Clinical translatability of the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

Authors
Henrik H. Hansen, Maja W. Andersen, Martin Rønn Madsen, Denise Oró, Michael Feigh

Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark

Corresponding author
Henrik H Hansen - hbh@gubra.dk

Background & Aim

Translational animal models are essential in preclinical drug discovery for metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH). The Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse is an industry-standard, biopsy-confirmed translational model of MASH with progressive fibrosis. The present study aimed to assess robustness of liver histological outcomes following treatment with clinically relevant drugs in the GAN DIO-MASH mouse with reference to FDA/EMA-accepted histological endpoints.

Methods

Male C57BL/6J mice were fed the GAN diet (40 kcal-% fat, 22% fructose, 10% sucrose, 2% cholesterol) for ≥34 weeks. GAN DIO-MASH mice (n=14-18 per group) with biopsy-confirmed MASH (NAFLD Activity Score, NAS≥5) and fibrosis (fibrosis stage ≥F1) were administered resmetirom, semaglutide, lanifibranor, elafibranor, obeticholic acid, firsocostat or vehicle for 12 weeks. Histopathological pre-to-post assessment of NAS and fibrosis stage was evaluated against primary histological endpoints applied in corresponding clinical trials, i.e. resolution of MASH (inflammation score≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis; at least 1-stage fibrosis improvement without worsening of MASH. Data was pooled from at least two individual studies per compound. Statistical analyses were performed using Dunnett's test one-factor linear model (change in NAS, fibrosis stage) or Fisher's exact test (clinical primary histological endpoints). *p<0.05, **p<0.01, ***p<0.001 compared to vehicle controls.

Conclusion

+ Histological outcomes in GAN DIO-MASH mice are comparable to corresponding clinical trials for resmetirom (MAESTRO-NASH), semaglutide (Newsome et al. NJEM 2020) and lanifibranor (NATIVE).
+ Obeticholic acid reverses MASH but not fibrosis in GAN DIO-MASH mice, being line with the FLINT phase-2 trial, whereas the opposite effect has been reported in the pivotal REGENERATE trial.
+ Elafibranor resolves MASH in GAN DIO-MASH mice, being consistent with the GOLDEN-505 phase-2 trial but contrasting no histological benefits in the RESOLVE-IT phase-3 trial.
+ Firsocostat improves MASH in GAN DIO-MASH mice, although histological endpoints were not met in the ATLAS phase-2 trial.
+ The GAN DIO-MASH mouse model faithfully reproduces histological outcomes of key compounds in current late-stage clinical development, highlighting translatability and utility of GAN DIO-NASH mice in preclinical drug discovery for MASH.

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1 Resmetirom

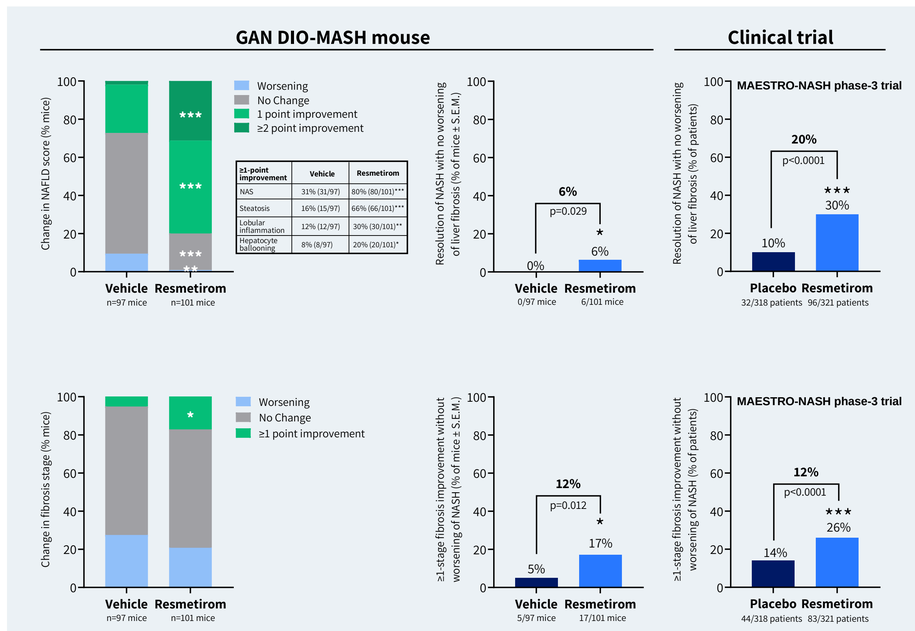


Figure 1. Resmetirom (MGL-3196, THR-β agonist) improves MASH and fibrosis stage in GAN DIO-MASH mice and MASH patients.
Left panels: Change in NAFLD Activity Score (NAS) and fibrosis stage in GAN DIO-MASH mice following 12 weeks of treatment with resmetirom (3 mg/kg, PO, QD). Pooled data from 6 individual studies in GAN DIO-MASH mice (n=15-18 mice per group in each study). **Right panels:** Primary clinical histological outcomes in GAN DIO-MASH mice with reference to corresponding clinical phase-3 trial (MAESTRO-NASH trial, Harrison *et al*., *NJEM*, 2024).

