Preclinical efficacy and clinical translatability of resmetirom in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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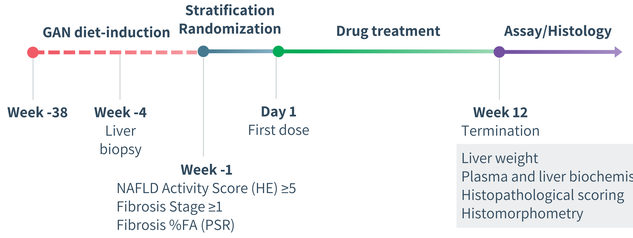
BACKGROUND & AIM

Resmetirom (MGL-3196), a selective THR-β agonist, has been reported to improve histopathological outcomes in a recent 52-week phase-3 clinical trial (MAESTRO-NASH) in patients with non-alcoholic steatohepatitis (NASH). The present study aimed to *(i)* evaluate the metabolic, biochemical and histopathological effects of resmetirom treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and *(ii)* compare to primary outcomes in the MAESTRO-NASH trial.

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dose
1	LEAN-CHOW	Male	10	**Vehicle**	PO	QD	-
2	DIO-NASH	Male	16	**Vehicle**	PO	QD	-
3	DIO-NASH	Male	15	**Resmetirom**	PO	QD	3mg/kg

2 Metabolic and biochemical markers

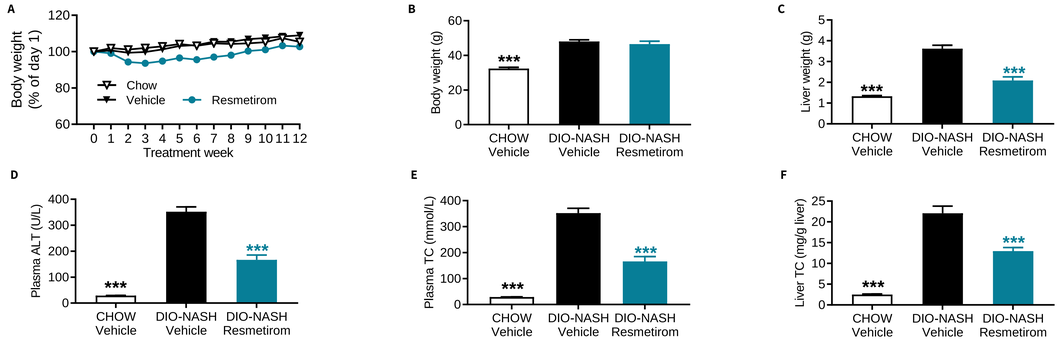


Figure 1. Resmetirom is weight-neutral and improves both hepatomegaly and biochemical markers in GAN DIO-NASH mice. **(A)** Body weight change relative to baseline (day 0). **(B)** Terminal body weight (g). **(C)** Liver weight. **(D)** Plasma alanine aminotransferase (ALT). **(E)** Plasma total cholesterol (TC). **(F)** Liver total cholesterol (TC). ***p<0.001 compared to corresponding DIO-NASH vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Stage

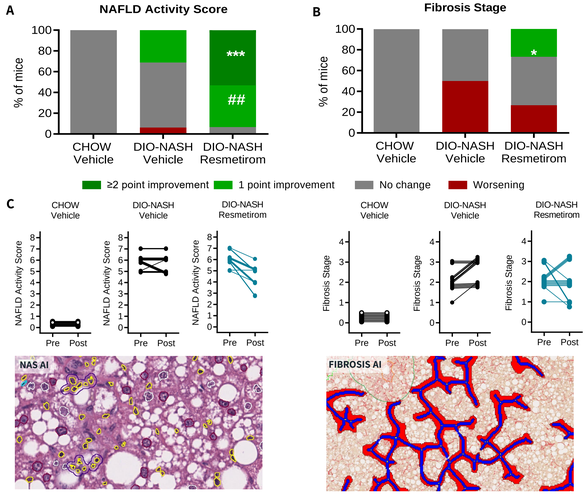


Figure 2. Resmetirom improves liver histopathological scores in GAN DIO-NASH mice.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis Stage. **(C)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation. ##p<0.01 with 1 point improvement, *p<0.05) ≥1 stage fibrosis improvement, ***p<0.001 with more than 2-point improvement compared to corresponding DIO-NASH vehicle group (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

