Lanifibranor improves liver histology and markers of cardiometabolic health in patients with NASH independent of PNPLA3 genotype: a retrospective analysis of the NATIVE study

Louis H. Griffel[1], Sven M. Francque[2], Manal F. Abdelmalek[3], Philippe Huot-Marchand[1], Lucile Dzen[1], Martine Baudin[1], Jean-Louis Junien[1], Pierre Broqua[1], Michael P. Cooreman[1]

1 INVENTIVA, Daix, France. 2 Department of Gastroenterology and Hepatology, Antwerp University Hospital, Belgium. 3 Division of Gastroenterology and Hepatology and Surgical Pathology, Mayo Clinic and Foundation, Rochester, USA.

1-INTRODUCTION

A polymorphism of patatin-like phospholipase domain-containing protein 3 (PNPLA3), I148M, is strongly associated with the risk for and the progression of nonalcoholic steatohepatitis (NASH) **[1]**. Lanifibranor, a pan-PPAR agonist, has shown efficacy on histological disease activity and fibrosis as well as on metabolic-immune markers of NASH in the phase 2b NATIVE study, corresponding to the role of PPAR signaling in the disease biology of NASH. We evaluated the impact of the PNPLA3 variant I148M on the histologic and metabolic-immune response to lanifibranor.

2-MATERIAL/METHODS

NATIVE **[2]** evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients with non-cirrhotic NASH for 24 weeks of treatment. Of these, 219 patients consented to genotyping for the PNPLA3 rs738409 SNP. Sixty five were II, 105 IM and 49 MM, which is highest risk for disease severity and progression. Paired liver biopsy results were available for 207/219 patients. Histologic and metabolic-immune marker response was evaluated by PNPLA3 genotype.

3-RESULTS

PNPLA3 result	Placebo	Lanifibranor			Total
		800 mg	1200 mg	Pooled	
N	65	79	75	154	219
II	18 (28%)	25 (32%)	22 (29%)	47 (31%)	65 (30%)
IM	31 (48%)	38 (48%)	36 (48%)	74 (48%)	105 (48%)
MM	16 (25%)	16 (20%)	17 (23%)	33 (21%)	49 (22%)

There was no significant difference in demographics between the PNPLA3 types, although those with MM genotype were younger (mean age 50.9 vs 55.4 for II and 53.1 for IM) and were more likely to have Type 2 Diabetes (45% MM, 38% II, 41% IM).

Mean ± SD or n (%)	PNPLA3 II	PNPLA3 IM	PNPLA3 MM	Pvalue*
Age (years)	55.4 ± 10.2	53.1 ± 12.1	50.9 ± 15.0	0.32
Female	38 (59%)	62 (59%)	28 (57%)	0.98
White	62 (95%)	97 (92%)	47 (96%)	0.91
Patients with T2DM	25 (38%)	43 (41%)	22 (45%)	0.79
BMI (kg/m²)	32.7 ± 5.3	32.7 ± 5.3	32.5 ± 5.8	0.22

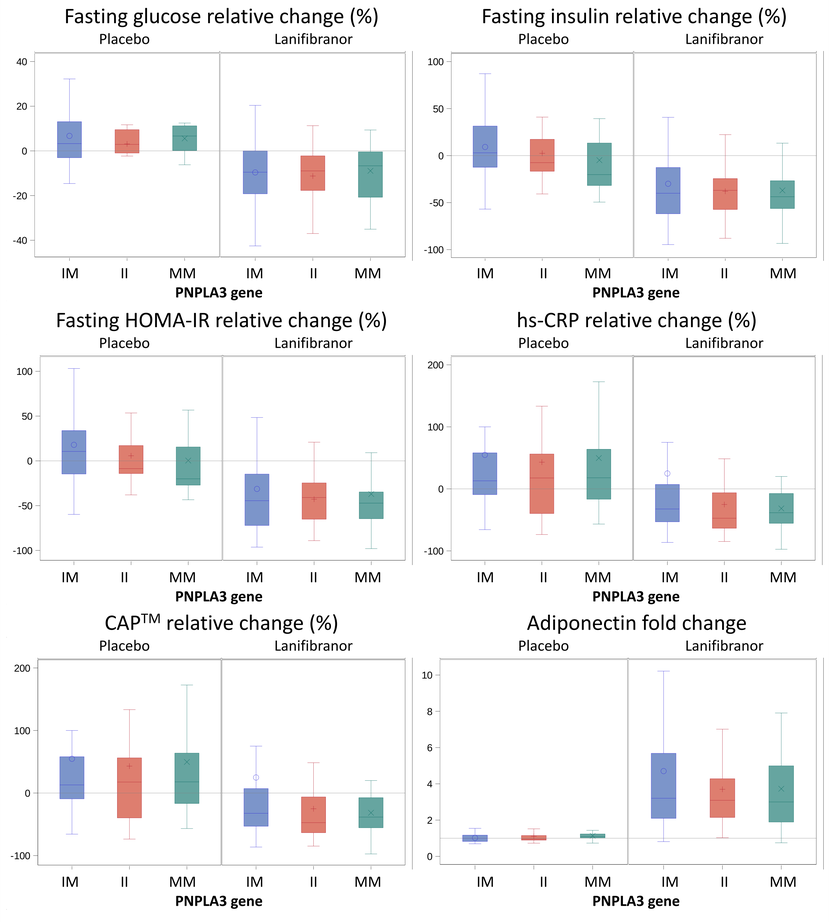
*ANOVA, Kruskal-Wallis, Chi² or Fisher test

