Reproducible hepatoprotective effects and clinical translatability of resmetirom in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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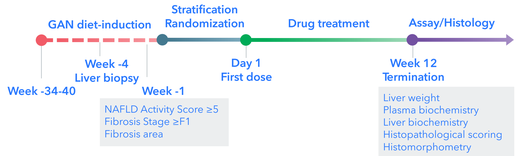
Background & Aim

Resmetirom, a selective THR-β agonist, has been demonstrated to improve NAFLD Activity Score (NAS) and fibrosis stage in a recent phase-3 clinical trial (MAESTRO-NASH) in patients with metabolic dysfunction-associated steatohepatitis (MASH). FDA has recently granted accelerated approval for resmetirom (Rezdiffra) for the treatment of MASH patients with moderate to advanced liver fibrosis. The present study aimed to evaluate robustness of therapeutic outcomes following treatment with resmetirom in the translational GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis.

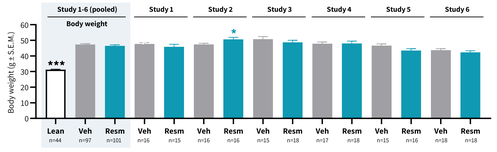
Methods

Resmetirom was characterized in 6 individual studies. C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 34-40 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAS≥5) and fibrosis (stage ≥F1) were included and stratified into treatment groups. GAN DIO-MASH mice (n=15-18 per group) received resmetirom (Resm, 3 mg/kg, PO) or vehicle (Veh, PO) once daily for 12 weeks. Vehicle-dosed chow-fed controls served as healthy controls (Lean). Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage by GHOST. Terminal quantitative endpoints included plasma/liver biochemistry and quantitative liver histology. Furthermore, histopathological pre-to-post assessment of NAS and fibrosis stage were evaluated against primary histological endpoints applied in a corresponding clinical trial, (i.e. resolution of MASH with no worsening of liver fibrosis; at least 1-stage fibrosis improvement without worsening of MASH). Statistical analyses were performed using Dunnett's test one-factor linear model (individual studies), Fisher's exact test (pooled study data on semiquantitative histopathological scoring variables) or one-way ANOVA with Dunnett's post-hoc test (pooled study data on quantitative endpoints), respectively. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle controls.

