Reproducible therapeutic effects of semaglutide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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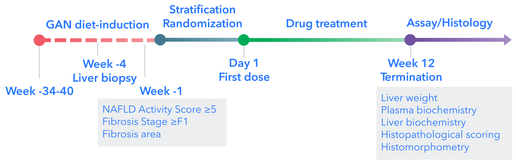
Background & Aim

The glucagon-like-peptide (GLP)-1 analogue semaglutide is currently approved for the treatment of type 2 diabetes and obesity. Semaglutide has been reported to promote benefits on histological outcomes in MASH patients (Newsome et al., NEJM, 2020) and is currently in phase 3 clinical trial (ESSENCE) for MASH. 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.

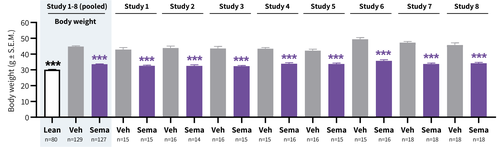
Methods

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. Terminal quantitative endpoints included plasma/liver biochemistry and AI-based quantitative liver histology. 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.

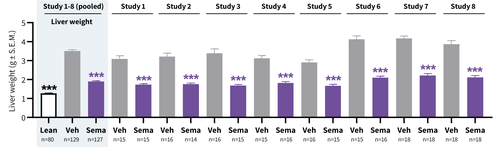
1 Study outline

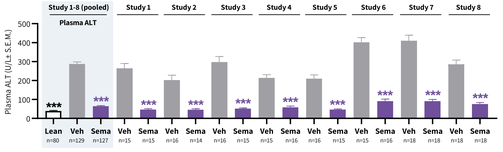


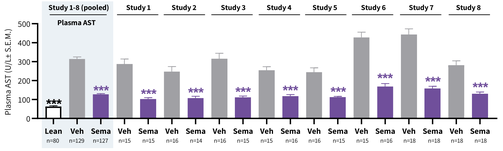
2 Body weight



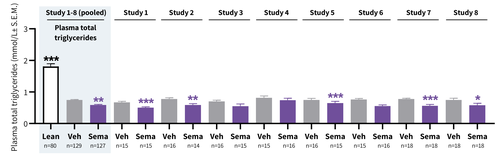
3 Liver weight & transaminases

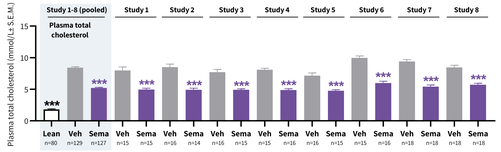




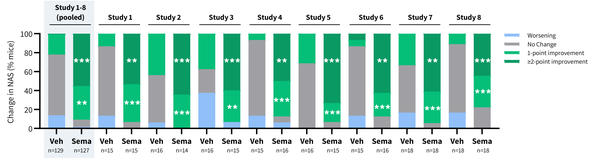


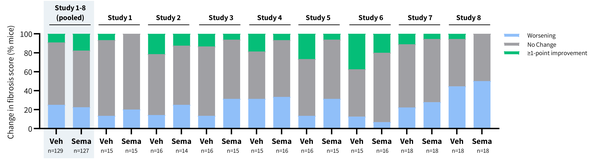
4 Plasma total cholesterol & triglycerides



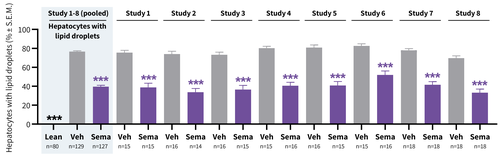


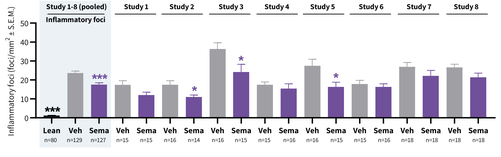
5 NAFLD Activity Score (NAS) & Fibrosis stage

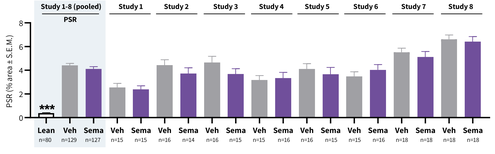


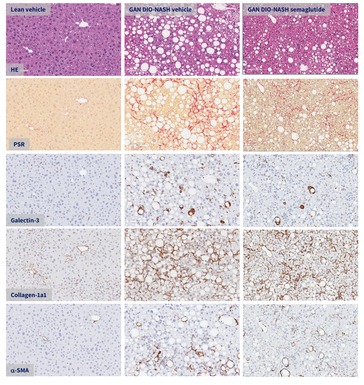


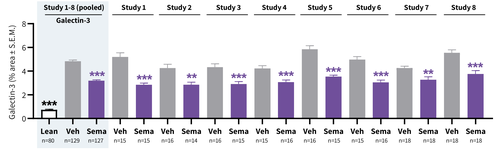
6 Quantitative histological markers of steatosis, inflammation & fibrosis

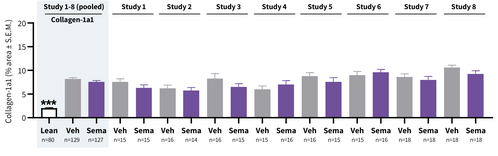


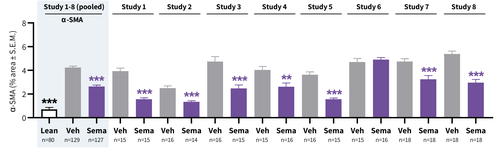












Conclusion

- Semaglutide was characterized in 8 individual studies in GAN DIO-MASH mice
- Semaglutide reduced body weight and consistently improves hepatomegaly, transaminases and hypercholesterolemia
- Semaglutide reproducibly improves MASH, primarily by reducing steatosis score
- Semaglutide does not improve fibrosis scores
- Benefits on histopathological scores were supported by quantitative histology

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