Beyond the Liver: Cardiovascular Effects of the Pan-PPAR Agonist Lanifibranor in Patients with Mash

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SCAN AND VIEW POSTER ON OUR WEBSITE

INTRODUCTION

Cardiovascular (CV) events are the leading cause of death in metabolic dysfunction-associated steatohepatitis (MASH). CV disease such as heart failure with preserved ejection fraction (HFpEF) and MASH are manifestations of a shared systemic metabolic disorder with similar drivers. We assessed whether the investigational pan-PPAR agonist, lanifibranor, improves CV risk factors, and whether nonclinical data may support a rationale of CV safety and vascular benefit.

METHODS

CV endpoints were evaluated in the phase 2b NATiVE trial (247 patients, non-cirrhotic MASH; lanifibranor 1200 mg, 800 mg or placebo once daily, 24 weeks): lipids, glucose metabolism, insulin resistance (IR), systemic inflammation, blood pressure (BP), adiponectin and a validated CV-risk classification.

Nonclinical data comprised a rat study comparing plasma volume, glomerular filtration rate (GFR) and organ weights with reference PPAR agonists, and a thioacetamide cirrhosis model assessing portal haemodynamics and endothelial phenotype.

RESULTS

A Clinical Cardiometabolic Effects — NATIVE Phase 2b[3]

Compared with placebo, lanifibranor demonstrated broad and clinically relevant cardiometabolic improvements (adjusted mean difference vs placebo at week 24[3])

Triglycerides
−0.5 mmol/L
Both doses; significant

HDL-Cholesterol
+0.10 to +0.16 mmol/L
1200 / 800 mg; significant

Apolipoprotein-B
-10 mg/dL
Both doses; significant

HOMA-IR
≈ -4.0
Both doses; significant

HbA1c
-0.5%
Both doses; significant

Fasting Glucose
-0.8 to -1.0 mmol/L
1200 / 800 mg; significant

hs-CRP
-1.5 to -2.2 mg/L
1200 / 800 mg; significant

Ferritin
-72 to -84 µg/L
1200 / 800 mg; significant

Diastolic BP
-3.9 mmHg
800 mg (p=0.012); 1200 mg -2.5 mmHg not significant (p=0.110)

Adiponectin
↑ ≈4-fold (4.5× / 3.8×)
1200 / 800 mg; increased in 95% / 86% of patients vs 10% placebo

High-CV-Risk → Lower Risk
38% / 44% of patients
1200 / 800 mg vs 26% placebo

NT-proBNP (balancing signal)
↑ ≈ +34 to +71 pg/mL
Correlated with weight gain; no clinical congestion

B Nonclinical Safety & Fluid Handling – Rat vs Reference PPAR Agonists[1]

In nonclinical studies, lanifibranor did not increase fluid volume or promote serous effusions (GFR unchanged)

PARAMETER	LANIFIBRANOR	REFERENCE PPAR AGONISTS
Plasma Volume	No increase	Increases with rosiglitazone / muraglitazar / tesaglitazar
Heart Weight	No increase	Increases with reference agonists
Serous Effusions	None	Produced by rosiglitazone and tesaglitazar
GFR	Unchanged	All compounds

C Nonclinical Vascular & Endothelial Effects – Thioacetamide Cirrhotic Rat[2]

Lanifibranor improved portal haemodynamics and endothelial markers without affecting systemic arterial pressure

Portal Pressure
-15% p=0.003

ICAM-1 (endothelial)
-52% p=0.038

Hepatic Vascular Resistance
-29% p=0.002

E-selectin (endothelial)
-85% p=0.020

Mean Arterial Pressure / HR
No Change
Systemic Haemodynamics Preserved

VCAM-1 (endothelial)
-44% p=0.097
(not significant)

Table 1) Summary of Results

Abbreviations & Notes:
BP, blood pressure; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VCAM-1, vascular cell adhesion molecule-1.

Clinical values are adjusted mean differences vs placebo at week 24; where two figures are shown they correspond to the 1200 mg and 800 mg doses respectively, or a range across doses. Figures should be confirmed against the source publications before submission. Section C reflects hepatic (sinusoidal) endothelium; the atherogenesis relevance of the adhesion-molecule changes is by shared mechanism rather than direct systemic vascular measurement.

Table 2) Shared Drivers of MASH and HFpEF

SHARED DRIVER	CONSEQUENCES IN MASH	CONSEQUENCES IN HFPEF
Visceral adiposity and altered adipokines	Increased hepatic steatosis Adiponectin falls	Increases epicardial fat; Low adiponectin removes an anti-hypertrophic and anti-fibrotic signal
Insulin resistance	Drives de novo lipogenesis and steatosis	Shifts the myocardium toward fatty acid oxidation and away from glucose
Lipotoxicity and ectopic lipid	Hepatocyte injury (inflammation and ballooning)	Myocardial triglyceride accumulation and diastolic impairment
Systemic inflammation	Macrophage recruitment and activation; steatohepatitis	Coronary microvascular endothelial activation, reducing nitric oxide availability to adjacent cardiomyocytes
Oxidative stress & impaired nitric oxide signaling	Endothelial dysfunction and portal hypertension	Reduced nitric oxide, cGMP, and PKG activity.
Fibrogenesis	Stellate cell activation and collagen deposition	Cardiac fibroblast activation and interstitial fibrosis

CONCLUSION

Lanifibranor produced coordinated improvement across established cardiovascular risk factors (atherogenic dyslipidemia, IR, systemic inflammation, BP and adiponectin), while nonclinical evidence of favorable fluid handling and an improved endothelial phenotype support cardiovascular benefit and suggests mitigation of the PPAR-γ-class heart-failure concern. Through improvement of lipids and glucose metabolism, and cardioprotection against oxidative stress and inflammation, lanifibranor may directly target diseases that have similar drivers of MASH such as HFpEF. These findings support prospective evaluation of lanifibranor on cardiovascular outcomes in MASH.

REFERENCES

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