# Reproducible hepatoprotective effects and clinical translatability of semaglutide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH


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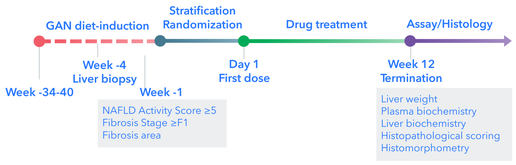
## Background & Aim

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.

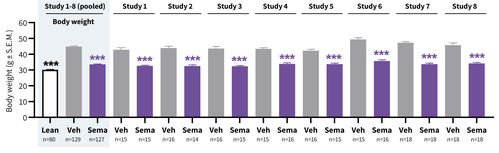
## Methods

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.

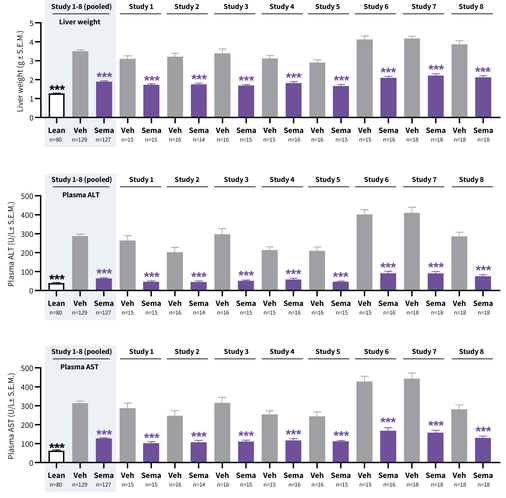
## 1 Study outline



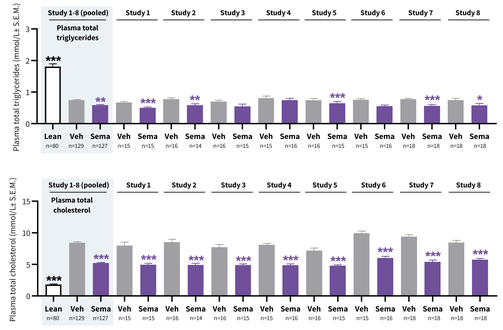

## 2 Body weight



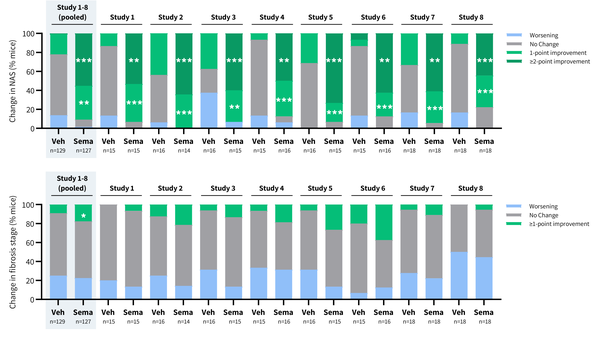

## 3 Liver weight & transaminases



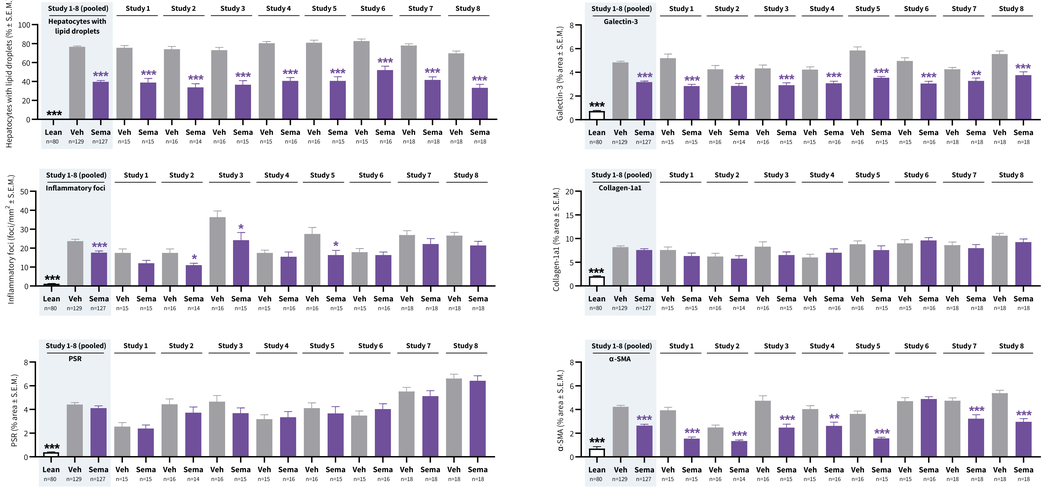

## 4 Plasma total cholesterol & triglycerides



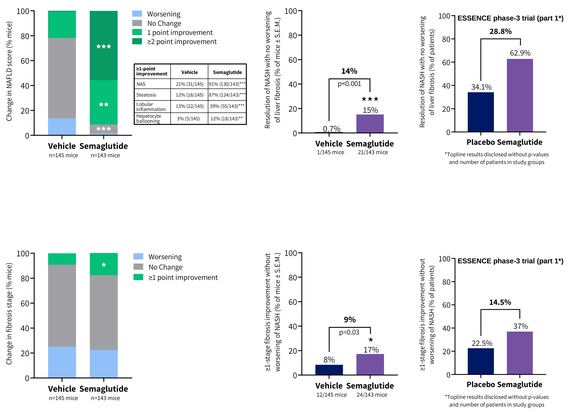

## 5 NAFLD Activity Score (NAS) & Fibrosis stage




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




## 7 Clinical translatability




## Conclusion

***Short-term semaglutide therapy in GAN DIO-MASH mice:***

- **Improves body weight, hepatomegaly, transaminases and hypercholesterolemia**
- **Improves NAFLD Activity Score and quantitative histological markers of steatosis and inflammation**
- **Improves Fibrosis Stage (pooled data), albeit not quantitative histological markers of fibrosis**
- **Improves quantitative histological marker of fibrogenesis**

**Histological outcomes of semaglutide treatment in GAN DIO-MASH mice are comparable to corresponding topline results reported from the clinical phase 3 trial (ESSENCE).**

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