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

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Background & Aim

Resmetirom (THR-β agonist) and semaglutide (GLP-1 receptor agonist) are currently in late-stage clinical development for non-alcoholic steatohepatitis (NASH). The present study aimed to *(i)* evaluate the metabolic, biochemical and histopathological effects of resmetirom and semaglutide monotherapy in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and *(ii)* compare preclinical study data to primary outcomes in corresponding clinical trials.

1 Study outline

Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing concentration
1	LEAN-CHOW	Male	10	**Vehicle**	SC	QD	-
2	DIO-NASH	Male	15	**Vehicle**	SC	QD	-
3	DIO-NASH	Male	16	**Semaglutide**	SC	QD	30nmol/kg
4	DIO-NASH	Male	15	**Resmetirom**	PO	QD	3mg/kg

2 Metabolic and biochemical parameters

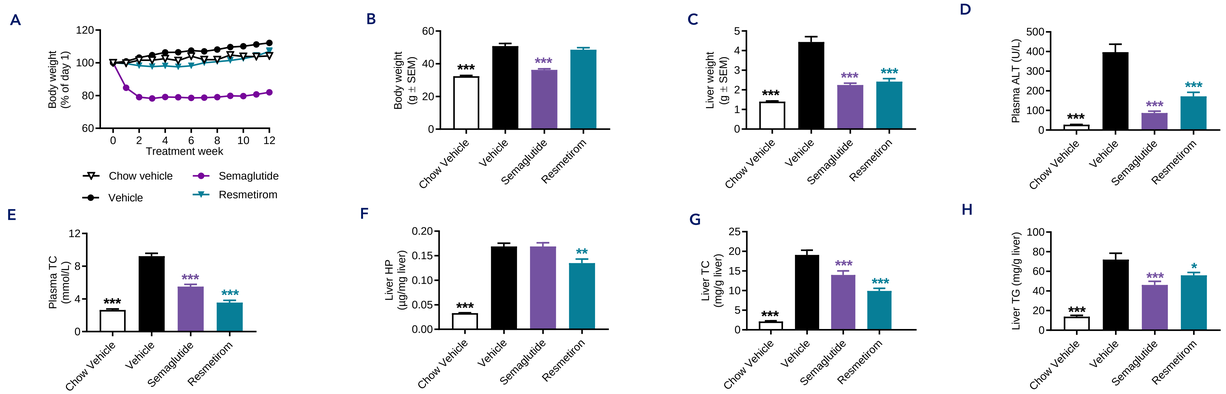

Figure 1. Semaglutide and resmetirom improve hepatomegaly and biochemical parameters but have differential effects on body weight. (A) Relative body weight during study period. (B) Terminal body weight. (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal plasma total cholesterol. (F) Liver hydroxyproline (HP). (G) Terminal liver total cholesterol. (H) Liver triglycerides (TG).*p<0.05, ***p<0.001 compared to corresponding vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Stage

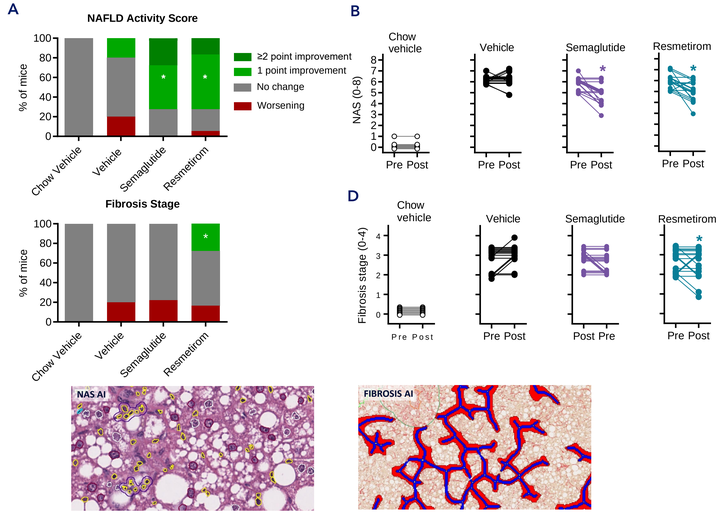

Figure 2. Semaglutide and resmetirom improve NAFLD Activity Score, and resmetirom improves Fibrosis Stage, in GAN DIO-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Individual pre-post NAS. (C) Fibrosis stage. (D) Individual pre-post fibrosis stage. *p<0.05 compared to corresponding vehicle control (One-sided Fisher's exact test).

