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

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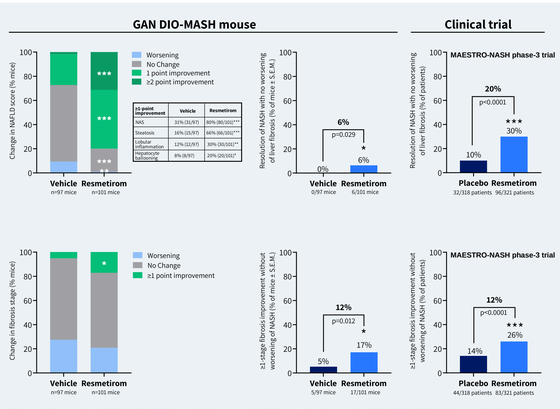
Background & Aim

Translational animal models are essential in preclinical drug discovery for metabolic dysfunction-associated steatohepatitis (MASH), formerly known as 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.

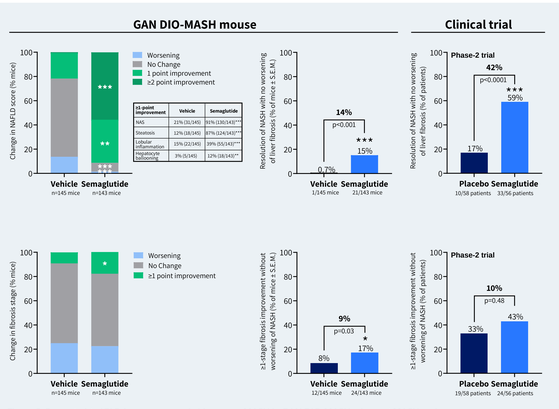
1 Resmetirom



≥1-point improvement	Vehicle	Resmetirom
NAS	31% (31/97)	80% (80/101)***
Steatosis	16% (15/97)	66% (66/101)***
Lobular inflammation	12% (12/97)	39% (39/101)**
Hepatocyte ballooning	8% (8/97)	29% (29/101)*

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).

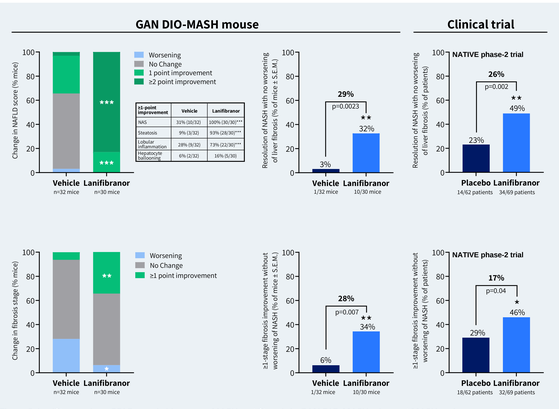
2 Semaglutide



≥1-point improvement	Vehicle	Semaglutide
NAS	21% (31/145)	91% (130/143)***
Steatosis	12% (18/145)	87% (124/143)***
Lobular inflammation	15% (22/145)	99% (95/143)***
Hepatocyte ballooning	3% (5/145)	12% (18/143)**

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).

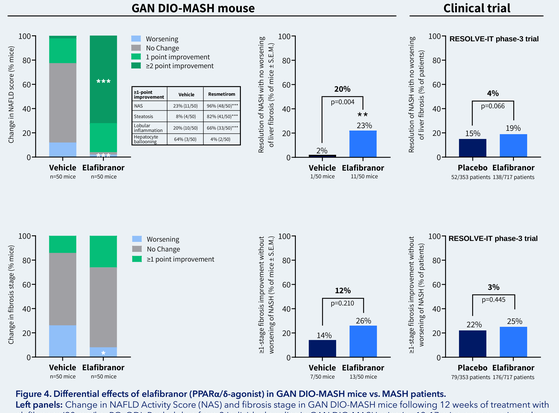
3 Lanifibranor



≥1-point improvement	Vehicle	Lanifibranor
NAS	31% (10/32)	100% (30/30)***
Steatosis	9% (3/32)	93% (28/30)***
Lobular inflammation	28% (9/32)	73% (22/30)***
Hepatocyte ballooning	6% (2/32)	16% (5/30)

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).

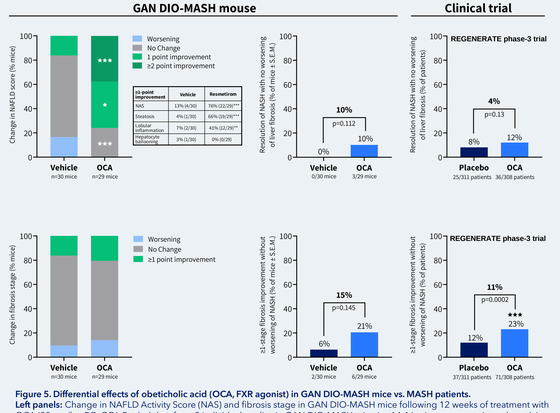
4 Elafibranor



≥1-point improvement	Vehicle	Resmetirom
NAS	23% (11/50)	94% (48/50)***
Steatosis	8% (4/50)	82% (41/50)***
Lobular inflammation	20% (10/50)	66% (33/50)***
Hepatocyte ballooning	64% (5/50)	4% (2/50)

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).

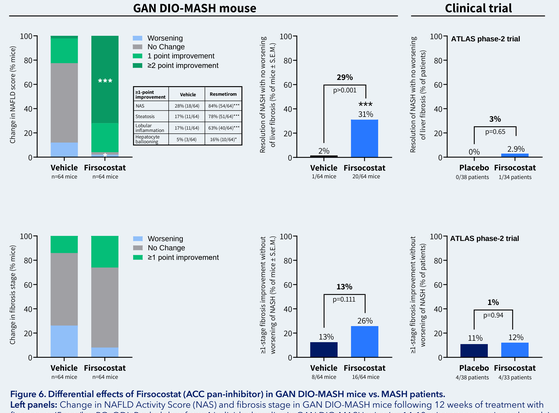
5 Obeticholic Acid



≥1-point improvement	Vehicle	Resmetirom
NAS	13% (4/30)	76% (22/29)***
Steatosis	4% (1/30)	66% (19/29)***
Lobular inflammation	7% (2/30)	41% (12/29)**
Hepatocyte ballooning	3% (1/30)	0% (0/29)

Figure 5. Differential effects of obeticholic acid (OCA, FXR 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 OCA (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



≥1-point improvement	Vehicle	Resmetirom
NAS	28% (5/64)	84% (54/64)***
Steatosis	17% (11/64)	78% (51/64)***
Lobular inflammation	17% (11/64)	63% (40/64)***
Hepatocyte ballooning	5% (3/64)	16% (10/64)*

Figure 6. Differential effects of Firsocostat (ACC pan-inhibitor) 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 firsocostat (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).

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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