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Lanifibranor improves markers of cardiometabolic health in patients with NASH and Type 2 Diabetes, correlated with responses in adiponectin levels

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Background / Objective

Lanifibranor, a pan-PPAR agonist, has shown efficacy on liver histology and metabolic-immune markers of NASH in the phase 2b NATIVE study.[1,2] PPAR signaling is involved in common pathways of NASH and type 2 diabetes (T2D). Adiponectin (ADP) is a pleiotropic adipokine which improves insulin resistance (IR), lipid metabolism, inflammation and fibrosis; low ADP levels are associated with risk for cardiovascular disease and NASH.

Methods and Material

NATIVE evaluated lanifibranor 800 and 1200 mg/d versus placebo (PBO) in 247 patients with non-cirrhotic NASH for 24 weeks of treatment. 103 patients had T2D, 144 did not have T2D of whom 47 had prediabetes defined by fasting glucose levels (FGL) between 5.6-6.9 mmol/l. ADP serum levels, metabolic-immune (glycemic control, IR, lipids, and systemic inflammation) and hepatic markers were measured at baseline (BL) and end of treatment (EOT). In each diabetic subgroup, we evaluated ADP at BL and ADP fold at EOT, and correlation between ADP change and response of markers.

Results (1/2)

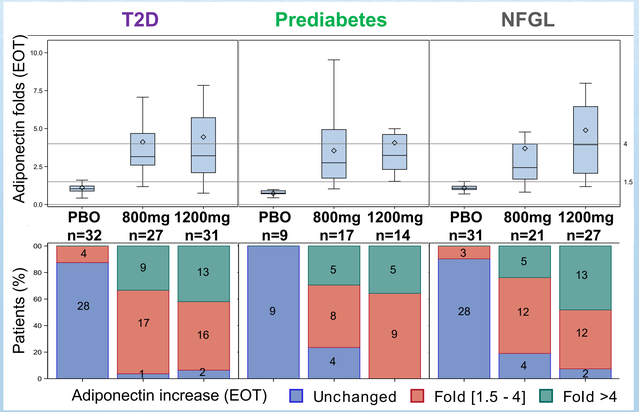
Baseline ADP levels were lower in patients with T2D compared to patients with prediabetes or normal FGL (NFGL).

Baseline ADP level	T2D N=103	Prediabetes N=47	NFGL N=94*
Mean ± SD	4.6 ± 2.8	5.5 ± 3.9	5.6 ± 4.0
<5	66 (65%)	29 (62%)	50 (54%)
[5 - 10]	30 (29%)	14 (30%)	33 (36%)
>10	6 (6%)	4 (9%)	9 (10%)

*3 patients with BL FGL>6.9mmol/L are not presented here

Results (2/2)

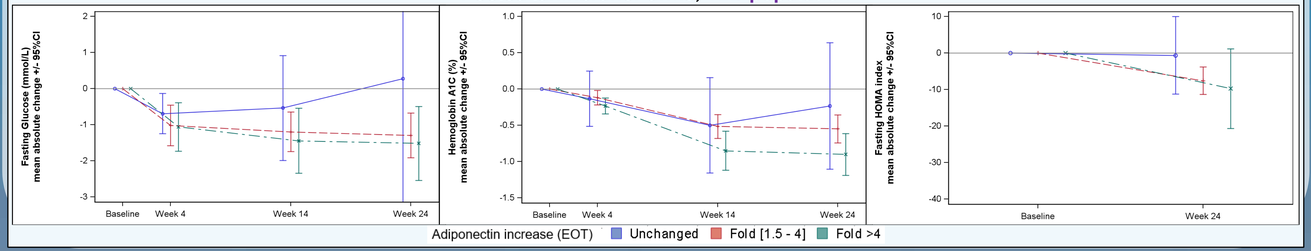
In the lanifibranor-treated group, ADP folds increase were similar in the 3 groups, with mean 4.3 folds, versus no increase in the placebo-treated group.



In the pooled lanifibranor arms, increase of ADP folds correlated with improvements in glycemic control, IR, lipid metabolism, and measures of systemic inflammation, consistently in the 3 groups, with higher improvements in patients with T2D and prediabetes compared to the NFGL group.

