Lanifibranor Improved Liver Sinusoidal Endothelial Cell Dysfunction And Vascular Alterations Across All Stages From MASH To Cirrhosis

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INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is traditionally characterized by steatosis, inflammation and fibrosis. However, growing evidence indicates that vascular dysfunction is an additional and crucial hallmark of disease pathogenesis. Liver sinusoidal endothelial cell (LSEC) capillarisation, increased intrahepatic vascular resistance and portal hypertension have been shown to develop early in the disease course, already at the stage of isolated steatosis, and to contribute to disease progression to steatohepatitis and progressive fibrosis through impaired hepatic microcirculation, inflammation and fibrogenesis.

AIM

We assessed the effects of the investigational pan-PPAR agonist product lanifibranor on LSEC phenotype and on vascular abnormalities across the spectrum from isolated steatosis over MASH to cirrhosis

METHOD

Human liver biopsies from patients with MASLD/MASH enrolled in the NATIVE Phase2b study were examined by CD34 staining. Also, preclinical models of early MASLD, MASH and cirrhosis, were analyzed. In the latter, LSEC capillarisation was also evaluated using CD34 staining and additionally by ultrastructural analyses using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM).

RESULTS

Figure 1: Design and Assessment of Liver CD34 Staining in NATIVE cohort

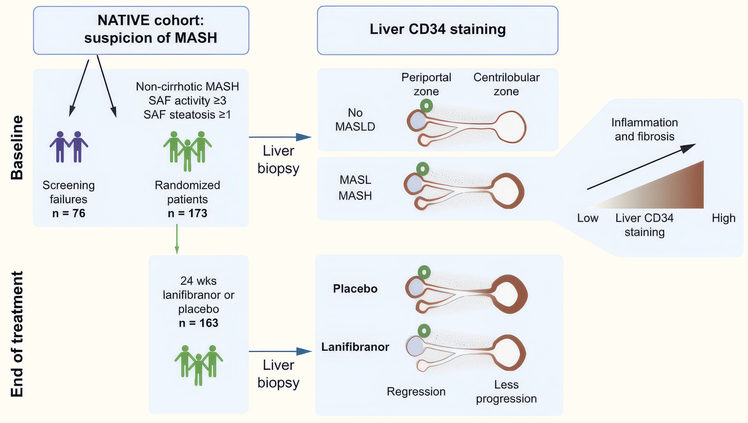


Figure 2: Disease Progression From MASH and Fibrosis to Cirrhosis

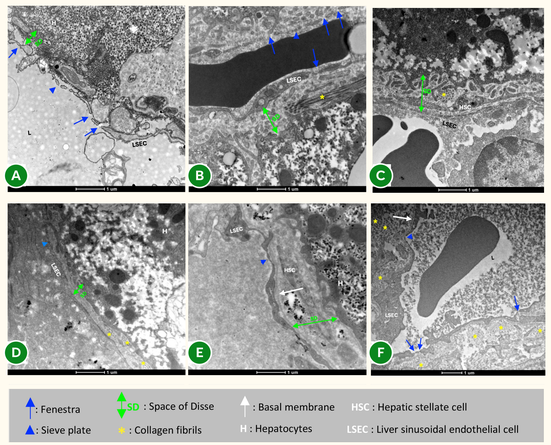


FIGURE 2: Progression of sinusoid capillarization as MASLD progress to MASH and fibrosis to cirrhosis. A) no MASLD normal architecture with abundant fenestrae organised in sieve plates. **B) MASL** with **F1** fibrosis and **C) F2** fibrosis; sieve plates and fenestrae remained present. **D)** In **MASH** with **F2** fibrosis and **E) F3** fibrosis, narrowed fenestrae, indicating capillarisation. **F)** In **MASH cirrhosis (F4)**, a few remaining narrowed fenestrae, the sinusoid becomes almost indistinguishable from a capillary-like vessel.

Figure 3: CD34 Staining as a Marker of Capillarization

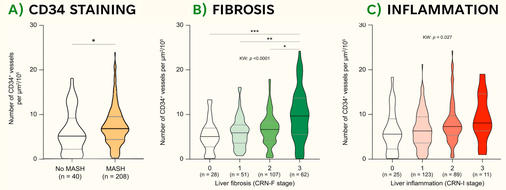


FIGURE 3: A) CD34 staining is more pronounce in patient with MASH campare to patients without MASH. CD34 increase as **B)** fibrosis and **C)** inflammation progress.

