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

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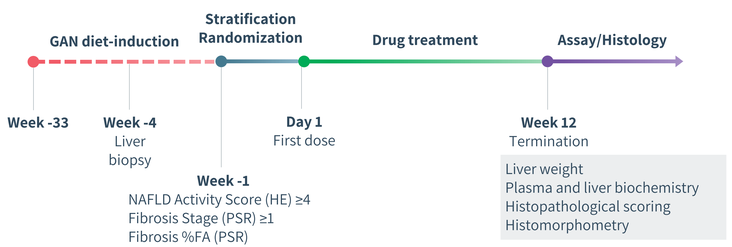
BACKGROUND & AIM

The glucagon-like-peptide (GLP)-1 analogue semaglutide is approved for the treatment of type 2 diabetes and obesity. Semaglutide has recently been reported to promote NASH resolution (Newsome et al., NEJM, 2020) and is currently in phase 3 clinical trial (ESSENCE) testing for treatment of NASH. The present study aimed to *(i)* evaluate the metabolic, biochemical and histopathological effects of semaglutide treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and *(ii)* compare to primary outcomes of recent clinical phase-2 trial data .

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dose
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

2 Metabolic and biochemical parameters

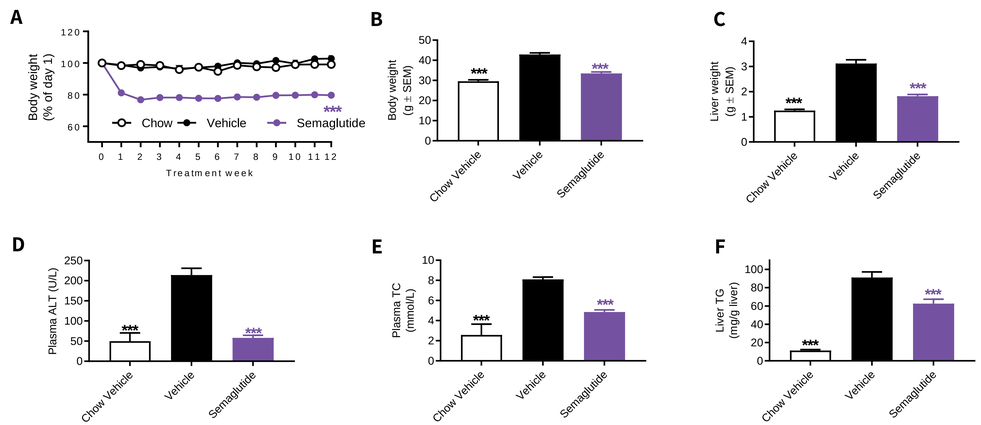


Figure 1. Semaglutide improves metabolic and biochemical parameters in GAN DIO-NASH mice. **(A)** Absolute body weight during study period. **(B)** Terminal body weight. **(C)** Terminal liver weight. **(D)** Terminal plasma alanine aminotransferase (ALT). **(E)** Terminal liver total cholesterol. **(F)** Terminal liver triglycerides. **p<0.01, ***p<0.001 compared to corresponding vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis stage

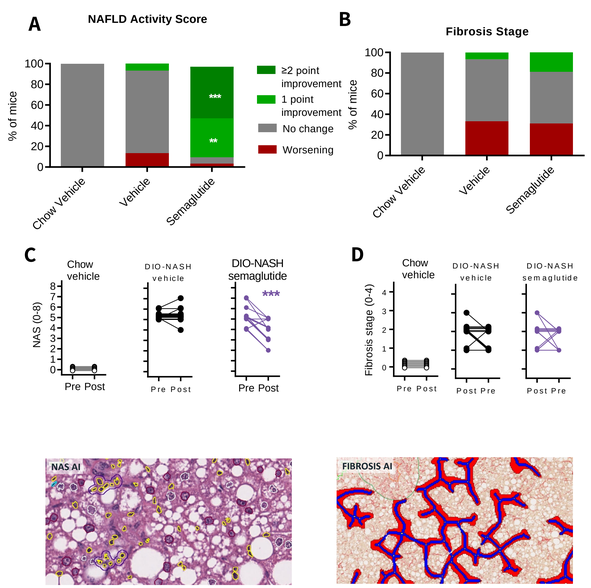


Figure 2. Semaglutide improves NAFLD Activity Score in GAN DIO-NASH mice.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C, D)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

