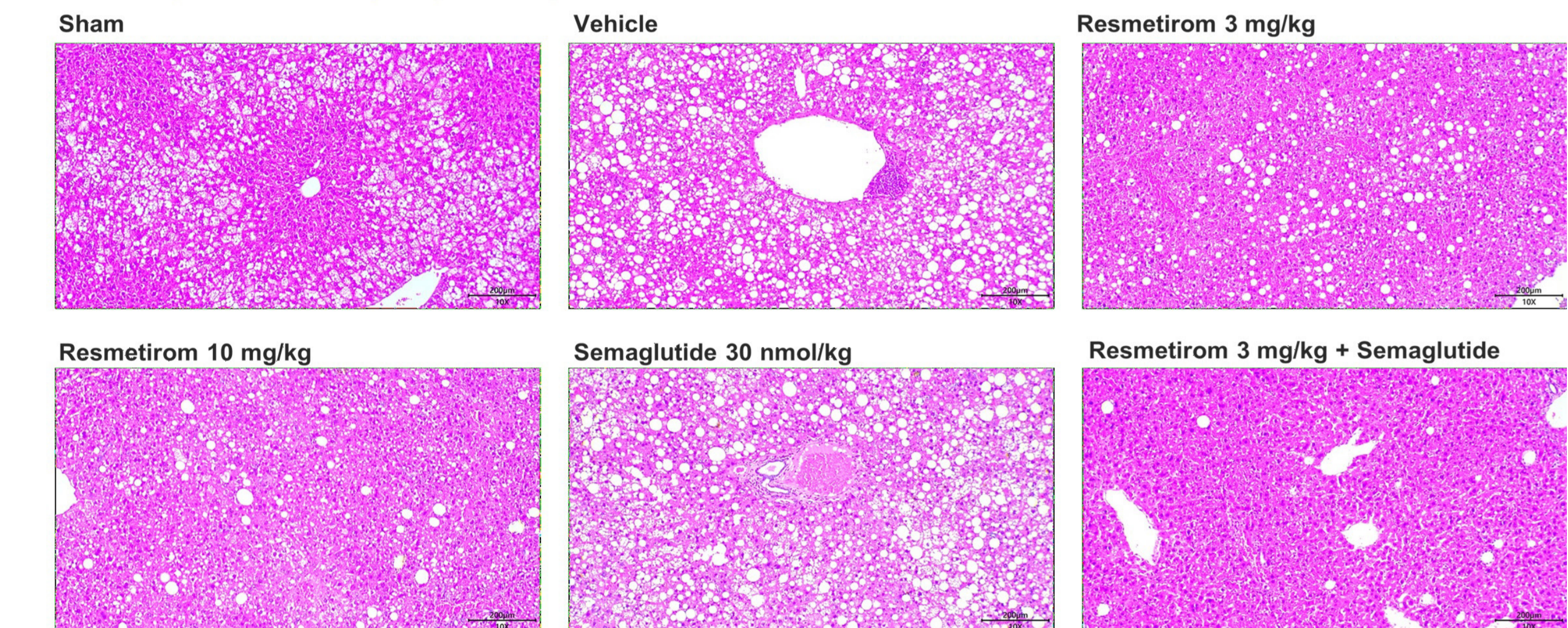


Figure 4: Body weight change in modified AMLN diet-induced MASH in C57BL/6 mice and preliminary synergy analysis using Bliss independence model. Body weight was recorded thrice weekly during the study period. Change in body weight (%) from day 0. $\dagger p < 0.05$, vs sham; $* p < 0.05$, vs vehicle control; two-way ANOVA followed by Bonferroni test. Error bars represent SEM values.

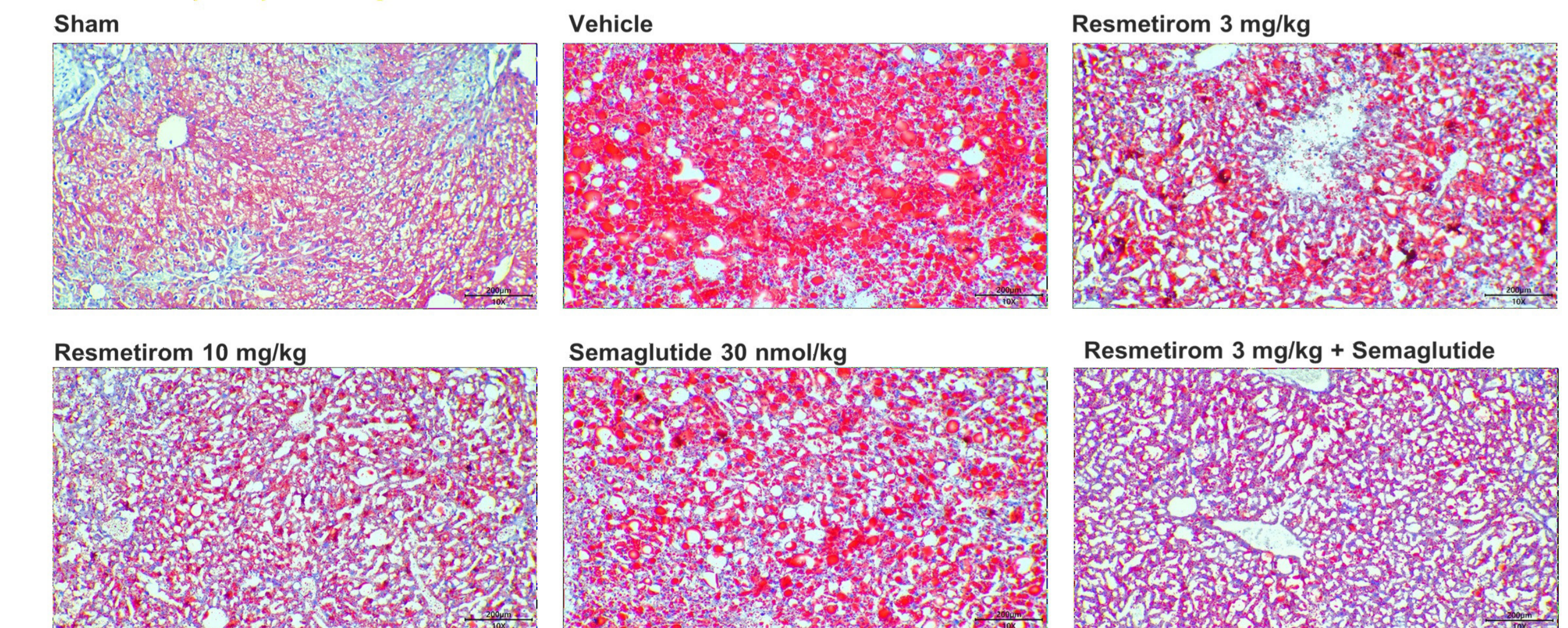
Bliss Synergy Score



Hematoxylin and Eosin (H&E) Staining



Oil Red O (ORO) Staining



Conclusion:

Combined treatment with semaglutide and resmetirom produced enhancing effects when compared to either treatment alone. These data warrant further investigation into combination therapies of THRbeta agonists and GLP-1 receptor agonists for the potential treatment of MASH or other metabolic disorders.

References

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- Zhang R, et al. Comparative pharmacodynamic analysis of resmetirom, semaglutide and obeticholic acid in translational mouse models of MASH. *Explor Endocr Metab Dis.* 2025;2:101433.