The pan-PPAR agonist lanifibranor improves increased portal pressure, endothelial dysfunction and liver histology in a rat model of early NAFLD

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Background & aim

In early **NAFLD** endothelial dysfunction and **increased intrahepatic vascular resistance** are demonstrated (1). These alterations are believed to contribute to disease progression.

The **pan-peroxisome proliferator-activated receptor** (pan-PPAR) agonist **lanifibranor** has shown beneficial effects on liver histology in NASH patients and in preclinical models of cirrhosis and portal hypertension (2, 3).

The effects of **lanifibranor** were studied on the intrahepatic vascular alterations and the histological features **in early NAFLD** in a preventive set-up in rats.

Methods

Wistar rat 250 g

- Control diet (CD)
  - Group 1: **Vehicle**
  - Group 2: **Lanifibranor** (100 mg/kg)
- Methionine-Choline deficient diet (MCD)
  - Group 3: **Vehicle**
  - Group 4: **Lanifibranor** (100 mg/kg)

Day 0 — •n=8/group •Diet + preventive dosing — •Oral gavage daily 1x/day •Weight 2x/week — **Day 29**

- ***In vivo*** portal venous pressure **(PVP)** assessment.
- ***In situ ex vivo*** **liver perfusion** in the same animal to assess baseline transhepatic pressure gradient **(THPG)** at different flows.
- **Histological staining** on liver tissue: **SAF**-score and particle analysis **(% steatosis quantification).**
- **Dose-response** measurements with endothelin-1 (ET-1), methoxamine (Mx), and acetylcholine (ACh).

1 Results

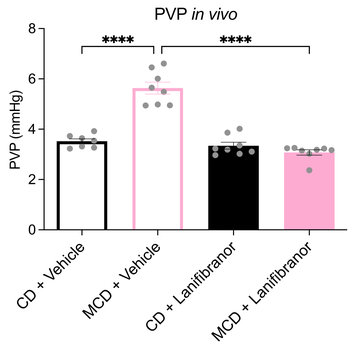

Figure 1: *In vivo* PVP

Strong elevation of PVP in vehicle-treated MCD rats vs. controls (5.64 ± 0.63 vs. 3.52 ± 0.24 mmHg, p < 0.0001). Lanifibranor normalised increased PVP in MCD rats to control values (from 5.64 ± 0.63 to 3.08 ± 0.28 mmHg, p < 0.0001).

Figure 2: *In situ ex vivo* THPG

THPG increased at all flows in MCD rats vs. CD rats (e.g., at 30 ml/min: from 8.78 ± 0.35 to 6.73 ± 0.28 mmHg, p < 0.001). Lanifibranor normalised elevated THPG in MCD rats at all flows (e.g., at 30 ml/min: from 8.78 ± 0.35 to 6.31 ± 0.15 mmHg, p < 0.001).

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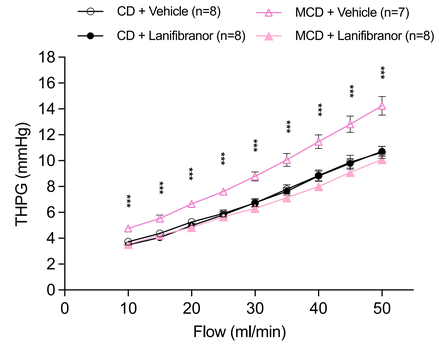

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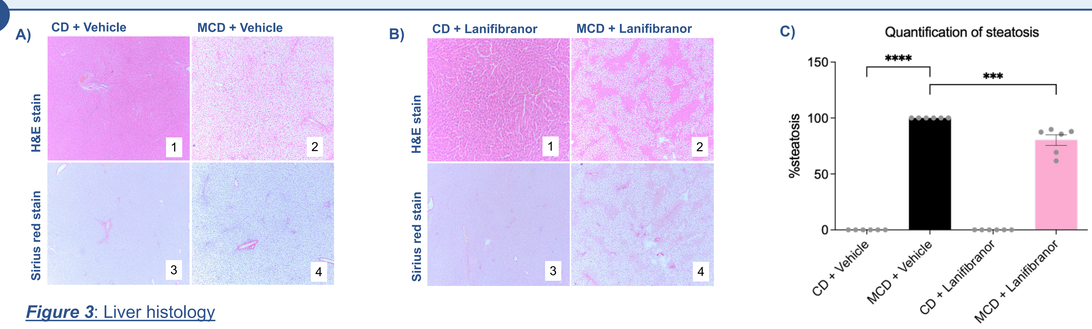

Figure 3: Liver histology

A) Vehicle-treated rats: 1) Normal healthy liver tissue in CD rat. **2)** Severe, grade 3 steatosis in MCD rat. **3-4)** No signs of fibrosis.
B) Lanifibranor-treated rats: 1) Healthy CD liver unchanged by lanifibranor. **2)** Improvement of steatosis by lanifibranor in MCD liver. **3-4)** No fibrotic tissue present.
C) Quantification of steatosis: Lanifibranor improved steatosis with a decrease of 19.7 ± 4.8 % (p = 0.0001).

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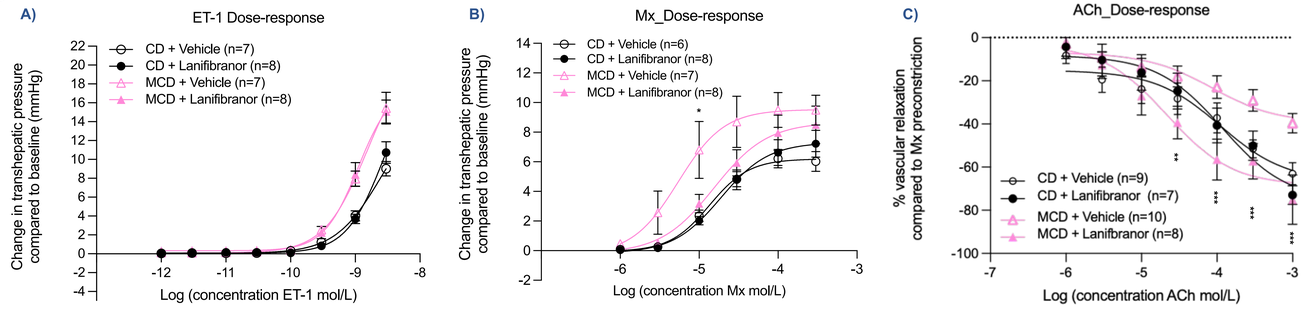

Figure 4: Dose-response curves

A) ET-1 dose-response: In the vehicle-treated groups, MCD rats are **hyperreactive** to ET-1 compared to controls. Lanifibranor did not normalise ET-1 hyperreactivity in MCD rats.
B) Mx dose-response: Vehicle-treated MCD rats are **hyperreactive** to Mx vs. CD rats. Lanifibranor improved Mx hyperreactivity in MCD animals.
C) ACh dose-response: Vehicle-treated MCD rats are **hyporeactive** to ACh in contrast to control animals. Lanifibranor normalised ACh hyporeactivity in MCD rats.

Conclusions

In early NAFLD lanifibranor:

- Normalises the increased portal pressure.
- Improves liver histology.
- Normalises functional intrahepatic vascular alterations (a direct effect of lanifibranor).

These data support the role of intrahepatic vascular alterations in the development of NAFLD and its related portal hypertension, and the potential of lanifibranor as a treatment for NAFLD.

References

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