2 Semaglutide

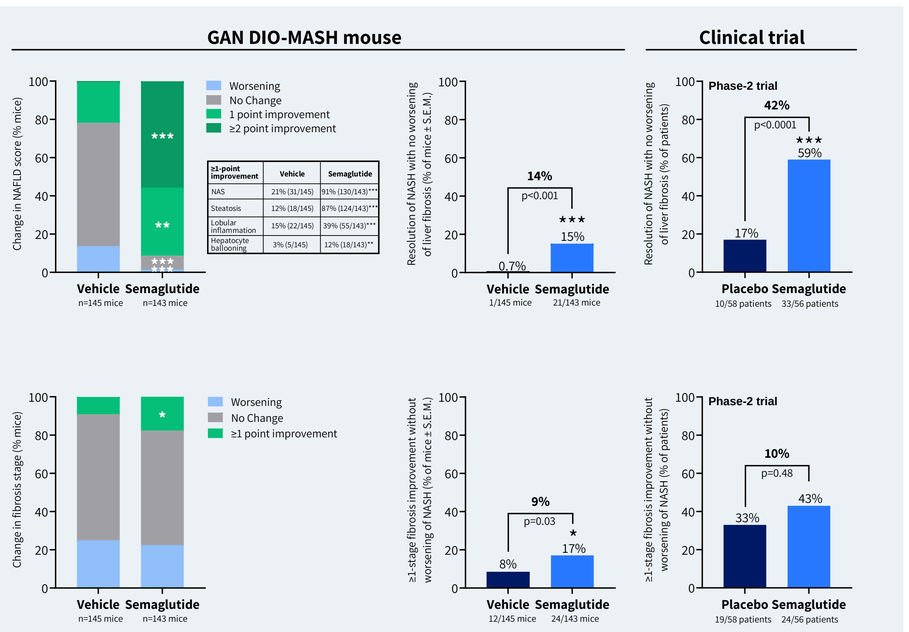


Figure 2. Semaglutide (GLP-1 receptor agonist) improves MASH in GAN DIO-MASH mice and MASH patients.
Left panels: Change in NAFLD Activity Score (NAS) and fibrosis stage in GAN DIO-MASH mice following 12 weeks of treatment with semaglutide (30 nmol/kg, SC, QD). Pooled data from 9 individual studies in GAN DIO-MASH mice (n=14-18 mice per group in each study). **Right panels:** Primary clinical histological outcomes in GAN DIO-MASH mice with reference to corresponding clinical phase-2 trial (Newsome *et al., NEJM,* 2020).