4 Quantitative histological markers of steatosis, inflammation and fibrosis

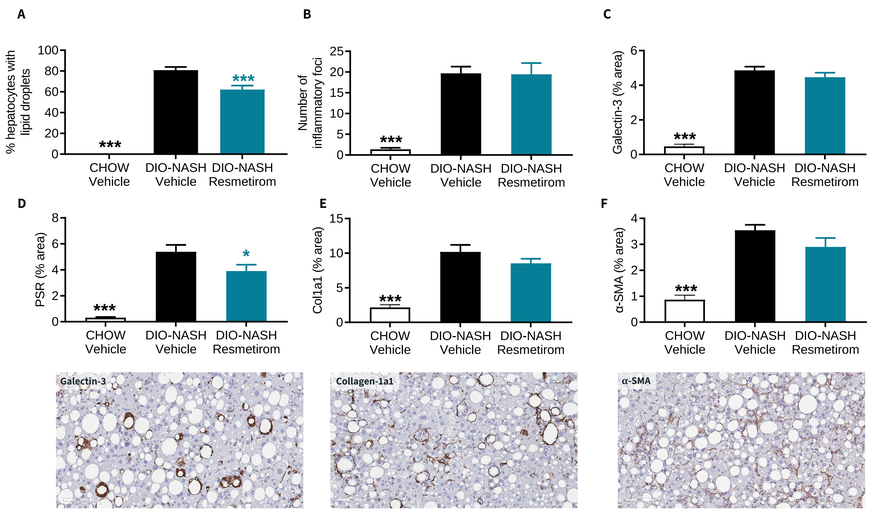


Figure 3. Resmetirom improves quantitative liver histological markers in GAN DIO-NASH mice.
Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area of galectin-3. **(D)** % area of PSR. **(E)** % area of collagen-1a1. **(F)** % area of alpha-smooth muscle actin (α-SMA) as marker for stellate cell activation. Mean ± SEM. *p<0.05, ***p<0.001 to corresponding DIO-NASH vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative photomicrographs (scale bar, 100 µm).

5 Clinical translatability

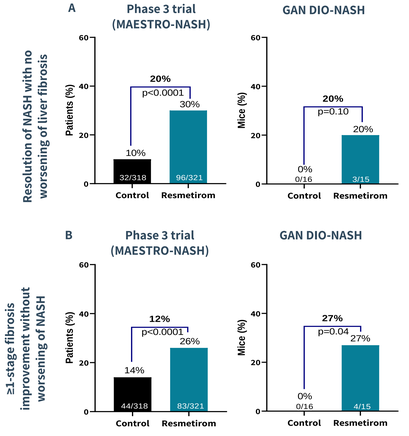


Figure 4. Resmetirom promotes NASH resolution and improves fibrosis stage in both GAN DIO-NASH mice and NASH patients. **(A)** Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis in GAN DIO-NASH mice compared to clinical phase-3 trial data (MAESTRO-NASH, press release Dec 19, 2022). **(B)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to the MAESTRO-NASH trial.

CONCLUSION

- Resmetirom reduces hepatomegaly, plasma ALT levels, and plasma/liver total cholesterol levels.
- Resmetirom promotes ≥2-point significant improvement in NAFLD Activity Score.
- Resmetirom promotes 1-point significant improvement in Fibrosis Stage.
- Resmetirom reduces quantitative histological markers of steatosis and fibrosis.
- Resmetirom demonstrates comparable efficacy on primary endpoints in NASH patients and GAN DIO-NASH mice.
- These findings highlight the clinical translatability of the GAN DIO-NASH mouse model.

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