The pan-PPAR agonist lanifibranor improves NonAlcoholic SteatoHepatitis (NASH) and glycemic control

MP. COOREMAN, [1], S. FRANCQUE[2], L. DZEN[1], P. HUOT-MARCHAND[1], JL. JUNIEN[1], MF. ABDELMALEK[3]

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

American Diabetes Association. 82ND SCIENTIFIC SESSIONS HYBRID | NEW ORLEANS | JUNE 3–7, 2022

Background / Objective

Lanifibranor therapy resulted in both NASH resolution and fibrosis reduction in the phase 2b NATIVE study in patients with non-cirrhotic NASH, compared to placebo. PPAR signaling is involved in common pathways of NASH and type 2 diabetes (T2D).

We evaluated the association between the effect of lanifibranor on glycemic control (GC) and NASH markers.

Methods and Material

NATIVE included 247 patients, randomized to lanifibranor 800, 1200 mg/d or placebo for 24 weeks of treatment; 228 patients completed the trial.

Efficacy in NASH was measured with SAF score (primary endpoint) and NASH-CRN grading and fibrosis staging.

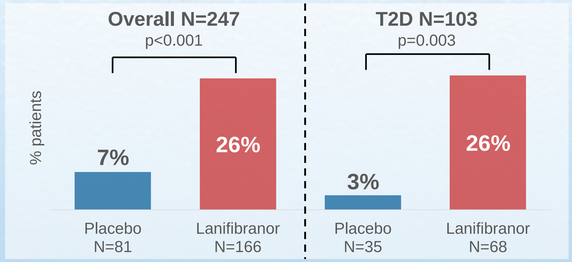
Biomarkers for insulin resistance (IR), GC, lipid metabolism, inflammation, liver enzymes and imaging of hepatic steatosis by continuous attenuation parameter (CAP) were analyzed at baseline (BL) and end of treatment (EOT).

Correlations between HbA1c (≤6, >6 - ≤7 and >7%) at BL and HbA1c change from BL to EOT with improvement in biomarkers and histologic features of NASH at EOT were assessed.

BL HbA1c	Placebo N=81	Lanifibranor N=166	800mg N=83	1200mg N=83
N	81	166	83	83
≤6%	51 (63%)	95 (57%)	47 (57%)	48 (58%)
>6% to ≤7%	23 (28%)	52 (31%)	25 (30%)	27 (33%)
>7%	7 (9%)	19 (11%)	11 (13%)	8 (10%)

Results

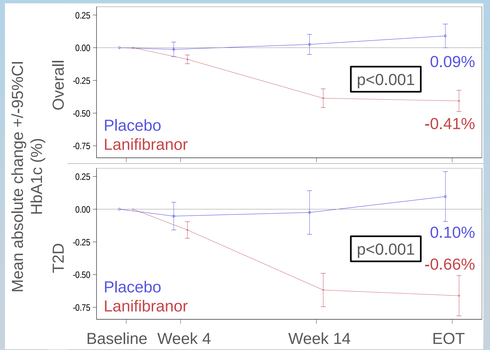
T2D was present in 103 (42%) patients.



The composite endpoint of NASH resolution and fibrosis improvement in the overall and T2D group for lanifibranor (pooled data) versus (vs) placebo was 26% vs 7% (p<0.001), and 26% vs 3% (p=0.003), respectively.

Irrespective of T2D status, lanifibranor improved fasting glucose (FG), IR, lipid metabolism, C-reactive protein, and liver enzymes (see REFERENCES).

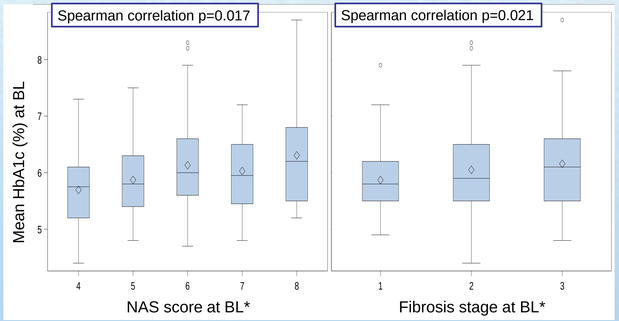
In contrast to placebo, lanifibranor improved HbA1c from BL in the overall and T2D groups, -0.41% and -0.66%, respectively



CI: Confidence interval

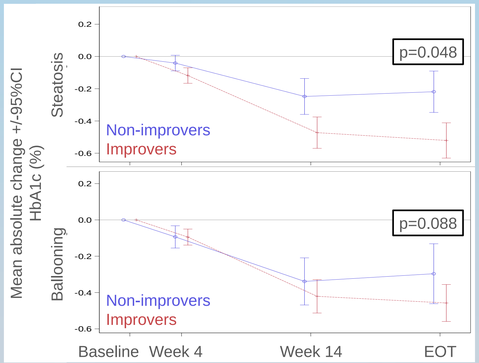
p: pvalue obtained from MMRM adjusted on baseline values

Using BL biopsies, BL HbA1c correlated with BL NASH activity and fibrosis.



* 2 patients with NAS=3 and 6 patients with Fibrosis stage=0 were not considered.

At time of the EOT (Week 24) biopsy in the lanifibranor group, greater HbA1c decrease was observed in steatosis and ballooning improvers versus non-improvers:



Under lanifibranor, HbA1c decrease at EOT correlated with improvement of FG, insulin, IR, liver enzymes, CAP, HDL-cholesterol, triglycerides (TG), ApoB, ApoB/ApoA1.

	FG	Insulin	IR	AST	ALT	GGT
Spearman p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	CAP	HDL-C	TG	ApoB	ApoB/ApoA1	
Spearman p-value	0.092	0.011	<0.001	0.008	0.002	

Conclusion or Discussion

Glycemic control correlates with NASH severity. The improvement of metabolic markers of NASH and hepatic steatosis with lanifibranor treatment is consistent with its beneficial effect on glycemic control.

References

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

S.M. Francque and al. Efficacy of the panPPAR agonist lanifibranor on the histological endpoints NASH resolution and fibrosis regression is similar in type-2 diabetic and non-diabetic patients: additional results of the NATIVE Phase 2b trial in non-cirrhotic NASH. *Poster presented at: AASLD 2020 Nov 13-17*

Financial Disclosures

Employees of Inventiva: MP. Cooreman, L.Dzen, P. Huot-Marchand, JL. Junien
Consultancy/Advisory Board: S. Francque, MF. Abdelmalek
Research Funding (paid to institution): MF. Abdelmalek, S. Francque
Stocks: None - *Patents/Inventions*: None - *Honorarium*: None

Contact

Dr. MP COOREMAN:
Michael.COOREMAN@inventivapharma.com

The authors thank all patients included in the trial, and all investigators and their staff