Fold Increase of Adiponectin at EOT		Pooled lanifibranor arms Absolute change at EOT (mean ± SD) T2D	Prediabetes	NFGL
FGL (mmol/L)	Unchanged <1.5 folds	0.28 ± 1.56	0.25 ± 0.86	0.13 ± 0.29
	Moderate [1.5 - 4] folds	-1.30 ± 1.71	-0.83 ± 0.83	-0.09 ± 0.47
	High >4 folds	-1.51 ± 2.31	-0.93 ± 0.65	-0.44 ± 0.46
HbA1c (%)	Unchanged <1.5 folds	-0.2 ± 0.4	0.0 ± 0.3	-0.1 ± 0.2
	Moderate [1.5 - 4] folds	-0.5 ± 0.5	-0.4 ± 0.4	-0.1 ± 0.2
	High >4 folds	-0.9 ± 0.6	-0.5 ± 0.3	-0.2 ± 0.2
Insulin (pmol/L)	Unchanged <1.5 folds	-23.8 ± 88.5	-25.6 ± 84.7	-6.8 ± 42.7
	Moderate [1.5 - 4] folds	-143.0 ± 191.1	-122.4 ± 101.0	-21.9 ± 81.8
	High >4 folds	-137.6 ± 220.7	-380.6 ± 635.6	-101.3 ± 105.5
HOMA-IR	Unchanged <1.5 folds	-0.63 ± 4.27	-0.76 ± 4.32	-0.21 ± 1.46
	Moderate [1.5 - 4] folds	-7.58 ± 10.14	-5.55 ± 4.32	-0.66 ± 2.85
	High >4 folds	-9.75 ± 22.59	-17.90 ± 29.19	-3.58 ± 3.95
AST (U/L)	Unchanged <1.5 folds	46 ± 76	-7 ± 17	21 ± 58
	Moderate [1.5 - 4] folds	-13 ± 19	-11 ± 32	-11 ± 17
	High >4 folds	-21 ± 34	-25 ± 45	-24 ± 40
ALT (U/L)	Unchanged <1.5 folds	43 ± 77	-9 ± 23	8 ± 42
	Moderate [1.5 - 4] folds	-23 ± 21	-21 ± 69	-32 ± 45
	High >4 folds	-34 ± 29	-44 ± 46	-30 ± 22
HDL cholesterol (mmol/L)	Unchanged <1.5 folds	-0.08 ± 0.16	-0.22 ± 0.30	0.12 ± 0.13
	Moderate [1.5 - 4] folds	0.16 ± 0.17	0.08 ± 0.22	0.10 ± 0.18
	High >4 folds	0.25 ± 0.25	0.19 ± 0.25	0.19 ± 0.18
Triglycerides (mmol/L)	Unchanged <1.5 folds	0.19 ± 0.51	-0.43 ± 0.22	-0.32 ± 0.80
	Moderate [1.5 - 4] folds	-0.52 ± 1.28	-0.21 ± 0.76	-0.20 ± 0.48
	High >4 folds	-0.58 ± 0.52	-0.76 ± 0.48	-0.50 ± 0.52
Apolipoprotein B (mg/dL)	Unchanged <1.5 folds	15 ± 24	-6 ± 27	-11 ± 21
	Moderate [1.5 - 4] folds	-10 ± 20	-9 ± 12	-7 ± 19
	High >4 folds	-15 ± 23	-27 ± 13	-19 ± 26
High-sensitivity C Reactive Protein (mg/L)	Unchanged <1.5 folds	7.77 ± 12.59	-2.47 ± 2.06	-0.02 ± 1.07
	Moderate [1.5 - 4] folds	-2.80 ± 6.23	-1.81 ± 6.39	-0.08 ± 3.82
	High >4 folds	-4.71 ± 6.60	-1.31 ± 1.86	-1.57 ± 1.95

Pooled lanifibranor arms, T2D population



Discussion & Conclusion

While PPARα and PPARδ agonists have demonstrated positive effects on HDL cholesterol, apolipoprotein B and CRP, those effects are not associated with an increase in ADP.[3] While other PPARs (through PPARδ) also improve IR and glycemia, lanifibranor, with its' additional effect on PPARγ has a further beneficial impact on these markers, as well as others as shown.

In the patients in this study, baseline ADP levels were low, and treatment with the pan-PPAR agonist lanifibranor significantly improved ADP levels.

This increase was correlated with improvement of markers of cardiometabolic health in patients with T2D and prediabetes.

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