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

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1-INTRODUCTION

Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with superior efficacy over single PPAR agonists in pre-clinical models of NASH and fibrosis. Lanifibranor increased HDL-cholesterol and adiponectin, while decreasing insulin resistance and triglycerides (TG), hallmarks of differential PPAR α, β/δ and γ activation in a 4-week phase 2a study in diabetic patients. Diabetic patients are at risk of more severe NASH and fibrosis and treatment response can be different compared to non-diabetics. The NATIVE phase 2b trial (NCT03008070) in non-cirrhotic NASH patients demonstrated beneficial effects of lanifibranor treatment on several histological endpoints including NASH resolution and improvement of fibrosis. We report here that the effects of lanifibranor on the histological endpoints NASH resolution and fibrosis regression is similar in Type-2 diabetic patients and non-diabetic patients.

Trial design

Screening ▶ **Liver biopsy**

24-week treatment + 4-week follow-up
Double blind, randomized, placebo-controlled

- Placebo
- Lanifibranor, 800 mg once daily
- Lanifibranor, 1200 mg once daily

End of treatment ▶ **Liver biopsy**

- Randomisation 1/1/1
- Stratification on type 2 diabetes mellitus (T2DM)

▶ **Main inclusion criteria**: patients with biopsy-proven NASH confirmed by central reader having Steatosis-Activity-Fibrosis (SAF) scores of 1-3 for steatosis, 3-4 for activity, and <4 for fibrosis

Patient population	# patients	Definition
Safety / Intention-to-treat (ITT)	247	Patients randomized having received at least one dose of lanifibranor/placebo

2-Material/Methods

We here report the results of lanifibranor in the diabetic subpopulation of the NATIVE trial, a phase 2b double-blind randomised-controlled trial of lanifibranor in patients with biopsy proven, non-cirrhotic NASH, with a SAF activity score of 3-4. Patients were randomised 1:1:1 to receive placebo, 800 or 1200 mg of lanifibranor for 24 weeks and stratified according to diabetes status as defined by the Investigator.

3-RESULTS

Patient Baseline Demographics and Characteristics:

Diabetics (N=103)

Parameter (unit) n (%) or mean ± SD		Placebo N = 35	Lanifibranor 800 mg/day N = 33	Lanifibranor 1200 mg/day N = 35	Overall N = 103
Demographics	Female	21 (60.0%)	23 (69.7%)	18 (51.4%)	62 (60.2%)
	Age (years)	56.6 ± 12.4	57.1 ± 8.1	55.3 ± 10.2	56.3 ± 10.3
	White	33 (94.3%)	32 (97.0%)	34 (97.1%)	99 (96.1%)
	Body Mass Index (kg/m²)	33.9 ± 5.3	32.4 ± 5.5	33.2 ± 5.5	33.1 ± 5.4
Liver biopsy characteristics					
	SAF Activity score (inflammation + ballooning)	3.3 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	3.3 ± 0.5
	NAFLD Activity Score (NAS)	5.9 ± 1.3	6.2 ± 0.8	6.1 ± 0.7	6.0 ± 1.0
	Fibrosis stage F2/F3	27 (77.1%)	27 (81.8%)	29 (82.9%)	83 (80.6%)
Liver enzymes	ALT (U/L)	57.7 ± 34.8	62.6 ± 35.0	58.0 ± 27.1	59.4 ± 32.2
	AST (U/L)	41.9 ± 23.5	53.1 ± 37.5	43.4 ± 22.2	46.0 ± 28.5
	GGT (U/L)	60.5 ± 41.9	123.7 ± 168.1	68.4 ± 107.0	83.4 ± 118.5
Plasma lipids levels	HDL-C (mmol/L)	1.1 ± 0.2	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.2
	Triglycerides (mmol/L)	2.2 ± 0.8	2.2 ± 1.2	2.1 ± 1.0	2.1 ± 1.0
Glucose metabolism					
	Fasting Glucose (mmol/L)	6.9 ± 2.0	7.3 ± 2.2	6.6 ± 1.2	6.9 ± 1.8
	HbA1c (%)	6.5 ± 0.7	6.7 ± 0.8	6.6 ± 0.7	6.6 ± 0.7
	Insulin (pmol/L)	222.7 ± 186.5	246.3 ± 213.4	278.5 ± 233.5	249.5 ± 211.3

Non-Diabetics (N=144)

Parameters (unit) n (%) or mean ± SD		Placebo N = 46	Lanifibranor 800 mg/day N = 50	Lanifibranor 1200 mg/day N = 48	Overall N = 144
Demographics	Female	20 (43.5%)	31 (62.0%)	31 (64.6%)	82 (56.9%)
	Age (years)	51.2 ± 13.4	53.6 ± 11.6	50.0 ± 15.6	51.6 ± 13.6
	White	41 (89.1%)	48 (96.0%)	44 (91.7%)	133 (92.4%)
	Body Mass Index (kg/m²)	32.1 ± 4.9	32.5 ± 5.6	33.3 ± 5.8	32.7 ± 5.4
Liver biopsy characteristics					
	SAF Activity score (inflammation + ballooning)	3.3 ± 0.5	3.2 ± 0.4	3.3 ± 0.5	3.2 ± 0.5
	NAFLD Activity Score (NAS)	5.9 ± 1.0	5.7 ± 1.0	5.9 ± 1.1	5.8 ± 1.0
	Fibrosis stage F2/F3	30 (65.2%)	41 (82.0%)	34 (70.8%)	105 (72.9%)
Liver enzymes	ALT (U/L)	66.3 ± 29.3	65.0 ± 45.4	67.7 ± 52.2	63.1 ± 43.5
	AST (U/L)	44.4 ± 24.7	54.5 ± 47.3	44.2 ± 26.8	47.8 ± 34.9
	GGT (U/L)	73.5 ± 100.4	86.9 ± 129.4	66.1 ± 82.6	75.7 ± 106.0
Plasma lipids levels	HDL-C (mmol/L)	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3
	Triglycerides (mmol/L)	1.8 ± 0.7	1.7 ± 0.6	1.9 ± 0.9	1.8 ± 0.7
Glucose metabolism					
	Fasting Glucose (mmol/L)	5.3 ± 0.6	5.5 ± 0.92	5.3 ± 0.7	5.4 ± 0.8
	HbA1c (%)	5.6 ± 0.4	5.7 ± 0.5	5.7 ± 0.4	5.6 ± 0.4
	Insulin (pmol/L)	242.3 ± 296.4	222.4 ± 178.2	271.9 ± 376.51	245.0 ± 291.6

