Reproducible therapeutic effects of lanifibranor and elafibranor in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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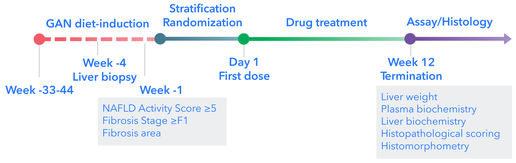
Background & Aim

Various peroxisome proliferator-activated receptor (PPAR) agonists, including lanifibranor (PPAR-α/δ/γ agonist), elafibranor (PPAR-α/δ agonist) and seladelpar (PPAR-δ agonist), have been profiled in clinical trials for metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to evaluate robustness of therapeutic outcomes following treatment with these clinically relevant PPAR agonists in the translational GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis.

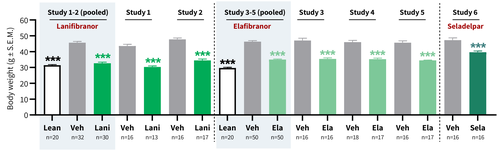
Methods

Lanifibranor (study 1-2), elafibranor (study 3-5) and seladelpar (study 6) monotherapy was profiled in GAN DIO-MASH mice. C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 33-44 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAS≥5) and fibrosis (stage ≥F1) were included and stratified into treatment groups. GAN DIO-MASH mice (n=14-18 per group) received (PO) lanifibranor (Lani, 30 mg/kg), elafibranor (30 mg/kg), seladelpar (14.1 mg/kg) or vehicle (Veh) once daily for 12 weeks. Vehicle-dosed chow-fed controls served as healthy controls (Lean). Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage. Terminal quantitative endpoints included plasma/liver biochemistry and AI-based quantitative liver histology. Statistical analyses were performed using Dunnett's test one-factor linear model (individual studies), Fisher's exact test (pooled study data on semiquantitative histopathological scoring variables) or one-way ANOVA with Dunnett's post-hoc test (pooled study data on quantitative endpoints), respectively. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle controls.

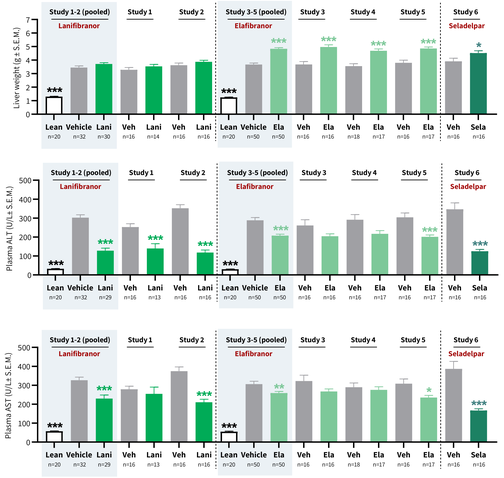
1 Study outline



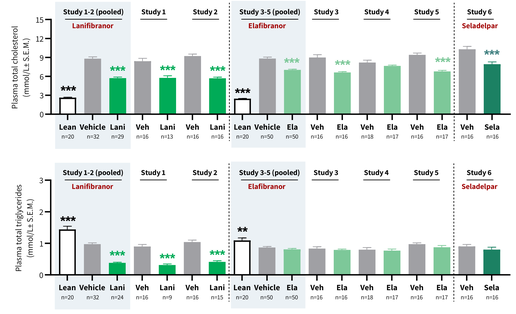
2 Body weight



3 Liver weight & transaminases

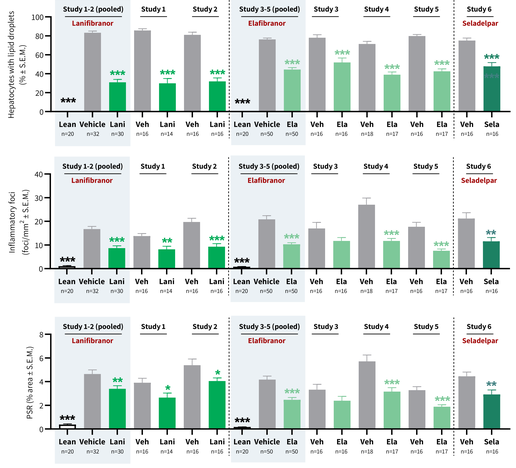


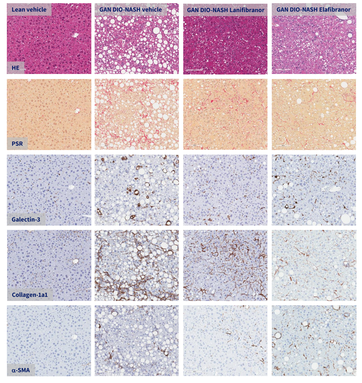
4 Plasma total cholesterol & triglycerides

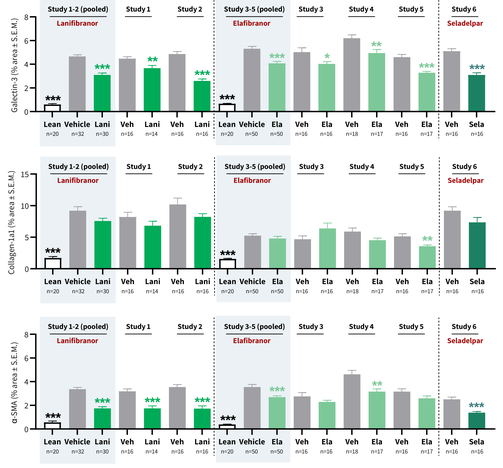


5 NAFLD Activity Score (NAS) & Fibrosis stage

6 Quantitative histological markers of steatosis, inflammation & fibrosis







Conclusion

- Three clinically relevant PPAR agonists were profiled in GAN DIO-MASH mice
- All compounds reduces body weight and improves transaminases and hypercholesterolemia. Elafibranor and seladelpar increases liver weight
- Lanifibranor and elafibranor reproducibly improves MASH by reducing steatosis and lobular inflammation scores. Seladelpar shows a comparable efficacy profile
- Inconsistent (lanifibranor) or no (elafibranor, seladelpar) effects on fibrosis scores were observed
- Benefits on histopathological scores were supported by quantitative histology

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