Lanifibranor reverses fasting glucose levels to normoglycemia in prediabetic patients with nonalcoholic steatohepatitis (NASH)

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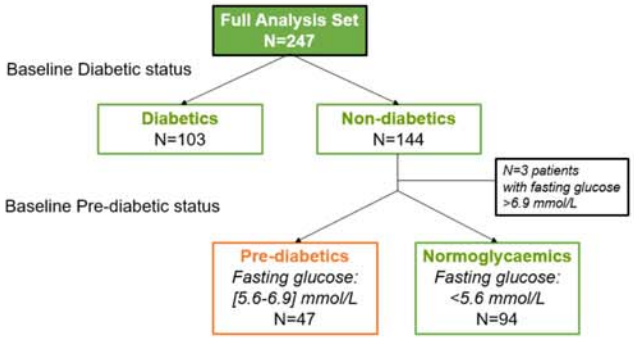
1-INTRODUCTION

NASH is associated with manifestations of metabolic syndrome that share a common disease biology, including type 2 diabetes (T2D) and cardiovascular disease (CVD). Patients with prediabetes also have an increased risk for CVD. Reversal of prediabetes diminishes the risk for subsequent T2D and therefore may also reduce the risk for CVD. We report the effect of the pan-PPAR agonist lanifibranor on markers of glucose metabolism in prediabetic patients enrolled in the phase 2b NATIVE trial.

2-MATERIAL/METHODS

NATIVE included 247 patients with non-cirrhotic NASH who were randomized to lanifibranor 800, 1200 mg/d or placebo, for a treatment duration of 24 weeks; 144 (58%) did not have overt type 2 diabetes.

At baseline, among the non-diabetic patients, 47 (33%) had prediabetes defined by fasting glucose levels (FGL) between 5.6 – 6.9 mmol/L, and 94 (65%) had normoglycemia (FGL < 5.6 mmol/L).



Of the 47 prediabetic patients, 20, 16 and 11 patients received lanifibranor 800 and 1200 mg/d and placebo, respectively. Markers of glucose metabolism measured at baseline and at end of treatment (EOT) included FGL, fasting insulin levels (FIL), HbA1c and HOMA insulin resistance (IR).

3-RESULTS

Change from baseline in prediabetic status at EOT in non-diabetics

At baseline: Pre-diabetics / Normoglycemic patients

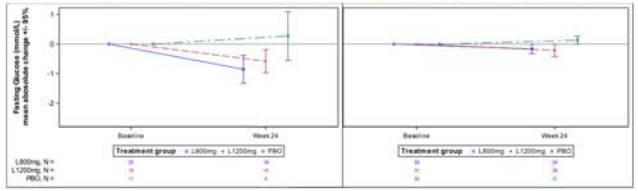
Fasting glucose (EOT)	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
N	9	18	14	31	24	28
<5.6 mmol/L	1 (11%)	12 (67%)	10 (71%)	23 (74%)	24 (100%)	28 (100%)
[5.6-6.9] mmol/L	6 (67%)	5 (28%)	4 (29%)	8 (26%)	0 (0%)	0 (0%)
>6.9 mmol/L	2 (22%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Among the subgroup of 41 patients with prediabetes at baseline who completed treatment, 67% and 71% in the lanifibranor 800 and 1200mg/d arms reversed to normoglycemia at EOT, versus 11% in the placebo arm. Conversely, among the 83 patients with normoglycemia at baseline who completed treatment, 0% in the lanifibranor 800 and 1200mg/d arms progressed to prediabetes at EOT, versus 26% in placebo arm.

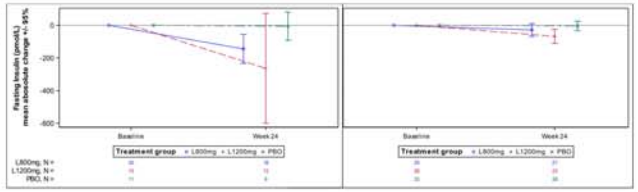
Absolute changes from baseline in glucose metabolism markers at EOT in non-diabetics

Pre-diabetics / Normoglycemic patients

Fasting glucose



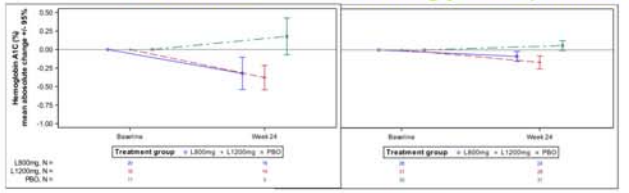
Fasting insulin



Insulin levels status (EOT)	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
N	8	18	14	30	24	26
Abnormal (>173 pmol/L)	5 (63%)	4 (22%)	2 (14%)	11 (37%)	4 (17%)	2 (8%)
Normal (≤173 pmol/L)	3 (37%)	14 (78%)	12 (86%)	19 (63%)	20 (83%)	24 (92%)

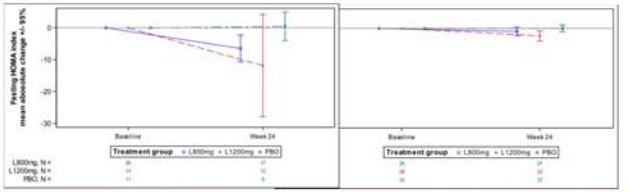
Pre-diabetics / Normoglycemic patients

HbA1c



HbA1c (EOT)	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
N	9	18	14	31	24	28
Abnormal (>6.5%)	5 (56%)	1 (6%)	1 (7%)	2 (7%)	0 (0%)	0 (0%)
Normal (≤6.5%)	4 (44%)	17 (94%)	13 (93%)	29 (93%)	24 (100%)	28 (100%)

HOMA IR



HOMA-IR (EOT)	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
N	8	17	14	28	24	26
Abnormal (>3)	8 (100%)	13 (77%)	11 (79%)	23 (82%)	14 (58%)	11 (42%)
Normal (≤3)	0 (0%)	4 (23%)	3 (21%)	5 (18%)	10 (42%)	15 (58%)

Decrease in glucose metabolism parameters was consistently higher in the prediabetic population compared to the normoglycemic population.

4-CONCLUSION

- The effect size on reversal to normoglycemia and improvement of insulin resistance suggest a therapeutic benefit of lanifibranor on glucose metabolism in prediabetic patients with NASH that warrants further study. These data also further support the relevance of screening patients with NASH for both overt T2D and prediabetes.
- Effective interventions on pre-diabetics can prevent or delay the vast majority of diabetics and its morbid complications.

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