# Lanifibranor Targets Multiple Hepatic Cell Populations and Reduce Fibrosis Through Balanced Pan-PPAR Activation

**Guillaume Wettstein[1], Sander Lefere[2], Jordi Gracia-Sancho[3], Frank Tacke[4], Manal F. Abdelmalek[5], Sven Francque[6]**

[1]Inventiva, Daix, France; [2]Liver Research Center Ghent, Ghent University, Ghent University Hospital, Ghent, Belgium; [3]Liver Vascular Biology Lab, IDIBAPS–Hospital Clínic de Barcelona–CIBEREHD, Barcelona, Spain; [4]Dept. of Hepatology & Gastroenterology, Charité–Universitätsmedizin Berlin, Germany; [5]Div. of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA; [6]Dept. of Gastroenterology and Hepatology, Antwerp University Hospital, Belgium

SCAN AND VIEW POSTER ON OUR WEBSITE

## INTRODUCTION

Fibrosis is the strongest predictor of liver-related morbidity and mortality in metabolic dysfunction-associated steatohepatitis (MASH). Fibrogenesis results from complex interactions between multiple hepatic cell populations including hepatocytes, Kupffer cells, liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs). Peroxisome proliferator-activated receptors (PPARs) are key regulators of metabolism, inflammation and fibrogenesis, with distinct but complementary functions across liver cell types.

## AIM

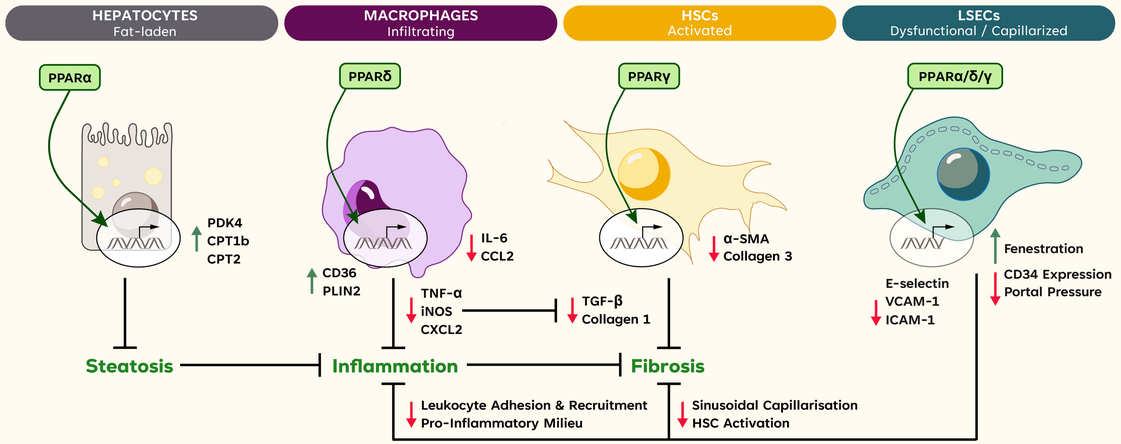
We investigated how balanced pan-PPAR activation by the investigational product lanifibranor simultaneously targets multiple cellular drivers of fibrosis in MASH.

## METHOD

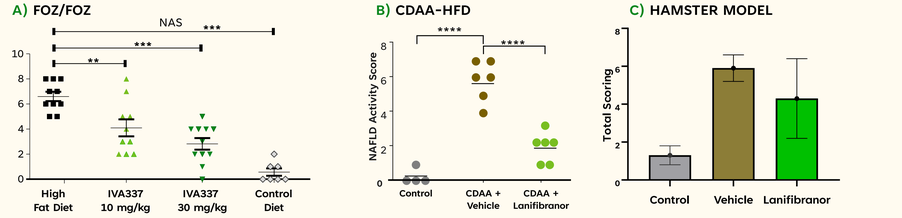
The effects of lanifibranor were evaluated across several preclinical models reproducing key features of MASH and fibrosis, including diet-induced steatohepatitis, CCl4-induced fibrosis and cirrhotic model. Liver histology, inflammatory and fibrotic pathways, macrophage phenotype, HSC activation and LSEC dysfunction were assessed using molecular, histological and functional analyses. Human hepatic cells and liver biopsies were also evaluated to characterize the translational relevance of pan-PPAR activation.

