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

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Background & Aim

Translational animal models are essential in preclinical drug discovery for metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatisis (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 liver histological outcomes and reproducibility of six clinically relevant drugs in the GAN DIO-MASH mouse with reference to primary histological endpoints applied in corresponding clinical trials.

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 performed and evaluated against FDA/EMA-accepted histological endpoints, i.e. resolution of NASH (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 NASH.

1 Resmetirom

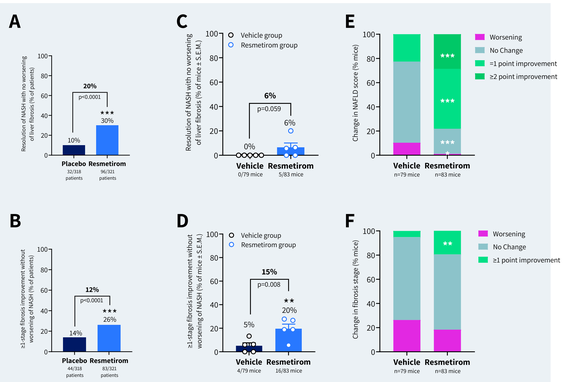

Figure 1. Resmetirom (MGL-3196, THR-β agonist) promotes NASH resolution and improves fibrosis stage in both NASH/MASH patients and GAN DIO-MASH mice. (A, B) Clinical phase-3 trial (MAESTRO-NASH, press release Dec 19, 2022). **(C-E)** 5 individual studies in GAN DIO-MASH mice (n=16-18 mice per group in each study). Resmetirom 3 mg/kg (PO, QD). *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed GAN DIO-MASH mouse controls (Fisher's exact test, Dunnett's test one-factor linear model).

2 Semaglutide

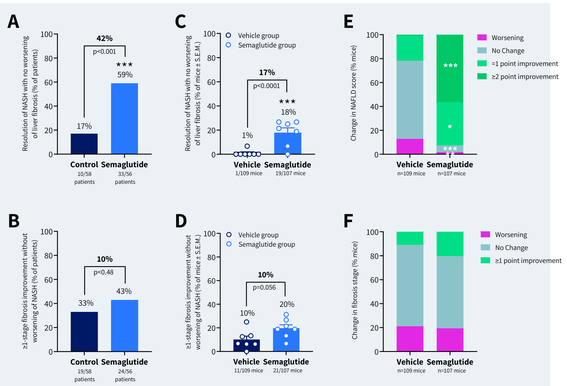

Figure 2. Semaglutide (GLP-1 receptor agonist) promotes NASH resolution in both NASH/MASH patients and GAN DIO-MASH mice. (A, B) Clinical phase-2 trial (*Newsome et al., NEJM, 2020*). **(C-E)** 7 individual studies in GAN DIO-MASH mice (n=14-16 per group in each study). Semaglutide 30 nmol/kg (SC, QD). *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed GAN DIO-MASH mouse controls (Fisher's exact test, Dunnett's test one-factor linear model).

3 Lanifibranor

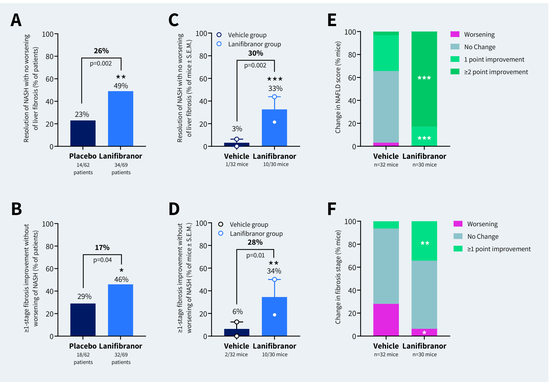

Figure 3. Lanifibranor (pan-PPAR agonist) promotes NASH resolution and improves fibrosis stage in NASH/MASH patients and GAN DIO-MASH mice. (A, B) clinical phase-2 trial (NATIVE trial, *Francque et al., NEJM, 2021*). **(C-E)** 2 individual studies in GAN DIO-MASH mice (n=14-16 per group in each study). Lanifibranor 30 mg/kg (PO, QD). *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed GAN DIO-MASH controls (Fisher's exact test, Dunnett's test one-factor linear model).

