Lanifibranor improves markers of cardio-metabolic health in NASH patients independent of weight change

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INTRODUCTION & AIM

Lanifibranor therapy resulted in significant efficacy on the histological endpoint 'NASH resolution and improvement of fibrosis' as well as on markers of cardiometabolic health (CMH) in the phase 2b NATIVE study.

Modest weight gain was reported as a PPARγ effect, which has been ascribed to the maturation of insulin-sensitive, metabolically healthy subcutaneous adipose tissue. We evaluated markers of CMH by changes in weight in the lanifibranor and placebo arms.

METHOD

NATIVE enrolled 247 patients with SAF activity score 3-4, fibrosis stage F0-F3 in 3 arms: lanifibranor 800, 1200 mg/d and placebo for 24 weeks; 217 (lanifibranor: 144, placebo: 73) patients who completed the trial with weight data at baseline and end of treatment (EOT) were included in the analyses.

Mean weight increase at EOT was 2.4 (2.6%) and 2.7 (3.1%) kg for 800 and 1200 mg lanifibranor, respectively. Patients were divided in 3 groups according to % weight change as shown below.

	Lanifibranor (800+1200mg)	Placebo
N	144	73
Stable (≤2.5%) *	73 (51%)	61 (84%)
Increase (>2.5%) *	-	12 (16%)
Moderate increase [2.5% - 5%[	23 (16%)	-
Increase (>5%)	48 (33%)	-

* Only two %weight change groups for placebo due to few patients >5%

Biomarkers of lipid and glucose metabolism, insulin resistance, inflammation, liver tests, diastolic blood pressure (DBP), hepatic steatosis (NASH-CRN grading) and Controlled Attenuation parameter (CAP) were evaluated at screening and EOT, and compared between the weight change groups.

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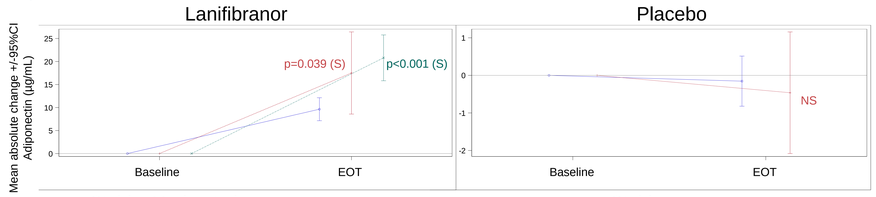
RESULTS (1/2)

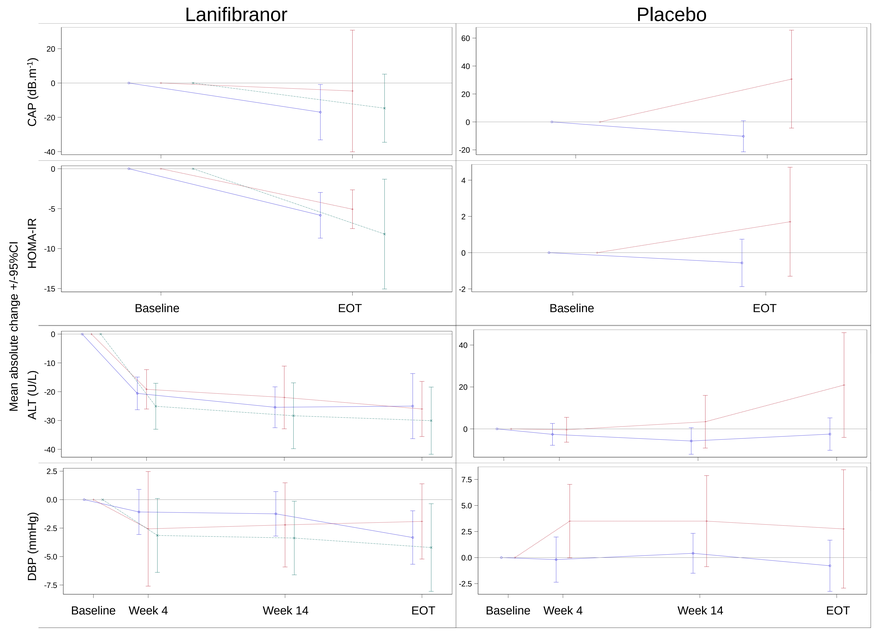
Adiponectin, a PPARγ downstream mediator, increased in all 3 weight change groups, with a higher increase in the >2.5% weight increase groups, compared to the ≤2.5% weight stable group.



CI: Confidence interval

P-values obtained from MMRM adjusted on baseline values, comparing respectively 'Moderate increase' and 'Increase' to 'Stable'.

Focusing on **steatosis** (CAP), **HOMA-IR**, **DBP** (see Figures) and **liver tests** (ALT below, AST and GGT see Table), improvement of CMH markers at EOT compared to baseline occurred to the same degree in the 3 weight change groups for the pooled lanifibranor arms, where even worsening of these parameters were observed in the placebo-treated patients with a weight increased at EOT.



CI: Confidence interval

RESULTS (2/2)

For the **other CMH markers** assessed, improvement at EOT compared to baseline occurred to the same degree in the 3 weight change groups for the pooled lanifibranor arms, where placebo-treated patients with a weight change at EOT had no improvement of CMH markers:

Change from baseline in CMH parameters at EOT	Weight change				
	Lanifibranor			Placebo	
Mean (standard deviation)	Stable N = 73	Moderate increase N = 23	Increase N = 48	Stable N = 61	Increase N = 12
Lipids					
HDL-cholesterol (mmol/L)	0.15 (0.23)	0.13 (0.23)	0.12 (0.20)	0.02 (0.20)	0.01 (0.14)
Triglycerides (mmol/L)	-0.42 (0.97)	-0.44 (0.57)	-0.45 (0.60)	0.03 (1.02)	0.12 (0.71)
APO-B (mg/dL)	-9.66 (15.76)	-13.04 (25.36)	-14.56 (24.12)	-2.58 (13.08)	-0.08 (30.21)
APO-B/APO-A1	-0.08 (0.12)	-0.06 (0.15)	-0.07 (0.21)	-0.01 (0.16)	-0.01 (0.20)
APO-C3 (µg/mL)	-10.72 (37.90)	-7.30 (36.80)	-9.33 (31.75)	8.85 (37.76)	19.08 (49.19)
Glucose Metabolism					
Fasting glucose (mmol/L)	-0.86 (1.34)	-0.86 (0.81)	-0.65 (1.76)	0.26 (0.91)	0.04 (0.87)
Insulin resistance					
Insulin (pmol/L)	-122.6 (226.2)	-98.1 (112.1)	-155.2 (352.9)	-24.8 (109.2)	46.9 (110.2)
Inflammation					
hs-CRP (mg/L)	-0.55 (4.82)	-4.13 (7.61)	-2.65 (4.57))	0.63 (3.85)	-0.08 (2.06)
Liver					
AST (U/L)	-10.9 (31.0)	-12.9 (21.3)	-21.0 (46.4)	-1.2 (22.0)	12.3 (20.6)
GGT (U/L)	-33.2 (68.4)	-28.0 (25.5)	-40.8 (48.7)	1.0 (22.1)	12.0 (19.3)

CONCLUSIONS

Biomarkers of CMH improve with lanifibranor therapy, independent of weight change. These beneficial effects occur in parallel with a marked increase of adiponectin, which marks adipose tissue health and improves insulin sensitivity; the data provide further evidence that PPARγ-induced weight gain is metabolically distinct from lifestyle-related weight gain.

ACKNOWLEDGEMENTS

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