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

Authors
Henrik H. Hansen, Marco Tozzi, Martin Rønn Madsen, Michael Feigh

Gubra, Hørsholm, Denmark

Corresponding author
Michael Feigh- mfe@gubra.dk

BACKGROUND & AIM

Preclinical validation of novel drug candidates for the treatment of non-alcoholic steatohepatitis (NASH) requires an applicable animal model that should recapitulate hallmarks of the human disease and demonstrate back translation of clinically observed endpoints.

The present study aimed to further investigate the translatability of the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse by comparing model vs. human data on *(i)* liver transcriptome profiles; *(ii)* primary endpoint outcomes of drug candidates in late-stage clinical development for NASH.

For GAN DIO-NASH studies, treatment for 12 weeks was performed for semaglutide (30 nmol/kg, SC, QD), lanifibranor (30 mg/kg, PO, QD), resmetirom (3 mg/kg, PO, QD) and OCA (30 mg/kg, PO, QD).

1 Transcriptomic profile of NASH and ECM organization during fibrotic progression

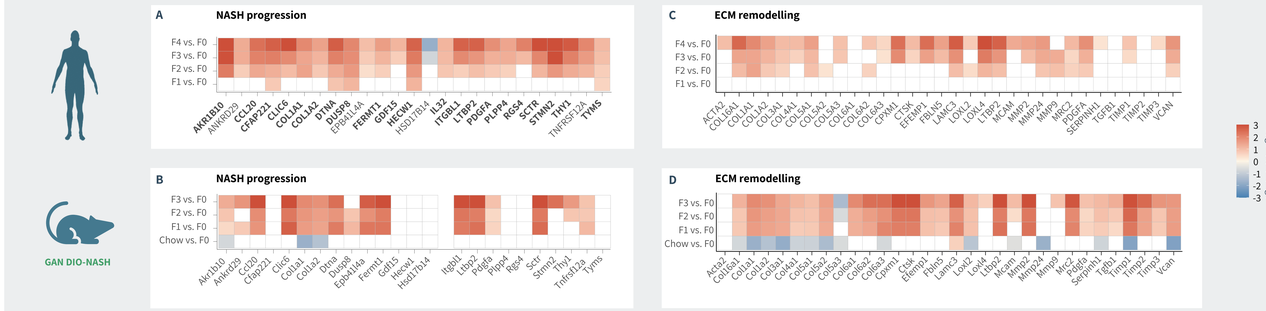

Figure 1. Significant overlap in core genes associated with disease progression in NASH patients and GAN DIO-NASH mice. (**A**,**B**) Differential expression of 25 core genes associated with progression of fibrosis in NASH patients (panel A) compared to GAN DIO-NASH mice (panel B). (**C**,**D**) Differential expression of extracellular matrix (ECM) candidate genes in NASH patients (panel C) compared to GAN DIO-NASH mice (panel D). Data are expressed as log2-fold change. Blue and red colour gradients indicate significantly (p<0.05) down-regulated and up-regulated gene expression, respectively. White boxes indicate genes not significantly regulated (p>0.05). Empty columns in panel B indicate no IL32 homologue in mice. Human data were from Govaere *et al.* Sci Transl Med 12, eaba4448, 2020; GAN DIO-NASH data were from Møllerhøj *et al.* Clin Transl Sci 15(5):1167-1186, 2022.

CONCLUSION

- The regulation of NASH core and ECM remodelling genes predictive of fibrosis progression is highly similar in GAN DIO-NASH mouse model and NASH patients.
- The effects of semaglutide, lanifibranor and resmetirom on clinical primary histological endpoints are reproducible in GAN DIO-NASH mouse model and demonstrated back translation with corresponding clinical phase-2 and phase-3 trial data in NASH patients.
- Obeticholic acid (OCA) shows differential effects on clinical primary histological endpoints in GAN DIO-NASH mouse model and demonstrate modest back translation with corresponding clinical phase-3 trial data in NASH patients.
- Overall, the GAN DIO-NASH mouse model shows very good clinical translatability with respect to *(i)* core NASH and ECM gene signatures of disease progression and *(ii)* histological clinical endpoints observed for compounds in advanced clinical development for NASH.

www.gubra.dk

2 Semaglutide

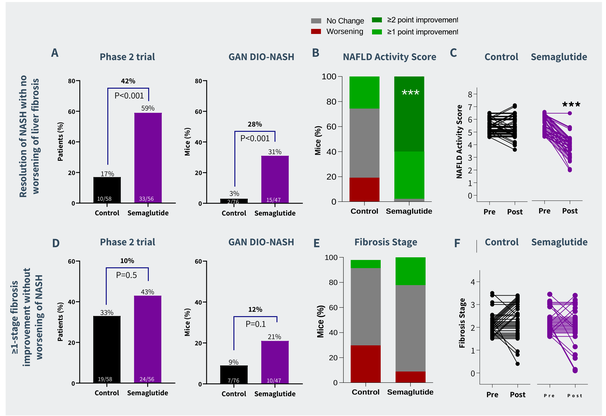

Figure 2. Semaglutide (GLP-1 analogue) promotes NASH resolution without improvement in fibrosis stage in both GAN DIO-NASH mice and NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for semaglutide in GAN DIO-NASH mice (30 nmol/kg, SC, QD, 12 weeks) compared to clinical phase-2 trial data (Newsome *et al.*(NJEM 2020). **(B)** Change in NAFLD Activity Score (NAS) in GAN DIO-NASH mice. **(C)** Comparison of individual pre-post NAS in GAN DIO-NASH mice **(D)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-2 trial data (Newsome. *et.al* (NJEM 2020). **(E)** Change in fibrosis scores in GAN DIO-NASH mice. **(F)** Comparison of individual pre-post fibrosis stage in GAN DIO-NASH mice. ***p<0.001 compared vehicle-dosed controls (Fisher's exact test, Dunnett's test one-factor linear model).