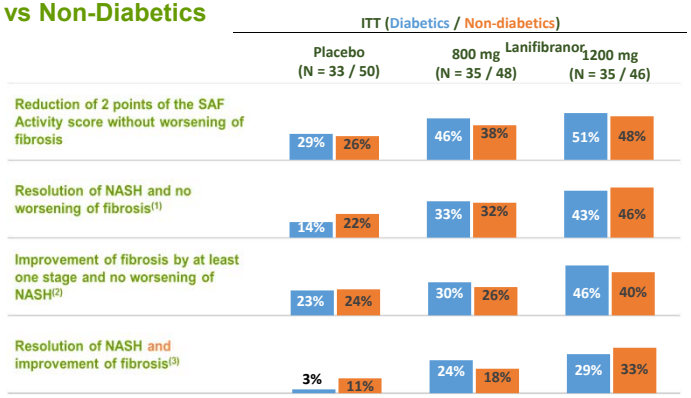
Baseline demographics and characteristics are similar in the treatment groups

Antidiabetic treatments in Diabetics

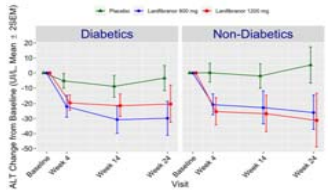
		Lanifibranor 800 mg (N=33)	Lanifibranor 1200 mg (N=35)	Placebo (N=35)	All (N=103)
Metformin at baseline	n (%)	27 (81.8%)	29 (82.9%)	29 (82.9%)	85 (82.5%)
Sulphonylurea at baseline	n (%)	8 (24.2%)	7 (20.0%)	8 (22.9%)	23 (22.3%)
DPP4i at baseline	n (%)	2 (6.1%)	4 (11.4%)	5 (14.3%)	11 (10.7%)
SGLT2 at baseline	n (%)	1 (3.0%)	0 (0.0%)	6 (17.1%)	7 (6.8%)
Main combinations (>5% overall)					
No antidiabetic treatment	n (%)	*5 (15.2%)*	*5 (14.3%)*	*3 (8.6%)*	*13 (12.6%)*
Metformin	n (%)	19 (57.6%)	21 (60.0%)	15 (42.9%)	55 (53.4%)
Metformin + Sulphonylurea	n (%)	5 (15.2%)	4 (11.4%)	5 (14.3%)	14 (13.6%)
Metformin + DPP4i	n (%)	1 (3.0%)	2 (5.7%)	3 (8.6%)	6 (5.8%)
Statins	n (%)	8 (24.2%)	13 (37.1%)	9 (25.7%)	30 (29.1%)

Antidiabetic concomitant medications are similar in the three treatment groups

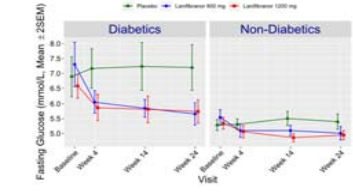
Histological endpoints: Similar Improvement in Diabetics vs Non-Diabetics



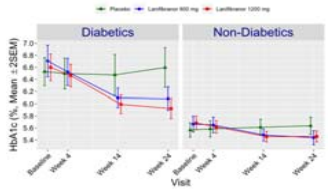
ALT



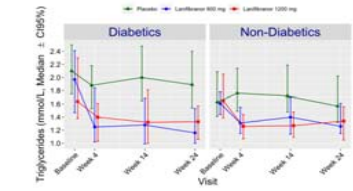
Fasting Glucose



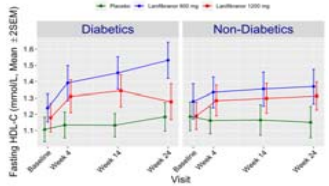
HbA1c



Triglycerides



HDL-C



- ALT decrease on Lanifibranor starting at week 4: similar pattern in diabetics and non-diabetics
- In the 103 T2DM patients, there was a reduction in fasting glucose starting at week 4 (lowest median decrease among both doses: 0.7 mmol/L) on lanifibranor
- HbA1c decrease starting at week 14 (lowest median decrease: 0.5%) and confirmed at all different time points onwards for both lanifibranor doses
- In diabetics and non-diabetics TG decrease on all time points from week 4 onwards, for both lanifibranor doses.
- Median HDL-c increase was > 8% on all time points from week 4 onwards, for both lanifibranor doses.

4-CONCLUSION

In the T2DM subpopulation of NATIVE,

- Lanifibranor produced major improvements in key histological endpoints (including both resolution of NASH and regression of fibrosis) after 24 weeks of treatment similar to non-diabetic patients.
- Furthermore, clinically significant improvements in parameters of glycaemic control and in lipid profile were already observed after 4 weeks.

Lanifibranor is hence a promising drug for NASH treatment in both non-diabetic and diabetic patients

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