Mean ± SD or n (%)	PNPLA3 II N=65	PNPLA3 IM N=105	PNPLA3 MM N=49	Pvalue*
Histology				
NAS score ≥ 6	48 (74%)	74 (70%)	40 (82%)	0.339
SAF-F 0/1/2/3 (n)	0/15/26/24	5/21/49/30	0/11/21/17	0.319
Glycemic control and Insulin resistance				
Glucose (mmol/L)	6.21 ± 1.62	5.90 ± 1.13	5.93 ± 1.84	0.379
Insulin (pmol/L)	236.0 ± 205.4	229.2 ± 270.1	260.1 ± 208.6	0.375
HOMA index	9.82 ± 9.71	9.10 ± 12.11	11.51 ± 16.33	0.499
HbA1c (%)	6.0 ± 0.7	6.1 ± 0.7	6.0 ± 0.7	0.626
Liver enzymes				
ALT (U/L)	52 ± 27	67 ± 49	64 ± 32	0.108
AST (U/L)	44 ± 24	51 ± 43	46 ± 20	0.443
GGT (U/L)	85 ± 124	79 ± 110	75 ± 121	0.486
Lipid metabolism and apolipoprotein levels				
Triglycerides (mmol/L)	1.96 ± 0.80	1.80 ± 1.00	2.05 ± 0.96	0.087
HDL (mmol/L)	1.22 ± 0.33	1.22 ± 0.30	1.20 ± 0.27	0.897
ApoA1 (mg/dL)	143 ± 23	146 ± 25	141 ± 23	0.334
ApoB (mg/dL)	112 ± 33	111 ± 30	107 ± 30	0.689
Adiponectin (µg/mL)	5.02 ± 3.54	5.35 ± 3.87	4.91 ± 2.34	0.761
Systemic inflammation				
Hs-CRP (mg/L)	5.66 ± 5.83	4.22 ± 4.21	5.64 ± 7.08	0.437
Ferritin (µg/L)	215 ± 164	265 ± 279	231 ± 239	0.745
NASH and fibrosis markers				
CK18M65 (µg/mL)	683.88 ± 613.43	904.74 ± 1090.65	713.76 ± 727.73	0.816
ProC3 (µg/L)	16.7 ± 8.4	17.1 ± 9.4	17.5 ± 7.5	0.582
ELF score	9.6 ± 0.9	9.7 ± 1.0	9.7 ± 1.1	0.728
Steatosis				
CAP (dB.m-1/L)	333 ± 44	330 ± 39	310 ± 53	0.131

There was no significant difference in response to lanifibranor by PNPLA3 genotype, despite the fact that MM genotype patients had more activity on biopsy than the II or IM patients (82% NAS≥6, vs 74%, 70%), while there was no difference in fibrosis.

		Overall	PNPLA3 II	PNPLA3 IM	PNPLA3 MM
NASH resolution AND fibrosis improvement	Placebo (N=65)	6 (9%)	2 (13%)	2 (8%)	2 (15%)
	Lanifibranor pooled (N=142)	42 (30%)	12 (27%)	21 (31%)	8 (31%)
NASH resolution and no worsening of fibrosis	Placebo (N=65)	15 (23%)	6 (38%)	5 (19%)	4 (31%)
	Lanifibranor pooled (N=142)	63 (44%)	18 (41%)	32 (48%)	11 (42%)
Improvement of fibrosis and no worsening of NASH	Placebo (N=65)	18 (28%)	4 (25%)	7 (27%)	3 (23%)
	Lanifibranor pooled (N=142)	56 (39%)	19 (43%)	24 (36%)	12 (46%)

Similarly, improvement of metabolic-immune markers for lanifibranor vs placebo was observed to the same degree in the 3 PNPLA3 genotypes including glycemic control, insulin, HOMA-IR, hs-CRP, CAP^{TM} and adiponectin.



4-CONCLUSION

The efficacy of lanifibranor on both liver histology and markers of cardiometabolic health appears to be independent of PNPLA3 status, despite MM genotype patients having more severe activity on liver biopsy.

References:

[1] R. Xu et al. Association between patatin-like phospholipase domain containing 3 gene (PNPLA3) polymorphisms and nonalcoholic fatty liver disease: a HuGE review and meta-analysis. *Scientific Rep* 2015;5:9284.

[2] S.M. Francque et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *N Engl J Med.* 2021;385:1547-58.

Contact information:

Vice President Clinical Development, INVENTIVA, Louis H. GRIFFEL: Louis.GRIFFEL@inventivapharma.com