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 (glucagon-like-peptide (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 phase II/III 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**	SC	QD	-
3	DIO-NASH	Male	16	**Semaglutide**	SC	QD	30nmol/kg
4	DIO-NASH	Male	16	**Vehicle PO**	PO	QD	-
5	DIO-NASH	Male	15	**Resmetirom**	PO	QD	3mg/kg

2 Metabolic and biochemical parameters

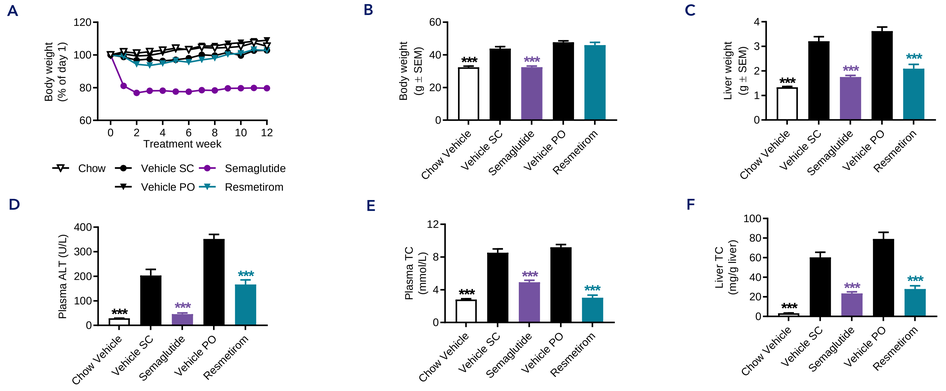

Figure 1. Semaglutide and resmetirom improve hepatomegaly and biochemical parameters but have differential effects on body weight. (A) Relative body weight during study period. (B) Terminal body weight. (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal plasma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

3 NAFLD Activity Score and Fibrosis Stage

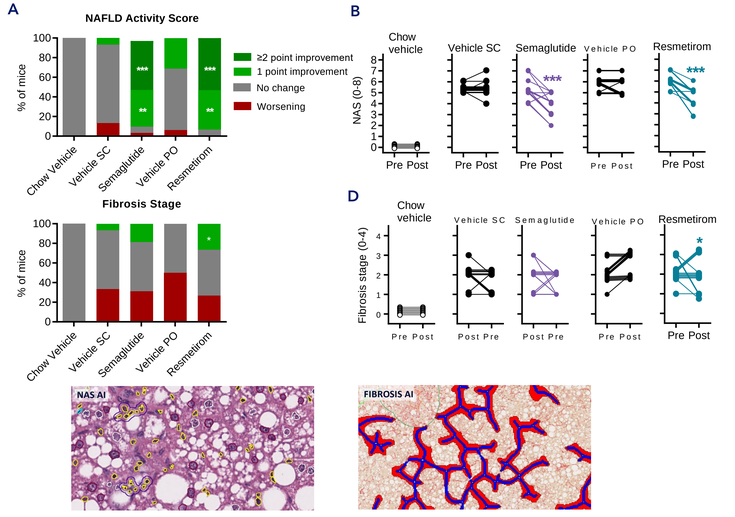

Figure 2. Semaglutide and resmetirom both improve NAFLD Activity Score, but only resmetirom improves Fibrosis Stage, in GAN DIO-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Individual pre-post NAS. (C) Fibrosis stage. (D) Individual pre-post fibrosis stage. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle control (One-sided Fisher's exact test with Bonferroni correction).

4 Histological markers of steatosis, inflammation and fibrosis

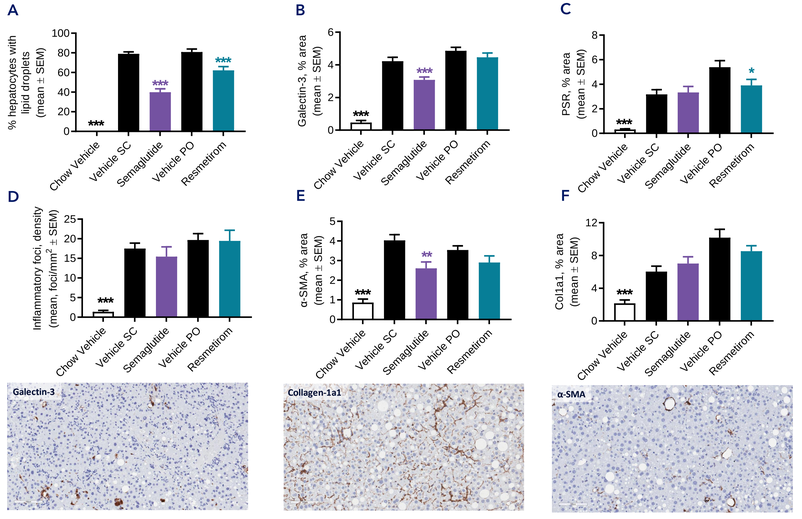

Figure 3. Semaglutide and resmetirom improves quantitative histological markers of steatosis, inflammation and fibrogenesis in GAN DIO-NASH mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area of galectin-3. (D) % area of alpha-smooth muscle actin (α-SMA, marker of stellate cell activation). (E) % area of PSR. (F) % area of collagen-1a1. Mean ± SEM. *p<0.05, **p<0.01, ***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

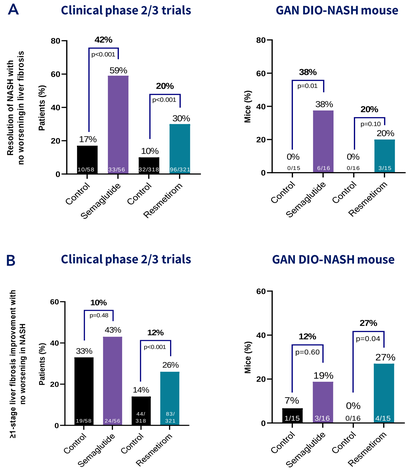

Figure 4. Comparative clinical endpoints of semaglutide and resmetirom treatment in GAN DIO-NASH mice and NASH patients. Study data in GAN-DIO-NASH mice compared to corresponding clinical trial data (semaglutide, phase 2 trial, Newsome et al. NJEM 2020); resmetirom, MAESTRO-NASH phase 3 trial, press release Dec 19, 2022). (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 for semaglutide. (B) ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical trial data.

Conclusion

- Resmetirom is weight-neutral, whereas semaglutide promotes ≈20% weight loss.
- Semaglutide and resmetirom improve hepatomegaly, plasma transaminases and plasma/liver lipid levels.
- Both semaglutide and resmetirom promote ≥2-point significant improvement in NAFLD Activity Score.
- Only resmetirom promotes 1-point significant improvement in fibrosis stage.
- Semaglutide and resmetirom have beneficial effects on quantitative steatosis histology.
- Only semaglutide reduces quantitative histology for galectin-3 (inflammation marker) and α-SMA (fibrogenesis marker).
- Only resmetirom significantly reduces quantitative histology for PSR (fibrosis marker).
- Overall, these data agrees with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model