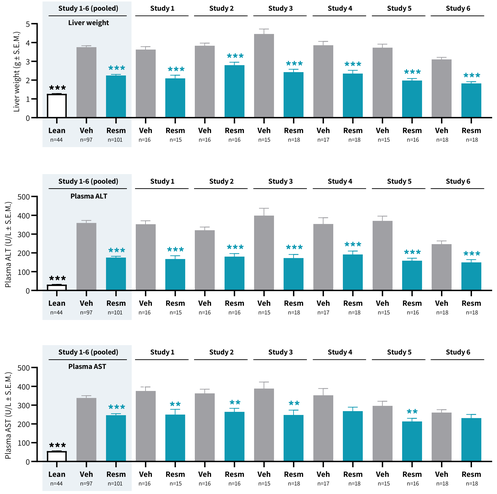
1 Study outline



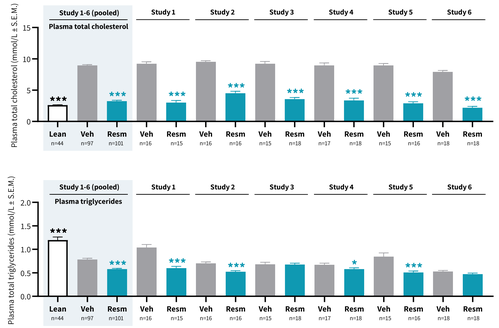
2 Body weight



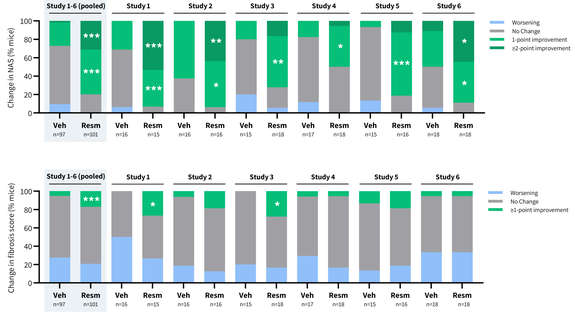
3 Liver weight & transaminases



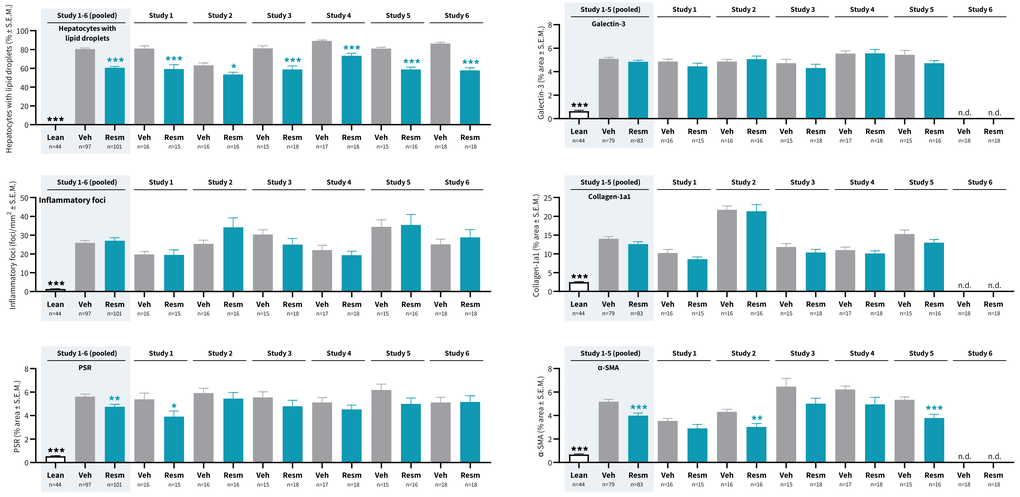
4 Plasma total cholesterol & triglycerides



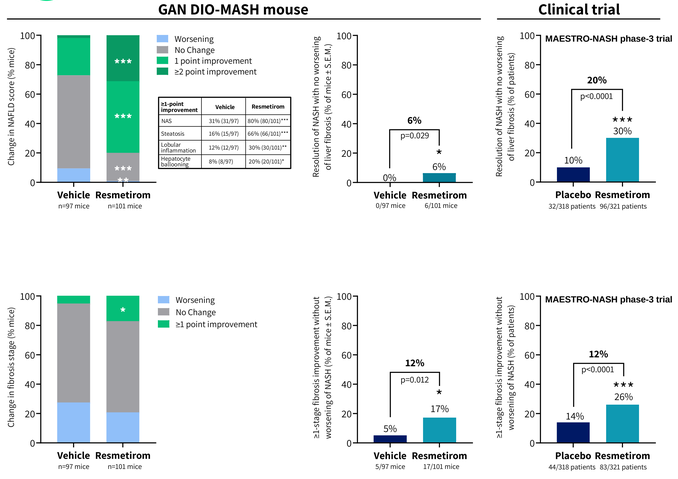
5 NAFLD Activity Score (NAS) & Fibrosis stage



6 Quantitative histological markers of steatosis, inflammation, fibrosis and fibrogenesis



7 Clinical translatability



≥1-point improvement	Vehicle	Resmetirom
NAS	31% (31/97)	80% (80/101)***
Steatosis	16% (15/97)	66% (66/101)***
Lobular inflammation	12% (12/97)	30% (30/101)**
Hepatocyte ballooning	8% (8/97)	20% (20/101)*

Conclusion

- Resmetirom was characterized in 6 individual studies in GAN DIO-MASH mice
- Resmetirom is weight-neutral and consistently improves hepatomegaly, transaminases and hypercholesterolemia
- Resmetirom reproducibly improves NAFLD Activity Score (NAS), primarily by reducing steatosis score
- Resmetirom shows inconsistent effects on Fibrosis Stage.
- Benefits on histopathological scores were supported by quantitative histology for steatosis, fibrosis and fibrogenesis.
- Histological outcomes in GAN DIO-MASH mice are comparable to the corresponding clinical trial for resmetirom (MAESTRO-NASH)

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