## RESULTS

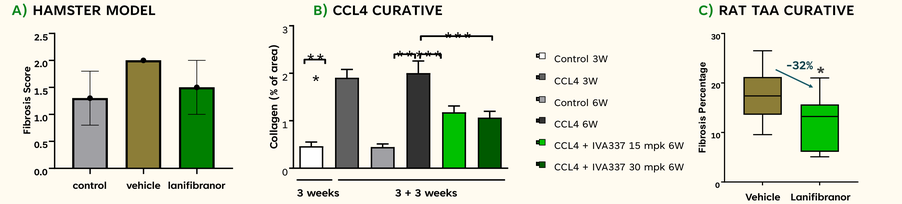
### Figure 1: Lanifibranor Balanced PPARα/δ/γ Agonism Across Multiple Hepatic Cell Types



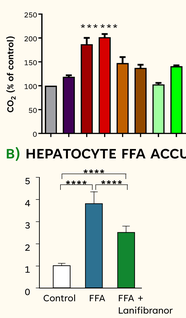

### Figure 2: Lanifibranor Reduced MAFLD Activity Score Across Different Preclinical Models




### Figure 3: Lanifibranor Reduced Fibrosis In Different Murine Models

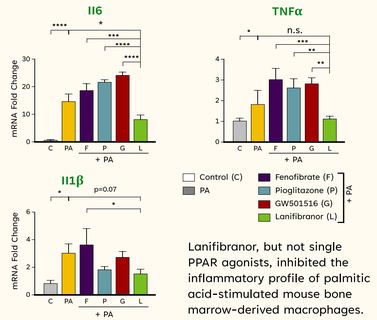



### Figure 4: Lanifibranor Acts on Hepatocytes



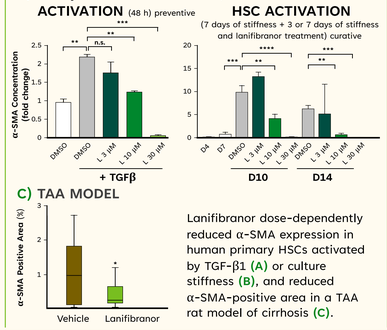

A) Lanifibranor increased β-oxidation in Huh-7 cells in a PPARδ-dependant way (B) reduced free fatty acid accumulation in primary murine hepatocytes.

### Figure 5: Lanifibranor Acts on Macrophages



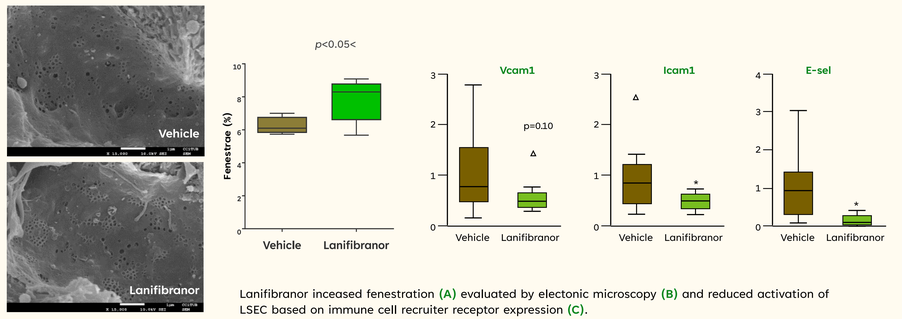

Lanifibranor, but not single PPAR agonists, inhibited the inflammatory profile of palmitic acid-stimulated mouse bone marrow-derived macrophages.

### Figure 6: Lanifibranor Acts on HSCs




Lanifibranor dose-dependently reduced α-SMA expression in human primary HSCs activated by TGF-β1 (A) or culture stiffness (B), and reduced α-SMA-positive area in a TAA rat model of cirrhosis (C).

### Figure 7: Lanifibranor Acts on Liver Sinusoidal Endothelial Cells (LSECs)




Lanifibranor inceased fenestration (A) evaluated by electonic microscopy (B) and reduced activation of LSEC based on immune cell recruiter receptor expression (C).

## CONCLUSIONS

Lanifibranor addresses liver fibrosis through coordinated actions on multiple hepatic cell populations involved in MASH pathogenesis. Balanced activation of PPARα, PPARδ and PPARγ was simultaneously associated with improved hepatocyte metabolism, dampened macrophage-driven inflammation, improved LSEC function and maintained HSC quiescence. This pleiotropic multicellular mechanism highlights the potential relevance of pan-PPAR activation supporting the further development of lanifibranor as an antifibrotic therapy for MASH.

## REFERENCES

1. Wettstein g, et al., The new-generation pan-peroxisome proliferator-activated receptor agonist IVA337 protects the liver from metabolic disorders and fibrosis. Hepatol Commun. 2017 Jun 19;1(6):524-537
2. Lefere S, et al., Differential effects of selective- and pan-PPAR agonists on experimental steatohepatitis and hepatic macrophages. J Hepatol. 2020 Oct;73(4):757-770
3. Boyer-Diaz Z, et al., Pan-PPAR agonist lanifibranor improves portal hypertension and hepatic fibrosis in experimental advanced chronic liver disease. J Hepatol. 2021 May;74(5):1188-1199