Differential hepatoprotective effects of semaglutide and lanifibranor in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH with advanced fibrosis and HCC

Authors
Malte Hasle Nielsen[1],, Susanne E. Pors[1], Jacob Nøhr-Meldgaard[1], Andreas Nygaard Madsen[1], Mathias Bonde Møllerhøj[1], Denise Oro[1], Mogens Vyberg[2], Henrik H. Hansen[1], Michael Feigh[1]

[1] Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark
[2] Center for RNA Medicine, Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark

Corresponding author
Michael Feigh- **mfe@gubra.dk**

Background & Aim

Non-alcoholic steatohepatitis (NASH) increases the risk for the development of liver fibrosis which may progress to cirrhosis and hepatocellular carcinoma (HCC). Semaglutide (glucagon-like-receptor (GLP)-1 agonist) and lanifibranor (pan-peroxisome proliferator-activated receptor agonist) are currently in late-stage clinical development for NASH. The present study aimed to evaluate the hepatoprotective effects of semaglutide and lanifibranor monotherapy in the Gubra Amylin NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse model of advanced fibrosing NASH and HCC.

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1 Study outline

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

2 Metabolic and biochemical parameters

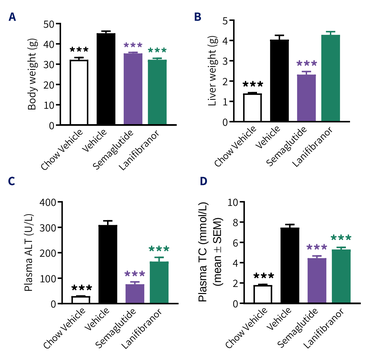

Figure 2. Semaglutide and lanibranor improves body weight and plasma transaminases in GAN DIO-NASH-HCC mice. **(A)** Terminal body weight (g). **(B)** Terminal liver weight (g). **(C)** Terminal plasma alanine transaminase (ALT, U/L). **(D)** Terminal plasma aspartate aminotransferase (AST, U/L). ***p<0.001 compared to DIO-NASH-HCC vehicle group (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Stage

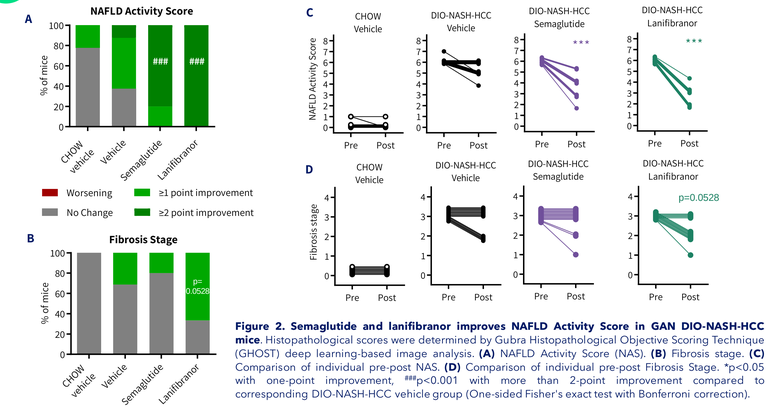

Figure 2. Semaglutide and lanifibranor improves NAFLD Activity Score in GAN DIO-NASH-HCC mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C)** Comparison of individual pre-post NAS. **(D)** Comparison of individual pre-post Fibrosis Stage. *p<0.05 with one-point improvement, ###p<0.001 with more than 2-point improvement compared to corresponding DIO-NASH-HCC vehicle group (One-sided Fisher's exact test with Bonferroni correction).

4 Histological markers of steatosis, inflammation and fibrosis

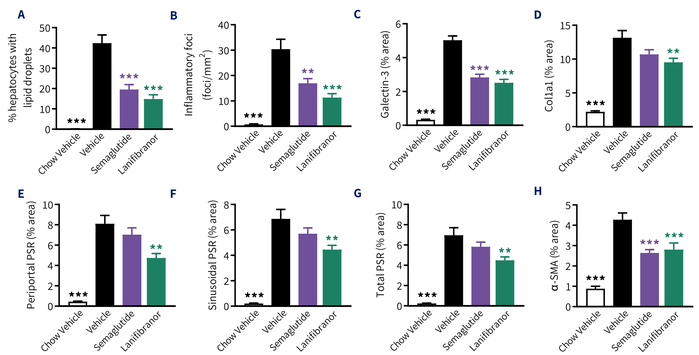

Figure 3. Semaglutide and lanifibranor improves quantitative histological markers of steatosis, inflammation and fibrogenesis in GAN DIO-NASH-HCC mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area of galectin-3. **D)** % area of collagen-1a1. **(E-G)** % area of PSR. **(H)** % area of alpha-smooth muscle actin (α-SMA). Mean ± SEM. *p<0.05, **p<0.01, ***p<0.001 to DIO-NASH-HCC vehicle group (Dunnett's test one-factor linear model).

