The pan-PPAR agonist lanifibranor improved altered liver vascular biology in MASH, associated with improved liver histology

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Background & aim

In early **MASLD** endothelial dysfunction and increased **intrahepatic vascular resistance** are shown (1, 2, 3).

Lanifibranor, a pan-PPAR (**peroxisome proliferator-activated receptor)** agonist had **beneficial effects** on liver histology in **MASH patients** (4) and on portal hypertension in preclinical **models of cirrhosis** (5).

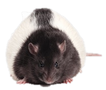
We showed that **lanifibranor** also **improved vascular alterations in** a rat model of **early MASLD** (6).

In this study, the **effects** of **lanifibranor**, previously demonstrated in a rat **model of isolated steatosis**, were validated in a rat **model of MASH.**

Materials & methods

Zucker lean rat (**ZLR**)200 g

Chow diet (CD)
- Group 1: **Placebo**
- Group 2: Lanifibranor (100 mg/kg) = **pan-PPAR**



Zucker fatty rat (**ZFR**) 250 g

High-fat high-fructose diet (HFHFD)
- Group 3: **Placebo**
- Group 4: Lanifibranor (100 mg/kg)

Day 0 — • n=6-8/group • Diet + preventive dosing — • Oral gavage 1x/day • Weight 2x/week — **Day 57** → **Experiments & analysis**

- ***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.
- **Liver histology: SAF**-score. Blinded semi-quantification of **CD34 staining** (capillarisation marker).
- **Dose-response** measurements with methoxamine (Mx), and acetylcholine (ACh) after Mx preconstriction.

1 Results

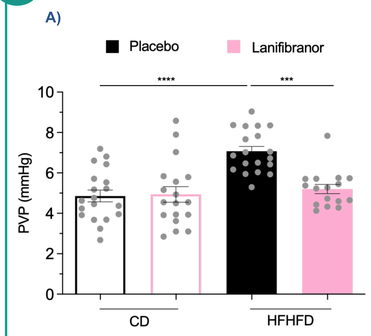
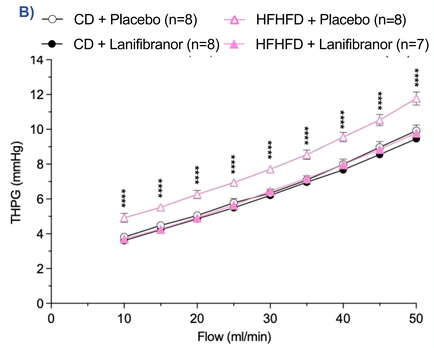


Figure 1A: *In vivo* PVP

PVP is strongly increased in placebo-treated ZFRs vs. ZLRs (7.1 ± 0.2 vs. 4.9 ± 0.3 mmHg, $p < 0.05$). Lanifibranor normalised PVP in ZFRs (from 7.1 ± 0.2 to 5.2 ± 0.2 mmHg, $p < 0.05$).

Figure 1B: *In situ ex vivo* THPG

THPG is increased at all flows in placebo-treated ZFRs vs. ZLRs (e.g., at 30 ml/min: 7.7 ± 0.2 vs. 6.3 ± 0.3 mmHg, $p < 0.05$). Lanifibranor normalised elevated THPG in ZFRs at all flows (e.g., at 30 ml/min: from 7.7 ± 0.2 to 6.4 ± 0.1 mmHg, $p < 0.05$).



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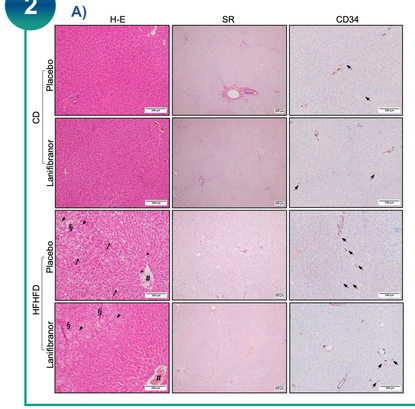

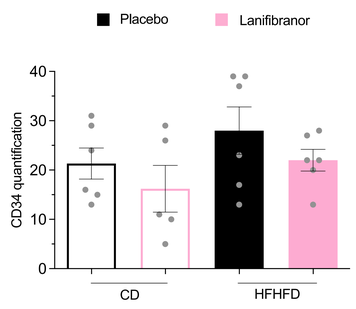

Figure 2: Liver histology

A) H-E: Livers of ZLRs showed no abnormalities. Placebo-treated ZFR livers displayed:
- Steatosis
  - Microvesicular (short arrows)
  - Macrovesicular (arrow heads)
- Ballooning (thin arrows)
- Inflammation

In lanifibranor-treated ZFRs ballooning was absent and steatosis was limited to the periportal area (§). The central area (#) had a healthy appearance.

Sirius red (SR): No signs of fibrosis.

CD34: Arrows point CD34 positive staining.

B) CD34 semi-quantification: CD34 staining was increased in placebo-treated ZFRs and treatment with lanifibranor decreased CD34 staining.

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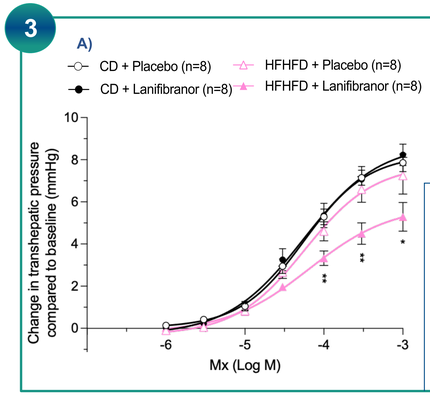
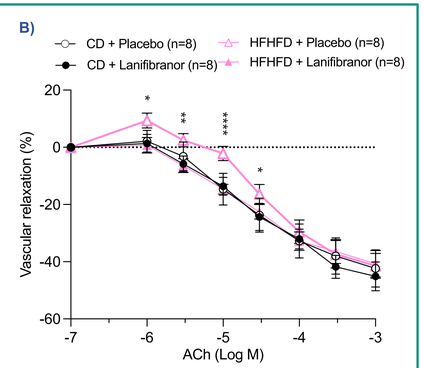


Figure 3A: Dose-response Mx

Placebo-treated ZFRs were not hyperreactive to Mx, however, lanifibranor significantly decreased Mx reactivity below control values.

Figure 3B: Dose-response ACh

In placebo-treated ZFRs, after pre-constriction with Mx, the vasodilatory response to ACh was blunted at lower doses. Treatment with lanifibranor normalised ACh hyporeactivity in ZFRs.



Conclusion

This study, performed in a dietary model more reflective of human MASH rather than isolated steatosis, **confirms** that **lanifibranor** significantly normalised **portal pressure** and **intrahepatic vascular resistance** by:

⇒ **Functional effects**
- ↓ reactivity to methoxamine
- ↑ reactivity to acetylcholine

⇒ **Structural effects**
- ↓ Steatosis
- ↓ Ballooning
- ↓ Inflammation

These findings support:

- The **role** of **intrahepatic vascular alterations** in:
  - The development of MASLD-related **portal hypertension**
  - The **progression** to **MASH**
- The **potential of lanifibranor** as an efficacious **treatment for MASH**

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