3 Lanifibranor

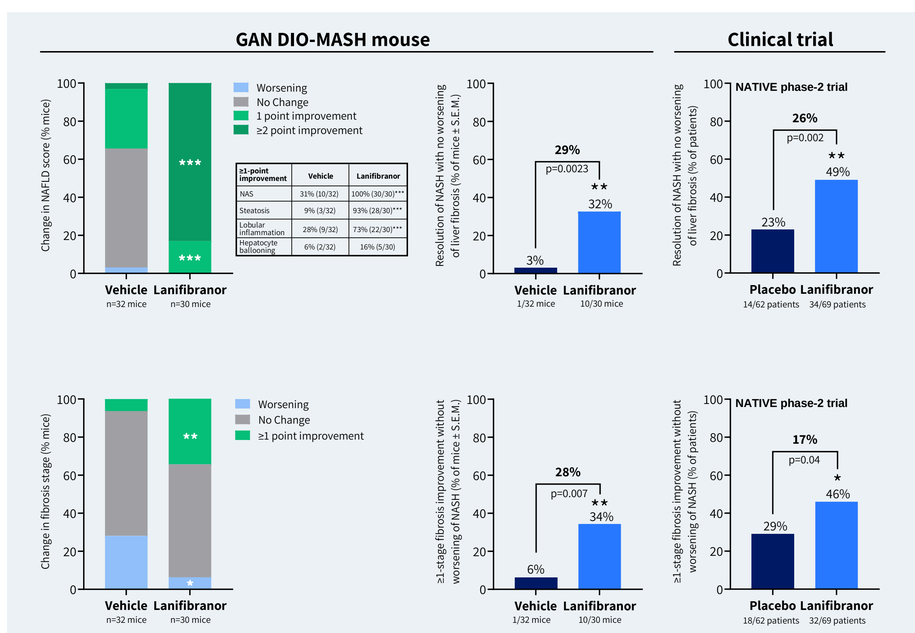


Figure 3. Lanifibranor (pan-PPAR agonist) improves MASH and fibrosis in GAN DIO-MASH mice and MASH patients.
Left panels: Change in NAFLD Activity Score (NAS) and fibrosis stage in GAN DIO-MASH mice following 12 weeks of treatment with lanifibranor (30 mg/kg, PO, QD). Pooled data from 2 individual studies in GAN DIO-MASH mice (n=14-16 mice per group in each study). **Right panels:** Primary clinical histological outcomes in GAN DIO-MASH mice with reference to corresponding clinical phase-2 trial (NATIVE trial, Franque *et al., NEJM,* 2021).

4 Elafibranor

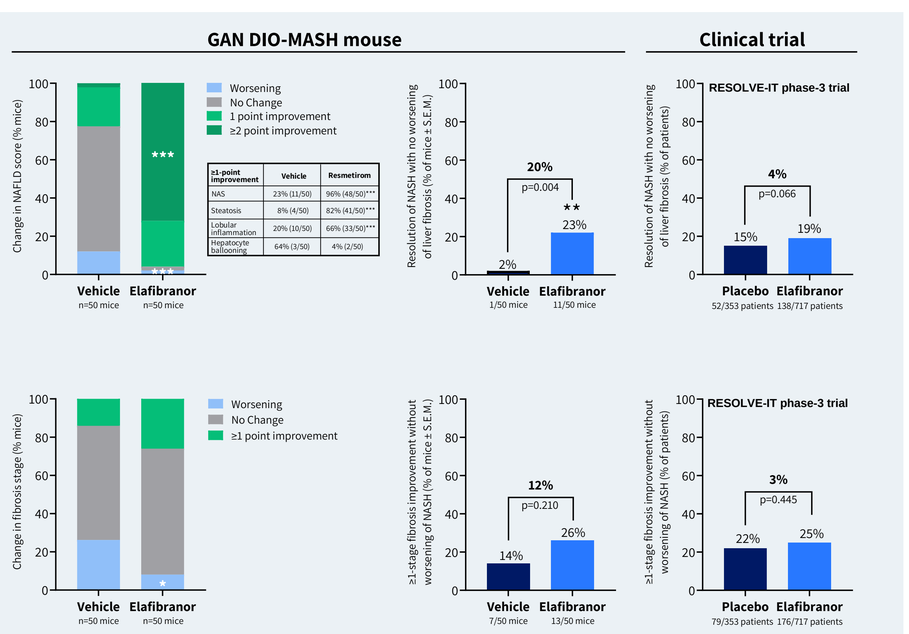
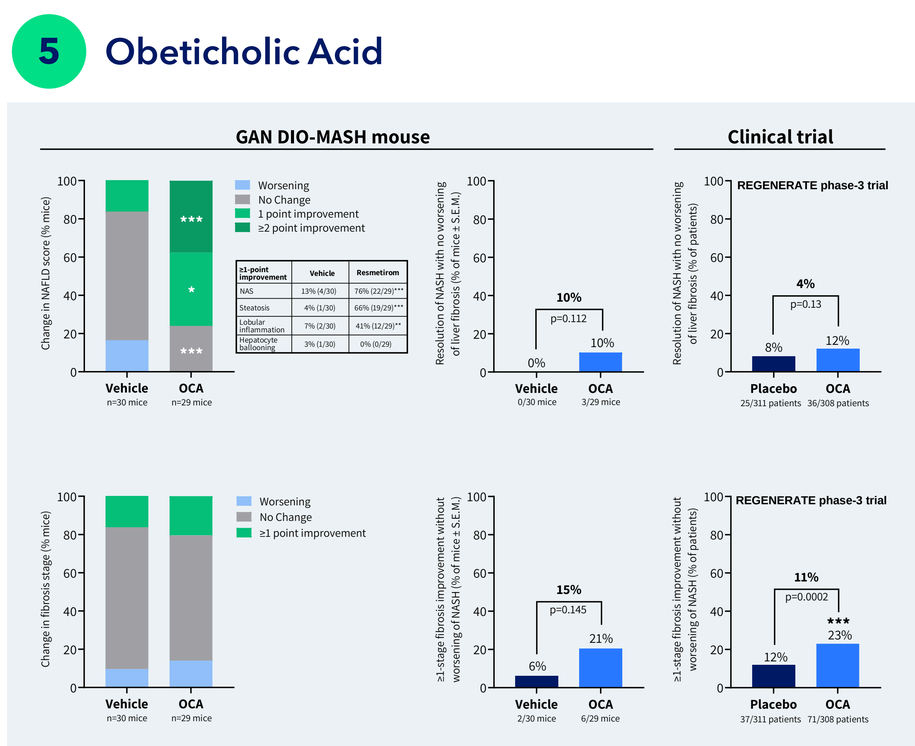