5 Hepatocellular carcinoma occurrence and burden

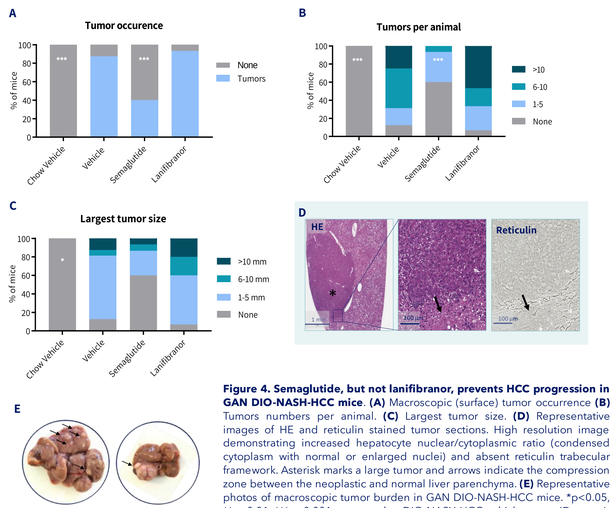

Figure 4. Semaglutide, but not lanifibranor, prevents HCC progression in GAN DIO-NASH-HCC mice. **(A)** Macroscopic (surface) tumor occurrence **(B)** Tumors numbers per animal. **(C)** Largest tumor size. **(D)** Representative images of HE and reticulin stained tumor sections. High resolution image demonstrating increased hepatocyte nuclear/cytoplasmic ratio (condensed cytoplasm with normal or enlarged nuclei) and absent reticulin trabecular framework. Asterisk marks a large tumor and arrows indicate the compression zone between the neoplastic and normal liver parenchyma. **(E)** Representative photos of macroscopic tumor burden in GAN DIO-NASH-HCC mice. *p<0.05, **p<0.01, ***p<0.001 compared to DIO-NASH-HCC vehicle group (Dunnett's test one-factor linear model).

5 Histological markers of proliferation and progenitor cell activation

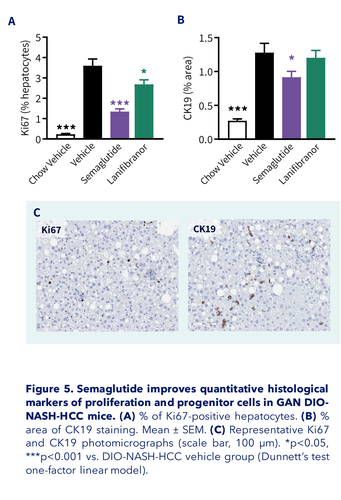

Figure 5. Semaglutide improves quantitative histological markers of proliferation and progenitor cells in GAN DIO-NASH-HCC mice. (A) % of Ki67-positive hepatocytes. **(B)** % area of CK19 staining. Mean ± SEM. **(C)** Representative Ki67 and CK19 photomicrographs (scale bar, 100 µm). *p<0.05, ***p<0.001 vs. DIO-NASH-HCC vehicle group (Dunnett's test one-factor linear model).

Conclusion

- Semaglutide and lanifibranor reduced body weight in GAN DIO-NASH-HCC mice.
- Semaglutide reduced hepatomegaly, while both compounds improved plasma ALT and TC.
- Semaglutide and lanifibranor promoted ≥2-point significant improvement in NAFLD Activity Score.
- Only lanifibranor promoted 1-point improvement in Fibrosis Stage and significantly reduced quantitative fibrosis levels.
- Both semaglutide and lanifibranor have beneficial effects on quantitative histological steatosis, inflammation and fibrogenesis markers.
- Semaglutide significantly reduces HCC burden
- The GAN DIO-NASH-HCC mouse is highly applicable for profiling novel drug therapies targeting NASH with advanced fibrosis and HCC.