4 Histological markers of steatosis, inflammation and fibrosis

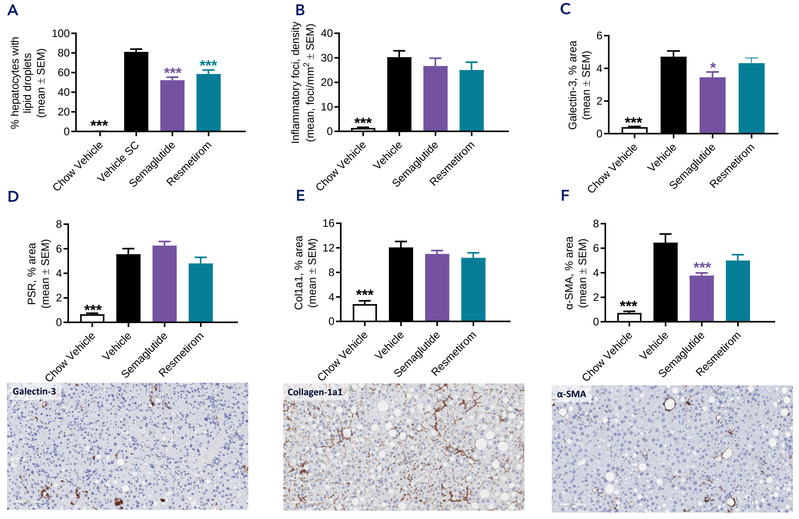

Figure 3. Semaglutide and resmetirom improves quantitative histological markers of NASH. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid 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, marker of stellate cell activation). Mean ± SEM. *p<0.05, ***p<0.001 to corresponding vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative photomicrographs of galectin-3, α-SMA and collagen 1a1 (scale bar, 100 µm).

5 Clinical translatability

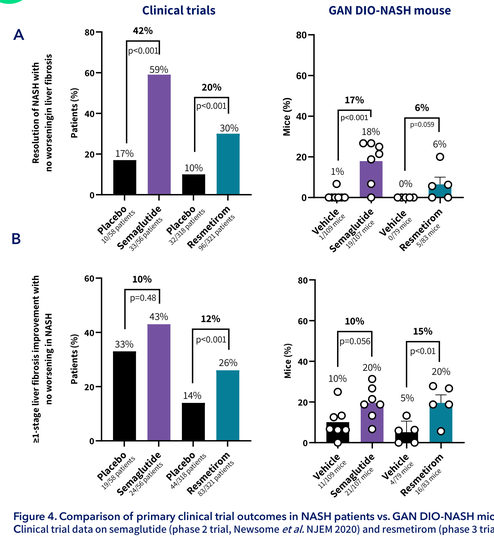

Figure 4. Comparison of primary clinical trial outcomes in NASH patients vs. GAN DIO-NASH mice. Clinical trial data on semaglutide (phase 2 trial, Newsome *et al.* NJEM 2020) and resmetirom (phase 3 trial, MAESTRO-NASH, press release Dec 19, 2022). (A) Resolution of NASH with no worsening of liver fibrosis .(B) ≥1-stage fibrosis improvement without worsening of NASH. Composite data from a series of individual GAN DIO-NASH mouse studies (n=16-18 mice per group in each study) with administration of semaglutide (7 studies; 30 nmol/kg, SC, QD), resmetirom (5 studies; 3 mg/kg, PO, QD), or corresponding vehicle. Mean values for each individual study is indicated.

Conclusion

- Resmetirom is weight-neutral, whereas semaglutide promotes a robust weight loss
- Semaglutide and resmetirom improve hepatomegaly, plasma transaminases and plasma/liver lipid, with resmetirom further reducing liver hydroxyproline levels
- Both semaglutide and resmetirom promote ≥1-point significant improvement in NAFLD Activity Score
- Resmetirom, but not semaglutide, improves fibrosis stage
- Semaglutide and resmetirom have beneficial effects on quantitative steatosis, with semaglutide further reducing histological markers of inflammation and fibrogenesis
- Overall, these data partially agrees with clinical findings, highlighting clinical translatability of the GAN DIO-NASH mouse model