Lanifibranor-Induced Histological and Cardiometabolic Improvements in MASH Are Independent of Weight Change and Associated With Adiponectin Induction

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INTRODUCTION

In the phase 2b NATIVE study, lanifibranor, a pan-PPAR agonist, demonstrated significant improvement in steatohepatitis and fibrosis as well as markers of cardiometabolic health (CMH) in patients with metabolic dysfunction–associated steatohepatitis (MASH). Adiponectin (ADP), a pleiotropic adipokine downstream of PPARγ activation that improves insulin sensitivity, lipid metabolism, and inflammatory and fibrotic pathways, was significantly increased with lanifibranor treatment.

AIM

The modest weight gain associated with PPARγ agonists may be attributable to the expansion of metabolically favourable subcutaneous adipose tissue. This analysis examined relationships between ADP induction, weight change, and histological and CMH outcomes following lanifibranor treatment.

METHOD

In NATIVE, 247 patients with non-cirrhotic MASH were randomized to lanifibranor 800 mg, 1200 mg, or placebo for 24 weeks. Circulating ADP levels were measured at baseline (BL) and end of treatment (EOT) in 211 patients; weight-based CMH analyses were performed in 217 completers. Patients were stratified by BL ADP level (< 5, 5–10, > 10 µg/mL) and by fold-change at EOT (< 1.5x, 1.5–4x, > 4x) and weight change (≤ 2.5%, 2.5–5% and > 5%). Glycemic, lipid, liver, and inflammatory markers, and hepatic steatosis (CAP and NASH-CRN) were compared across strata.

RESULTS

Mean Weight Increase At EOT

Weight at W24	Placebo	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor Pooled
N	73	71	73	144
Stable (≤ 2.5%)*	61 (84%)	41 (58%)	32 (44%)	73 (51%)
Increase (> 2.5%)*	12 (16%)	–	–	–
Increase (2.5% - 5%)	–	9 (13%)	14 (19%)	23 (16%)
Increase (> 5%)	–	21 (30%)	27 (37%)	48 (33%)

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

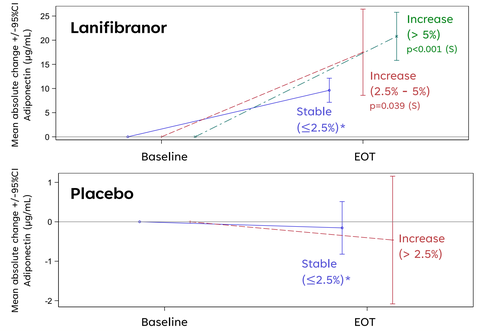
Mean weight increase at EOT was 2.4 (2.6%) and 2.7 (3.1%) kg for 800 and 1200 mg lanifibranor, respectively.

ADP Increase At EOT

Fold Adiponectin at W24	Placebo	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor Pooled
N	72	66	73	139
Mean (SD)	1.1 ± 0.3	3.8 ± 3.1	4.5 ± 3.5	4.2 ± 3.3
Median	1.0	2.8	3.5	3.0
(Min ; Max)	0.1; 2.5	0.8; 18.1	0.7; 17.4	0.7; 18.1
Unchanged	65 (90%)	9 (14%)	4 (5%)	13 (9%)
Fold (1.5 – 4)	7 (10%)	38 (58%)	38 (52%)	76 (55%)
Fold (> 4)	0 (0.0%)	19 (29%)	31 (42%)	50 (36%)

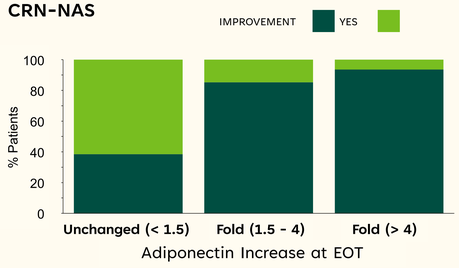
With lanifibranor, 87% of patients had an ADP increase at EOT vs only 10% of placebo patients; among placebo patients, all increases were < 4-fold.

Adiponectin Based on Weight Gain

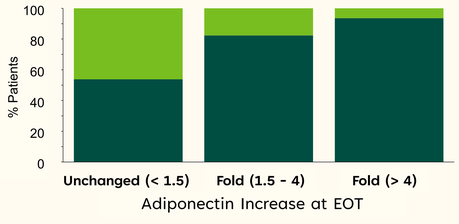


Adiponectin, a PPARγ downstream mediator, increased in all 3 weight change groups, with no correlation between ADP fold-change and magnitude of weight gain, indicating independence of these PPARγ-associated effects. In contrast placebo-treated patients showed no improvement in ADP even amongst those experiencing a > 2.5% weight gain.

