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

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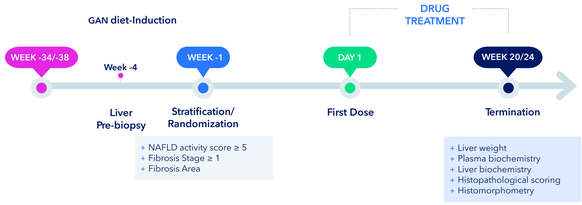
Background & Aim

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 outcomes of longer-term semaglutide treatment in the GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis with reference to clinical endpoints.

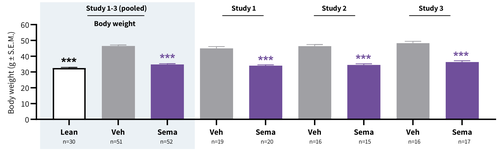
Methods

Semaglutide was profiled in three individual GAN DIO-MASH mouse studies. C57BL/6JRj mice were fed the GAN diet for 34-38 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAFLD Activity Score (NAS) ≥5) and fibrosis (stage ≥F1) were included and stratified into treatment groups. GAN DIO-MASH mice (n=14-20 per group) received (SC) semaglutide (Sema, 30 nmol/kg) or vehicle (Veh) once daily for 20 weeks (study 1) or 24 weeks (study 2 and 3). Vehicle-dosed chow-fed controls served as healthy controls (Lean). Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage using the Gubra Histopathological Objective Scoring Technique (GHOST) platform. Terminal quantitative endpoints included plasma/liver biochemistry and quantitative liver histology. Histopathological scoring outcomes in GAN DIO-MASH mice were evaluated against primary histological endpoints applied in clinical trials (resolution of MASH with no worsening of liver fibrosis; ≥1-stage fibrosis improvement without worsening of MASH). Statistical analyses were performed using Dunnett's test one-factor linear model (individual study data), Fisher's exact test (pooled study data, histopathological scores) or one-way ANOVA with Dunnett's post-hoc test (pooled study data, quantitative endpoints). #p<0.1, *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle controls.

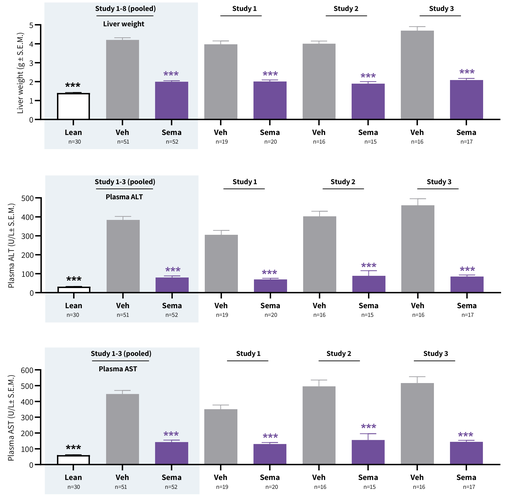
1 Study outline



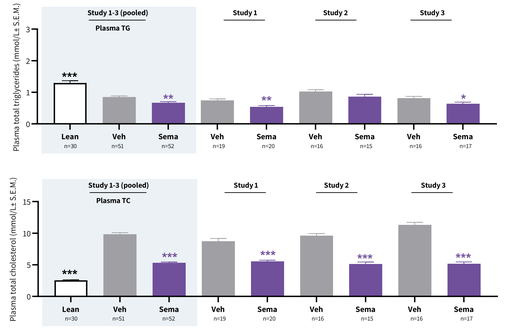
2 Body weight



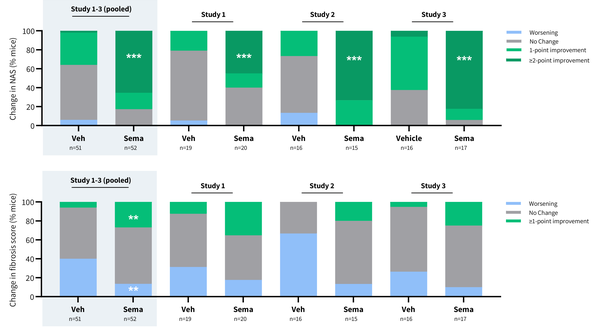
3 Liver weight & transaminases



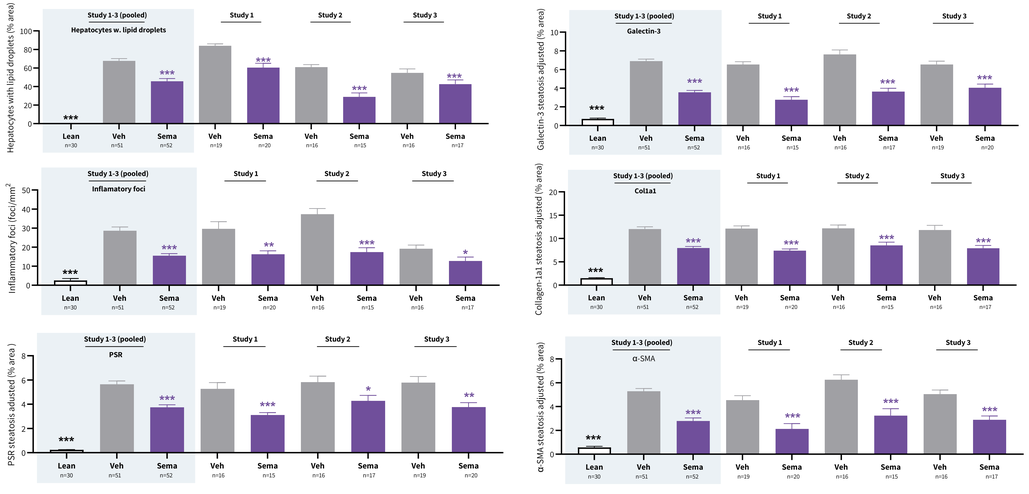
4 Plasma total cholesterol & triglycerides



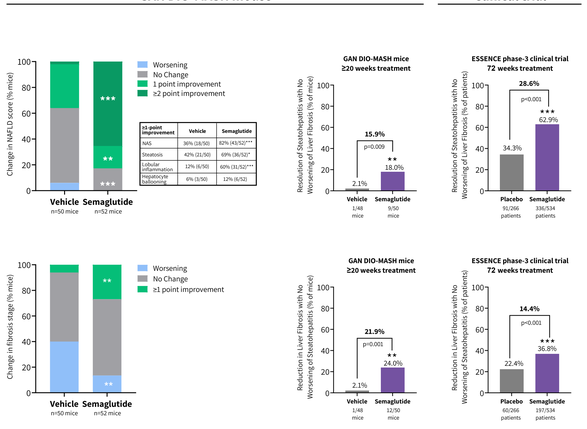
5 NAFLD Activity Score (NAS) & Fibrosis stage



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



7 Clinical translatability



Conclusion

Long-term semaglutide therapy in GAN DIO-MASH mice improves:

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

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

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