4 Elafibranor

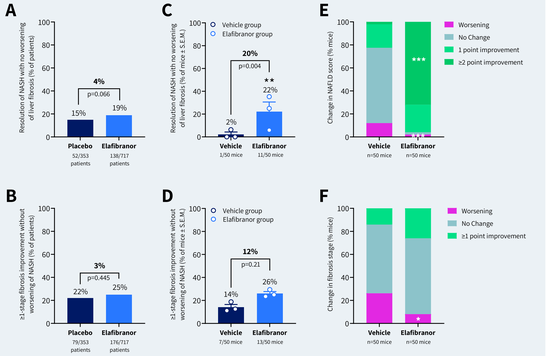

Figure 4. Differential effects of elafibranor (PPARα/δ-agonist) in NASH/MASH patients vs. GAN DIO-MASH mice. (A, B) Clinical phase-3 trial (RESOLVE-IT trial, press release May 5, 2020). **(B-F)** 3 studies conducted in GAN DIO-MASH mice (n=16-18 per group in each study). Elafibranor (30 mg/kg, PO, QD). *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed GAN DIO-MASH mouse controls (Fisher's exact test, Dunnett's test one-factor linear model).

5 Obeticholic Acid

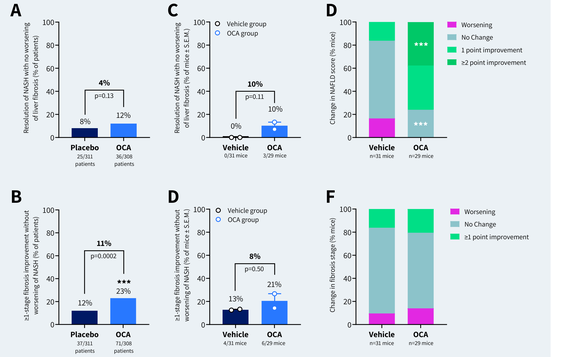

Figure 5. Differential effects of obeticholic acid (OCA, FXR agonist) in NASH/MASH patients vs. GAN DIO-MASH mice. (A, B) clinical phase-3 trial (REGENERATE trial, *Younassi et al., Lancet, 2019*). **(B-F)** 2 individual studies conducted in GAN DIO-MASH mice (n=14-16 per group in each study). Obeticholic acid 30 mg/kg (PO, QD). ***p<0.001 compared to vehicle-dosed GAN DIO-MASH mouse controls (Fisher's exact test, Dunnett's test one-factor linear model).

6 Firsocostat

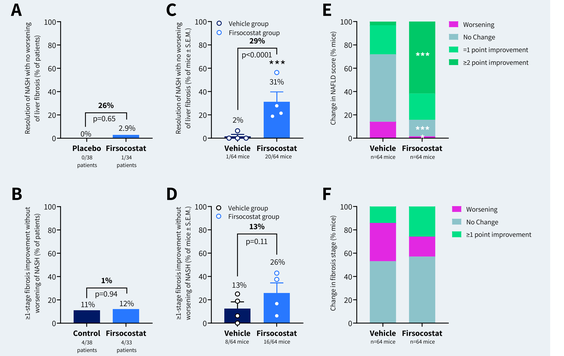

Figure 6. Differential effects of firsocostat (ACC pan-inhibitor) in NASH/MASH patients vs. GAN DIO-MASH mice. (A, B) clinical phase-2 trial (ATLAS trial, *Loomba et al., Hepatology, 2021*) and **(B-F)** 4 studies conducted in GAN DIO-MASH mice (n=14-18 per group in each study). Firsocostat 5 mg/kg (PO, QD). ***p<0.001 compared to vehicle-dosed GAN DIO-MASH mouse controls (Fisher's exact test, Dunnett's test one-factor linear model).

Conclusion

- Histological outcomes in GAN DIO-MASH mice are comparable to corresponding clinical trials for 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 the pivotal REGENERATE trial
- Elafibranor resolved 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 improved MASH in GAN DIO-MASH mice, although histological endpoints were not met in the ATLAS phase-2 trial
- **GAN DIO-MASH mice faithfully reproduce histological outcomes of key compounds in current late-stage clinical development, highlighting translatability and utility of the model in preclinical drug discovery**

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