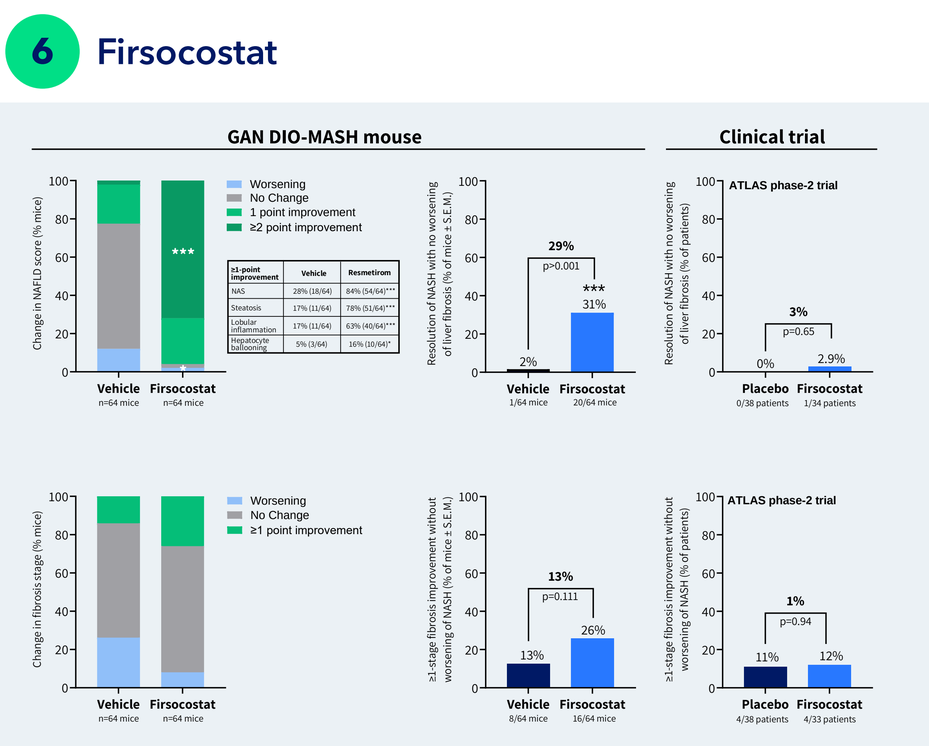
Figure 4. Differential effects of elafibranor (PPARα/δ-agonist) in GAN DIO-MASH mice vs. MASH patients.
Left panels: Change in NAFLD Activity Score (NAS) and fibrosis stage in GAN DIO-MASH mice following 12 weeks of treatment with elafibranor (30 mg/kg, PO, QD). Pooled data from 3 individual studies in GAN DIO-MASH mice (n=13-17 mice per group in each study). **Right panels:** Primary clinical histological outcomes in GAN DIO-MASH mice with reference to corresponding clinical phase-3 trial (RESOLVE-IT trial, press release May 5, 2020).

5 Obeticholic Acid



Left panels: Change in NAFLD Activity Score (NAS) and fibrosis stage in GAN DIO-MASH mice following 12 weeks of treatment with elafibranor (30 mg/kg, PO, QD). Pooled data from 2 individual studies in GAN DIO-MASH mice (n=14-16 mice per group in each study). **Right panels:** Primary clinical histological outcomes in GAN DIO-MASH mice with reference to corresponding clinical phase-3 trial (REGENERATE trial, Younossi *et al., Lancet,* 2019).

6 Firsocostat



Left panels: Change in NAFLD Activity Score (NAS) and fibrosis stage in GAN DIO-MASH mice following 12 weeks of treatment with elafibranor (5 mg/kg, PO, QD). Pooled data from 4 individual studies in GAN DIO-MASH mice (n=14-18 mice per group in each study). **Right panels:** Primary clinical histological outcomes in GAN DIO-MASH mice with reference to corresponding clinical phase-2 trial (ATLAS trial, Loomba *et al., Hepatology*, 2021).

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