4 Quantitative histological markers of steatosis, inflammation and fibrosis

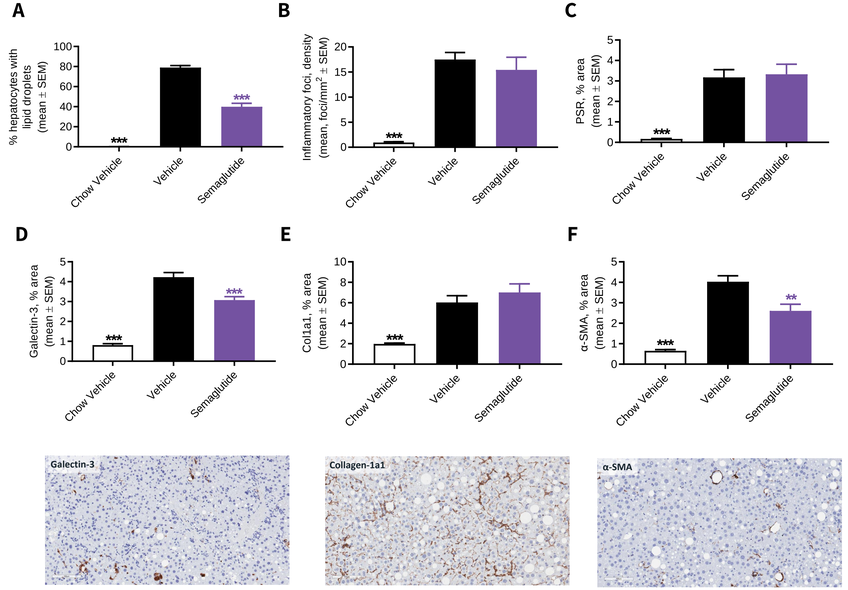


Figure 3. Semaglutide decreases histological markers for steatosis, inflammation and fibrogenesis in GAN DIO-NASH mice.
Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F).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

5 Clinical translatability

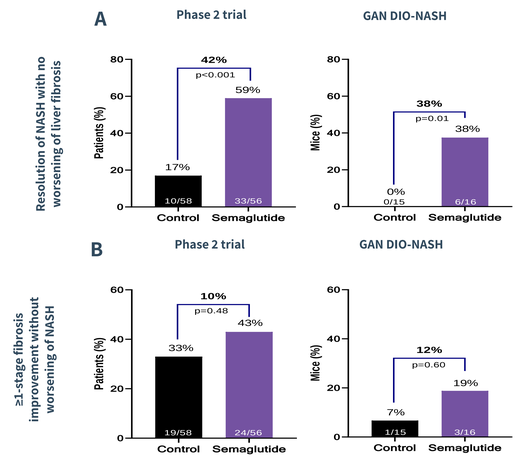


Figure 4. Semaglutide promotes NASH resolution without improvement in fibrosis stage in both GAN DIO-NASH mice and NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for semaglutide in GAN DIO-NASH mice compared to clinical phase-2 trial data (Newsome *et al.* NJEM 2020). **(B)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-2 trial data (Newsome. *et al.* NJEM 2020).

CONCLUSION

- Semaglutide reduces body weight, hepatomegaly, plasma ALT, plasma total cholesterol and liver triglycerides content.
- Semaglutide promotes ≥2-point significant improvement in NAFLD Activity Score.
- Semaglutide did not improve fibrosis stage.
- Semaglutide reduces quantitative histological markers of steatosis, inflammation and fibrogenesis.
- Semaglutide demonstrates comparable efficacy on primary endpoints in NASH patients and GAN DIO-NASH mice.
- These data agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model.

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