Reproducible efficacy and clinical translatability of semaglutide treatment in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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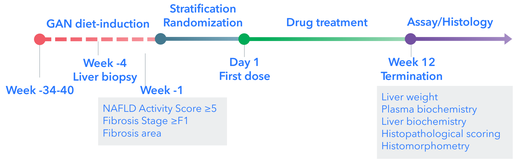
Background & Aim

The glucagon-like peptide-1 (GLP-1) analogue semaglutide has been reported to promote resolution of MASH and improve fibrosis stage in a recent clinical phase 3 trial (ESSENCE). The present study aimed to evaluate robustness of therapeutic outcomes of semaglutide treatment in the translational GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis.

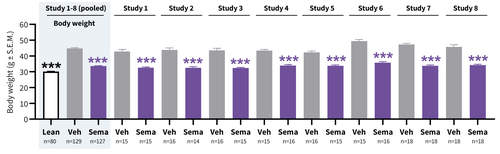
Methods

Semaglutide was profiled in 8 individual GAN DIO-MASH mouse studies with identical design. C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 34-40 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAS≥5) and fibrosis (stage ≥F1) were included and stratified into treatment groups. GAN DIO-MASH mice (n=14-18 per group) received semaglutide (Sema, 30 nmol/kg, SC) or vehicle (Veh, SC) once daily for 12 weeks. Vehicle-dosed chow-fed controls served as healthy controls (Lean). Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage by Gubra Histopathological Objective Scoring Technique (GHOST). Terminal quantitative endpoints included plasma/liver biochemistry and AI-based quantitative liver histology. Furthermore, histopathological pre-to-post assessment of NAS and fibrosis stage were evaluated against primary histological endpoints applied in a corresponding clinical trial, (i.e. resolution of MASH with no worsening of liver fibrosis; at least 1-stage fibrosis improvement without worsening of MASH). Statistical analyses were performed using Dunnett's test one-factor linear model (individual studies), Fisher's exact test (pooled study data on semiquantitative histopathological scoring variables) or one-way ANOVA with Dunnett's post-hoc test (pooled study data on quantitative endpoints), respectively. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle controls.

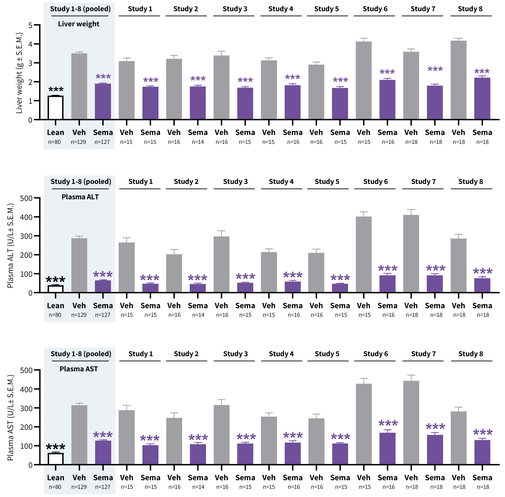
1 Study outline



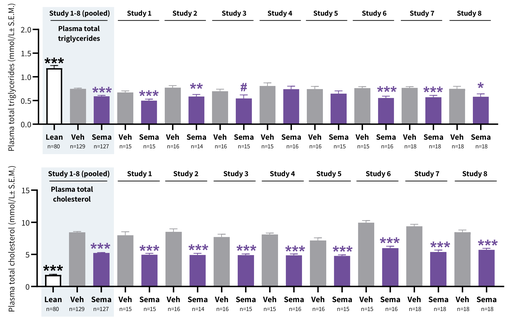
2 Body weight



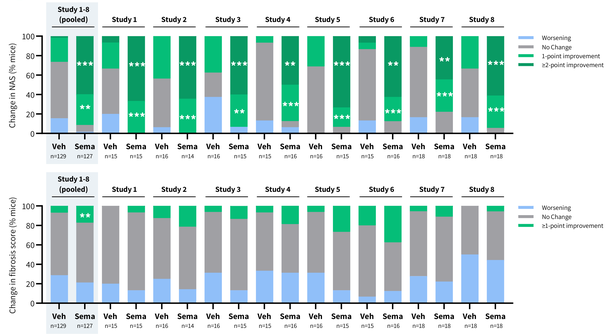
3 Liver weight & transaminases



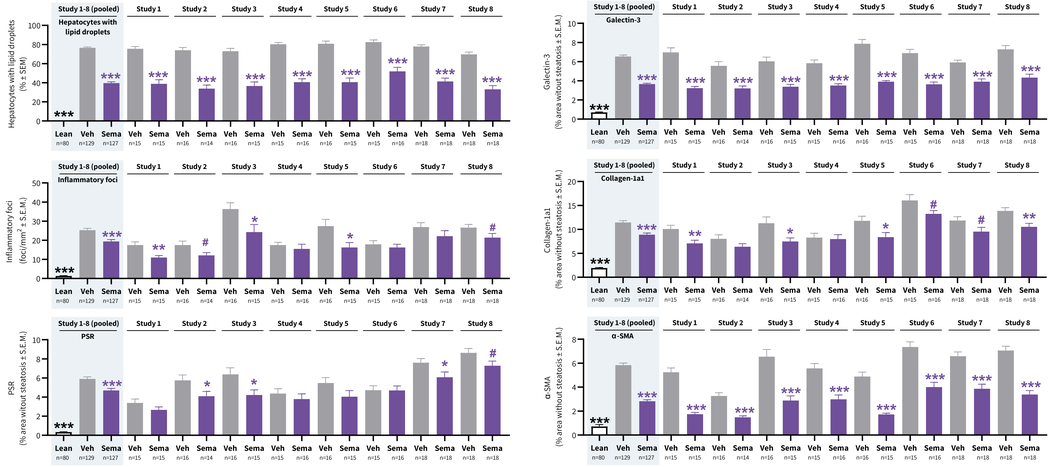
4 Plasma total cholesterol & triglycerides



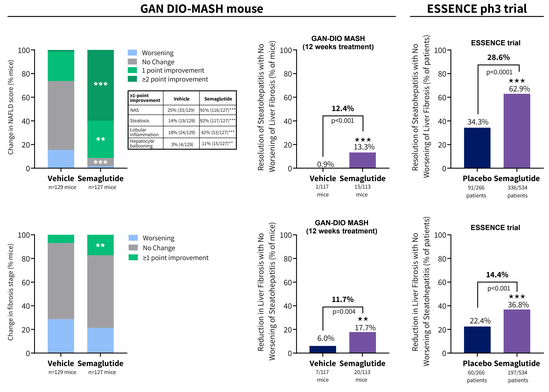
5 NAFLD Activity Score (NAS) & Fibrosis stage



6 Quantitative histological markers of steatosis, inflammation, fibrosis and fibrogenesis



7 Clinical translatability



Conclusion

12-week semaglutide therapy in GAN DIO-MASH mice improves:

- **Body weight, hepatomegaly, transaminases and hypercholesterolemia**
- **NAFLD Activity Score and steatosis/inflammation histomorphometrics**
- **Fibrosis stage and fibrosis histomorphometrics (pooled data)**
- **Improves fibrogenesis histomorphometrics**

Treatment outcomes in the GAN DIO-MASH mouse aligns with findings in the ESSENCE ph3 clinical trial

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