

# Prophylactic and therapeutic hepatoprotective effects of semaglutide in the CDAA-HFD mouse model of advanced NASH with progressive fibrosis

## Authors

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## Background & Aim

The long-acting glucagon-like peptide-1 (GLP-1) analogue semaglutide is approved for the treatment of type 2 diabetes and obesity. Semaglutide has recently been reported to improve liver histological outcomes in patients with non-alcoholic steatohepatitis (NASH) and fibrosis (Newsome et al., NEJM, 2020). Semaglutide is currently in phase-3 clinical trial (ESSENCE) for the treatment of NASH.

The present study aimed to evaluate prophylactic vs. therapeutic intervention with semaglutide in the non-obese choline-deficient L-amino-acid defined high-fat diet (CDAA-HFD) mouse model of advanced NASH with progressive fibrosis.

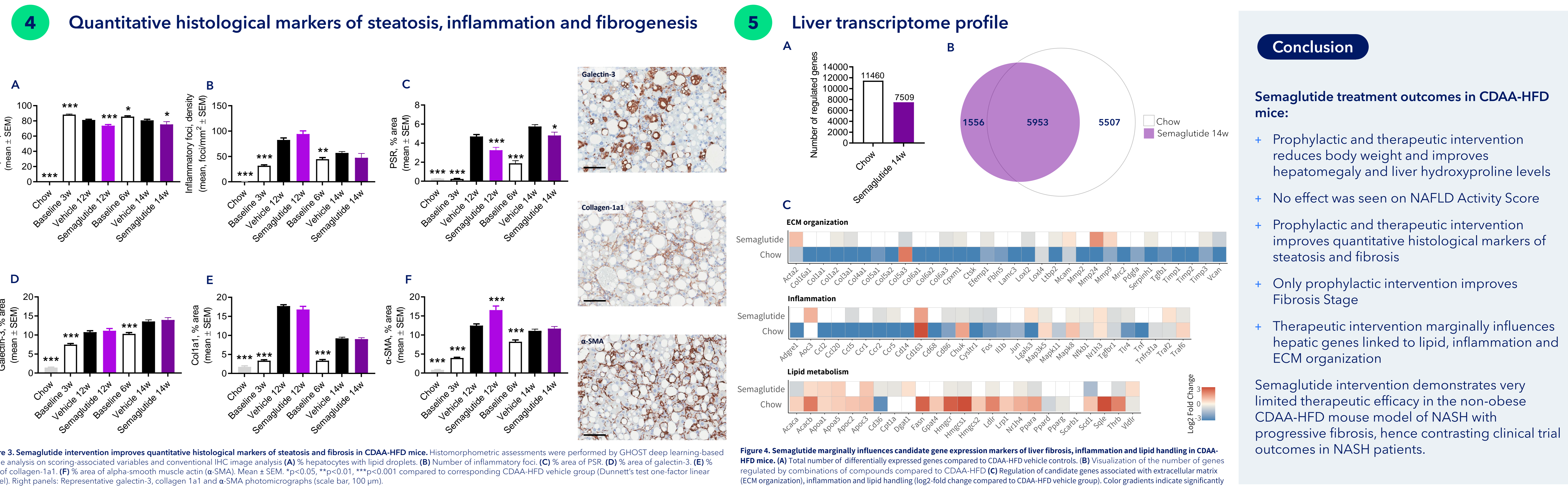
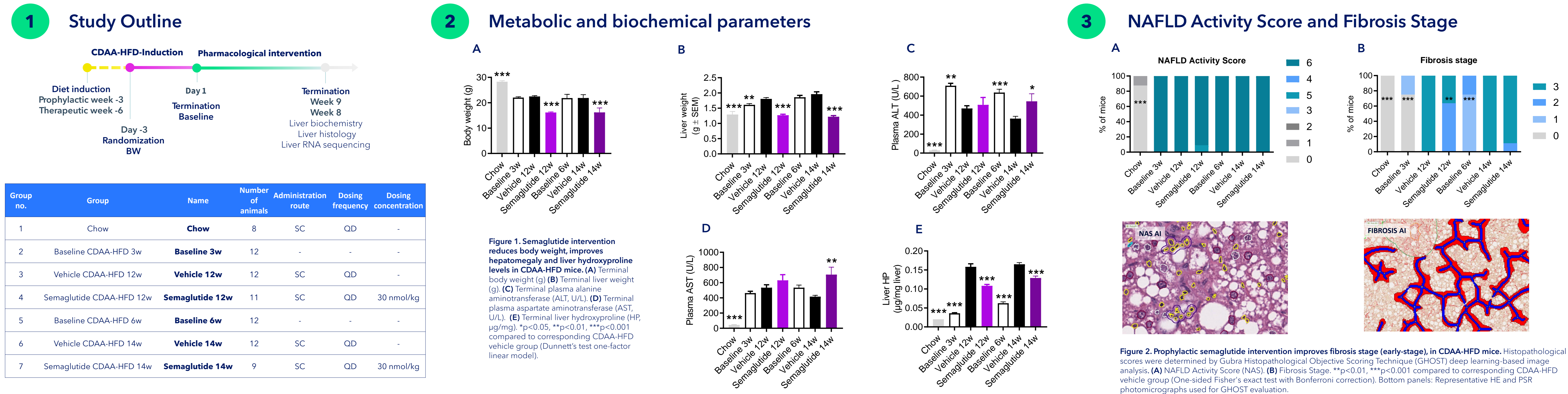
## Methods

C57BL/6JRj mice were fed chow or CDAA-HFD (45 kcal% fat, 0.1% methionine, 1% cholesterol, 28 kcal% fructose) for 3 or 6 weeks prior to treatment start (i.e. before or after onset of fibrosis, respectively). Animals were randomized into treatment groups based on body weight. A baseline group (n=12) was terminated at study start (3 and 6 weeks). CDAA-HFD fed mice (n=9 - 12 per group) received treatment (SC) with vehicle or semaglutide (30 nmol/kg) for 9 weeks (prophylactic, 12w on diet) or 8 weeks (therapeutic, 14w on diet). Chow-fed mice (n=8) served as normal controls. Terminal endpoints included plasma biomarkers [alanine/aspartate aminotransferase (ALT/AST)], liver biochemistry, NAFLD Activity Score (NAS), fibrosis stage, quantitative liver histology and liver RNA sequencing.

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## Conclusion

### Semaglutide treatment outcomes in CDAA-HFD mice:

- + Prophylactic and therapeutic intervention reduces body weight and improves hepatomegaly and liver hydroxyproline levels
- + No effect was seen on NAFLD Activity Score
- + Prophylactic and therapeutic intervention improves quantitative histological markers of steatosis and fibrosis
- + Only prophylactic intervention improves Fibrosis Stage
- + Therapeutic intervention marginally influences hepatic genes linked to lipid, inflammation and ECM organization

Semaglutide intervention demonstrates very limited therapeutic efficacy in the non-obese CDAA-HFD mouse model of NASH with progressive fibrosis, hence contrasting clinical trial outcomes in NASH patients.