CRN-NAS



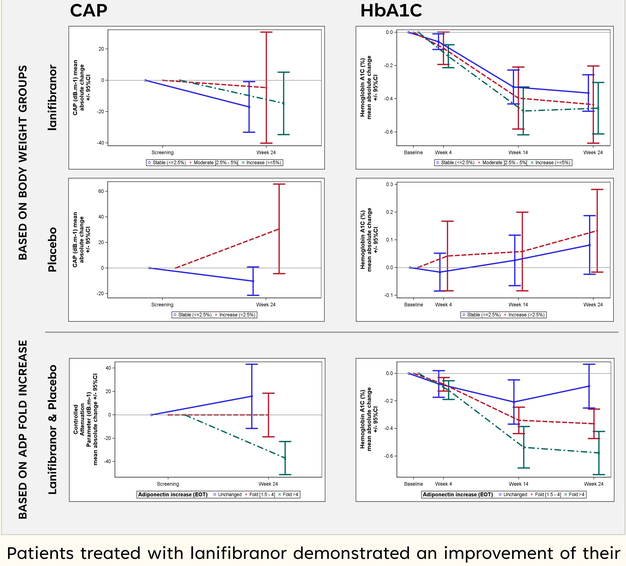
SAF-Activity



In the NATIVE study, the degree of adiponectin increase correlated with an improvement of MASH as measured by both CRN-NAS and SAF-Activity scores.

CAP

HbA1C



Change From Baseline In CMH Parameters At EOT Mean (Standard Deviation)

	WEIGHT CHANGE					ADIPONECTIN FOLD AT EOT		
	Lanifibranor			Placebo		Lanifibranor		
	Stable (≤ 2.5%)* N=73	Increase (2.5% - 5%) N=23	Increase (> 5%) N = 48	Stable (≤ 2.5%)* N = 61	Increase (> 2.5%) N = 12	Unchanged (< 1.5) N=13	Moderate (1.5 – 4) N=76	High (> 4) N=50
Glucose (mmol/L)	-0.86 (1.34)	-0.86 (0.81)	-0.65 (1.76)	0.26 (0.91)	0.04 (0.87)	0.20 (0.79)	-0.83 (1.33)	-1.01 (1.63)
Insulin (pmol/L)	-122.6 (226.2)	-98.1 (112.1)	-155.2 (352.9)	-24.8 (109.2)	46.9 (110.2)	-17.3 (64.3)	-115.4 (207.4)	-177.8 (342.1)
HOMA-IR	-5.6 (11.6)	-5.3 (5.8)	-5.3 (15.2)	-0.4 (4.7)	1.5 (4.4)	-0.50 (3.04)	-5.48 (10.72)	-7.20 (14.88)
Triglycerides (mmol/L)	-0.42 (0.97)	-0.44 (0.57)	-0.45 (0.60)	0.03 (1.02)	0.12 (0.71)	-0.23 (0.62)	-0.36 (0.96)	-0.59 (0.51)
Apolipoprotein B (APO-B) (mg/dL)	-9.66 (15.76)	-13.04 (25.36)	-14.56 (24.12)	-2.58 (13.08)	-0.08 (30.21)	-3 (24)	-9 (17)	-19 (22)
High-sensitivity C Reactive Protein (hs-CRP) (mg/L)	-0.55 (4.82)	-4.13 (7.61)	-2.65 (4.57)	0.63 (3.85)	-0.08 (2.06)	1.02 (6.63)	-1.73 (5.60)	-2.90 (4.82)
ALT (U/L)	-25 (48.46)	-26.0 (22.15)	-30.01 (40.18)	-2.48 (29.93)	20.92 (39.34)	11 (47)	-28 (46)	-35 (31)

Patients treated with lanifibranor demonstrated an improvement of their cardiometabolic health parameters irrespective of body weight gain. In contrast, patients in the placebo arm demonstrated a worsening of CMH parameters with an even greater worsening of key parameters such as HbA1c, triglycerides and HOMA-IR with comparable weight gain.

Lanifibranor induced a dose-dependent rise in ADP level associated with improvements in CMH markers independent of body-weight change. Patients with the highest increase in ADP saw the greatest improvement in CMH risk factors such as HbA1c, triglycerides and HOMA-IR.

CONCLUSIONS

Lanifibranor induced robust adiponectin increases that were associated with improvements in MASH histology and cardiometabolic health. These effects were independent of body-weight change. Although modest weight gain was observed with lanifibranor, it did not prevent improvement in MASH, fibrosis, or cardiometabolic parameters. The dose-dependent nature of adiponectin induction supports its role as a potential biomarker of lanifibranor pharmacodynamic activity and therapeutic response.

REFERENCES

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