Figure 4: Lanifibranor Improved CD34 Staining Dose-Dependently

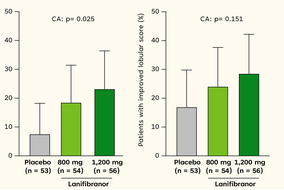


FIGURE 4: Percentage of patients with improved CD34 staining after lanifibranor treatment versus placebo: **A)** Improvement in periportal CD34 staining, defined as decreased staining and consistent with greater fenestration and reduced capillarization. **B)** Improvement in lobular CD34 staining.

Figure 5: HFHFD Mouse Model

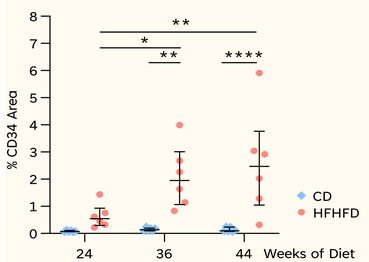


FIGURE 5: CD34 staining increased as HFHFD-fed mice progressed from isolated steatosis (weeks 24–36) to MASH with minimal fibrosis at week 44, while remaining negligible in CD-fed mice.

Figure 6: Lanifibranor Restored LSEC Fenestration, CD34 Staining, and Portal Pressure in MCDD-Fed Rats

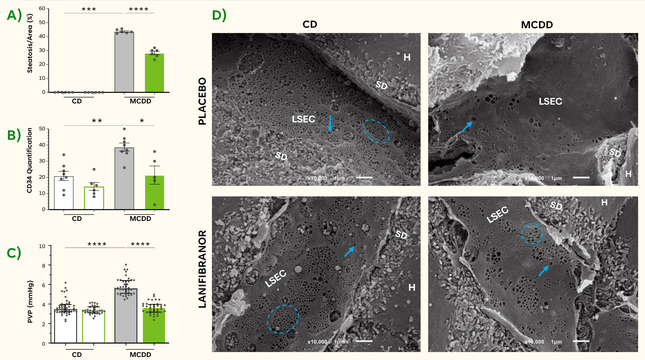


FIGURE 6: Lanifibranor had a limited effect on steatosis at the evaluated dose **(A)** but normalized CD34 staining **(B)** and portal venous pressure (PVP)**(C)**. SEM micrographs (×10,000 magnification) showed that lanifibranor restored LSEC fenestration **(D)**, as demonstrated by increased fenestra frequency **(E)** and porosity **(F)**, without affecting fenestra diameter **(G)**.

Figure 7: Lanifibranor Improved Fenestration and Haemodynamics in Cirrhotic Rats

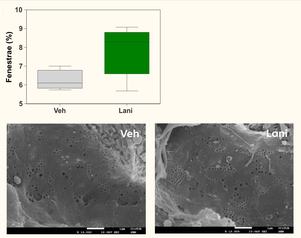


FIGURE 7: Lanifibranor increased the number of fenestrae in rat model of cirrhosis **(A & B)**. Lanifibranor improved haemodynamics parameters **(table 1)** especially reduced portal pressure, hepatic vascular resistance. Lanifibranor treatment also lead to less ascites development indicating a favourable effect of lanifibranor on decompensated cirrhosis.

Parameters	vehicle	Lanifibranor	P Value
Portal Pressure (mmHg)	13.1 ± 0.4	11.2 ± 0.5	0.003
Portal blood flow	19 ± 1.7	23.5 ± 2.1	0.1
Hepatic Vascular Resistance (mmHg.min.ml^{-1})	0.75 ± 0.1	0.53 ± 0.06	0.02
Mean Arterial Pressure (mmHg)	81 ± 3	84 ± 2	<0.2
Spleen weight (g)	1,6 ± 0,1	1,3 ± 0,1	0,08
Ascites (% of total animals)	67	16	0,02

CONCLUSIONS

Vascular dysfunction represents an early and central feature of MASH pathophysiology. LSEC alterations occur early in the disease course, contribute to early-onset portal hypertension and to disease progression and ultimate severity. Lanifibranor improved LSEC alterations and associated intrahepatic vascular abnormalities across multiple stages of disease, supporting its development in MASH, including patents with advanced disease.

REFERENCES

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