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

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Background and Aims: The Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse is an industry-standard model of metabolic dysfunction-associated steatohepatitis (MASH) with progressive fibrosis. The present study aimed to assess liver histopathological effects of 6 late-stage clinically drugs in the GAN DIO-MASH mouse with reference to primary endpoints in corresponding clinical trials in NASH patients with liver fibrosis.

Method: Male C57BL/6J mice were fed the GAN diet (40 kcal-% fat, 22% fructose, 10% sucrose, 2% cholesterol) for ≥34 weeks. Only mice with biopsy-confirmed NAFLD Activity Score (NAS≥5) and fibrosis (≥stage F1) were included. GAN DIO-MASH mice (n=14-18 per group) were administered resmetirom (THR-β agonist, 3 mg/kg, QD, PO), semaglutide (GLP-1 receptor agonist, 30 nmol/kg, SC, QD), obeticholic acid (FXR agonist, 30 mg/kg, PO, QD), lanifibranor (pan-PPAR agonist, 30 mg/kg, PO, QD), elafibranor (PPAR-α/δ agonist, 30 mg/kg, QD), (PPAR-δ agonist, 10 mg/kg, PO, QD), firsocostat (ACC inhibitor, 5 mg/kg, PO, QD), or vehicle for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed and evaluated against FDA/EMA-accepted co-primary/secondary histological endpoints (resolution of NASH with no worsening of liver fibrosis; ≥1-stage fibrosis improvement without worsening of NASH).

Results: Histological outcomes in GAN DIO-MASH mice were comparable to corresponding clinical trials for resmetirom (MAESTRO-NASH), semaglutide (Newsome et al. NJEM 2020), and lanifibranor (NATIVE). Obeticholic acid reversed NASH but not fibrosis in GAN DIO-MASH mice, being line with the FLINT trial, whereas the opposite effect has been reported the pivotal REGENERATE trial. Elafibranor only resolved NASH, being consistent with the GOLDEN-505 trial but contrasting no histological benefits in the pivotal RESOLVE-IT trial. Firsocostat improved both NASH and fibrosis, although these endpoints were not met in the ATLAS trial.

Conclusion: GAN DIO-MASH mice faithfully reproduce histological outcomes of several compounds profiled in clinical trials for MASH, highlighting clinical translatability and utility of the model in preclinical drug development.