3 Lanifibranor

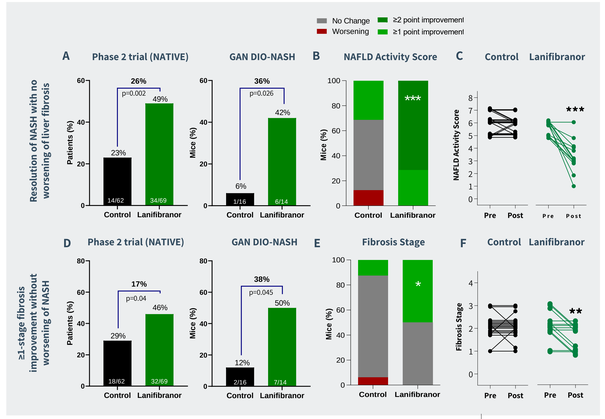

Figure 3. Lanifibranor (pan-PPAR agonist) promotes NASH resolution and improves fibrosis stage in both GAN DIO-NASH mice and NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for lanifibranor in GAN DIO-NASH mice (30 mg/kg, PO, QD, 12 weeks) compared to clinical phase-2 trial data (NATIVE trial; Francque *et al.* NJEM 2021). **(B)** Change in NAFLD Activity Score (NAS) in GAN DIO-NASH mice. **(C)** Comparison of individual pre-post NAS in GAN DIO-NASH mice **(D)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-2 trial data (NATIVE trial; Francque *et al.* NJEM 2021). **(E)** Change in fibrosis stage in GAN DIO-NASH mice . **(F)** Comparison of individual pre-post fibrosis scores in GAN DIO-NASH mice. *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed controls (Fisher's exact test, Dunnett's test one-factor linear model).

4 Resmetirom (MGL-3196)

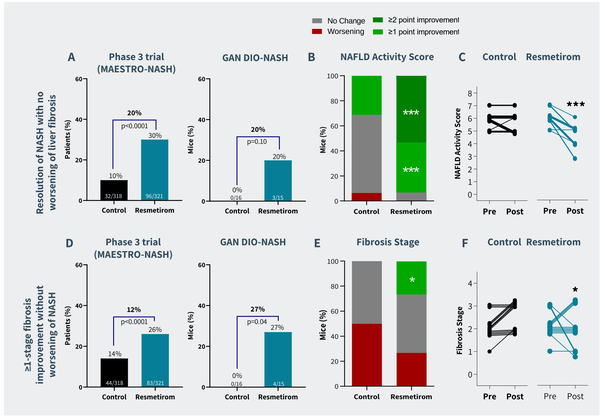

Figure 4. Resmetirom (MGL-3196, THR-β agonist) promotes NASH resolution and improves fibrosis stage in both GAN DIO-NASH mice and NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for resmetirom in GAN DIO-NASH mice (3 mg/kg , PO, QD, 12 weeks) compared to clinical phase-3 trial data (MAESTRO-NASH, press release Dec 19, 2022). **(B)** Change in NAFLD Activity Score (NAS) in GAN DIO-NASH mice. **(C)** Comparison of individual pre-post NAS in GAN DIO-NASH mice **(D)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-3 trial data (MAESTRO-NASH, press release Dec 19, 2022). **(E)** Change in fibrosis stage in GAN DIO-NASH mice. **(F)** Comparison of individual pre-post fibrosis scores in GAN DIO-NASH mice. *p<0.05, ***p<0.001 compared to vehicle-dosed controls (Fisher's exact test, Dunnett's test one-factor linear model).

5 Obeticholic acid (OCA)

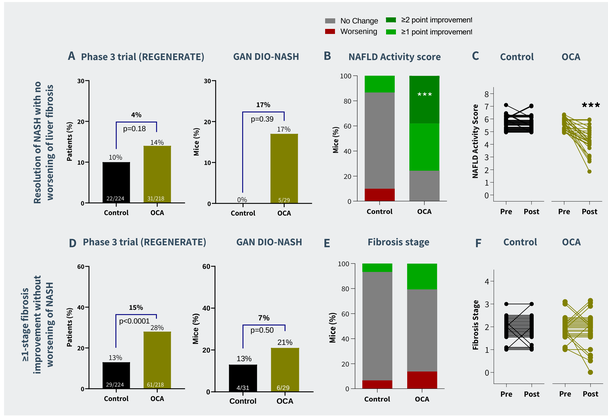

Figure 5. Differential effects of obeticholic acid (OCA, FXR agonist) on NASH resolution and improvement in fibrosis stage in GAN DIO-NASH mice and NASH patients. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for obeticholic acid in GAN DIO-NASH mice (30 mg/kg, PO, 12 weeks) compared to clinical phase-3 trial data (REGENERATE trial; Younossi *et al.*, Lancet, 2019). **(B)** Change in NAFLD Activity Score (NAS) in GAN DIO-NASH mice. **(C)** Comparison of individual pre-post NAS in GAN DIO-NASH mice **(D)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-3 trial data (REGENERATE trial; Younossi *et al.*, Lancet, 2019). **(E)** Change in fibrosis stage in GAN DIO-NASH mice. **(F)** Comparison of individual pre-post fibrosis scores in GAN DIO-NASH mice. ***p<0.01 compared to vehicle-dosed controls (Fisher's exact test, Dunnett's test one-factor linear model).