

Treatment Response to the pan-PPAR agonist Lanifibranor in the NATIVE Study: NASH Resolution and Fibrosis Improvement are correlated

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1-INTRODUCTION

Lanifibranor met both efficacy endpoints 'resolution of nonalcoholic steatohepatitis (NASH)' and 'improvement of fibrosis' in the phase 2b NATIVE study for patients with non-cirrhotic NASH. Given the biologically plausible link between steatosis, inflammation, ballooning and fibrogenesis, we evaluated the correlation between NASH activity score (NAS) and its components and fibrosis staging.

2-MATERIAL/METHODS

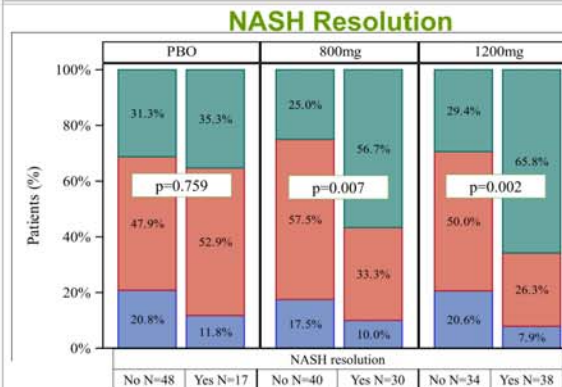
NATIVE demonstrated both NASH resolution and improvement of fibrosis in 24.3%, 34.7% and 9.2% of patients for lanifibranor 800, 1200 mg/d and placebo after 24 weeks of treatment. An analysis of pre- and post-treatment biopsies (n=207) was performed to test the hypothesis that improvement in severity of NASH is associated with improvement in fibrosis. The presence and severity of NASH and individual components, and fibrosis stage were determined according to NASH CRN criteria. Biopsies were read serially by one pathologist, who was unaware of the time point (pre- or post-treatment) and treatment allocation. Fibrosis change from baseline (worsening, no change or improvement) was analyzed by treatment group between NASH resolution responders vs non-responders, and similarly for steatosis, inflammation and ballooning, and association was assessed using a Chi² test.

3-RESULTS (1)

Histological characteristics at baseline

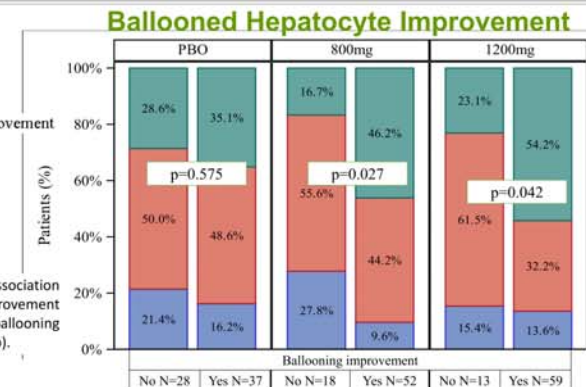
	Mean ± SD	Lanifibranor		Placebo N=65	Overall N=207
		800mg N=70	1200mg N=72		
Steatosis	Mean ± SD	2.6 ± 0.7	2.6 ± 0.6	2.5 ± 0.7	2.5 ± 0.7
Ballooning	Mean ± SD	1.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
Inflammation	Mean ± SD	1.6 ± 0.6	1.5 ± 0.6	1.6 ± 0.7	1.6 ± 0.6
NAS score	Mean ± SD	5.9 ± 1.0	5.9 ± 1.0	5.9 ± 1.1	5.9 ± 1.0
NAS score in class	≥6	53 (76%)	51 (71%)	45 (69%)	149 (72%)
Fibrosis score	Mean ± SD	2.1 ± 0.8	2.1 ± 0.8	2.0 ± 0.9	2.0 ± 0.8
Fibrosis score in class	Stage 0	2 (3%)	1 (1%)	3 (5%)	6 (3%)
	Stage 1	10 (14%)	18 (25%)	17 (26%)	45 (22%)
	Stage 2	36 (51%)	28 (39%)	25 (38%)	89 (43%)
	Stage 3	22 (31%)	25 (35%)	20 (31%)	67 (32%)

3-RESULTS (2)



Fibrosis change:
■ Worsening ■ No change ■ Improvement

P-values assessing the association between fibrosis improvement (Yes, No) and NASH resolution (Yes, No).

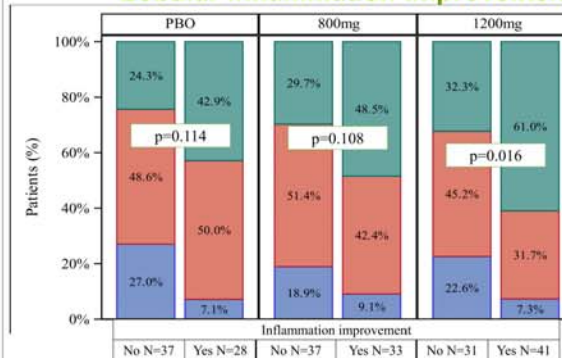


P-values assessing association between fibrosis improvement (Yes, No) and ballooning improvement (Yes, No).

NASH resolution responders were significantly more likely to be fibrosis improvers than non-improvers for lanifibranor arms, but not with placebo.

Ballooned hepatocyte improvers were significantly more likely to be fibrosis improvers than non-improvers for both lanifibranor arm, but not with placebo.

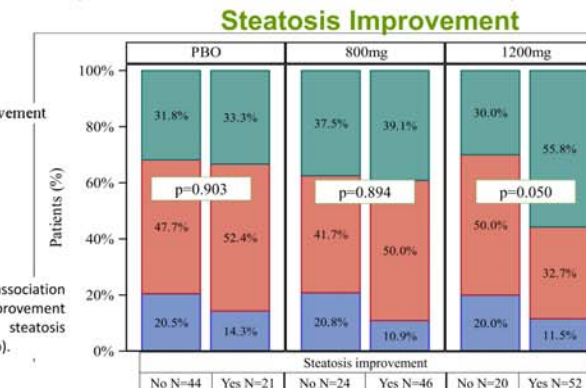
Lobular Inflammation Improvement



Fibrosis change:
■ Worsening ■ No change ■ Improvement

P-values assessing association between fibrosis improvement (Yes, No) and inflammation improvement (Yes, No).

Inflammation improvers were significantly more likely to be fibrosis improvers than non-improvers in lanifibranor 1200 mg, but not for lanifibranor 800 mg and placebo.



P-values assessing association between fibrosis improvement (Yes, No) and steatosis improvement (Yes, No).

Steatosis improvers were significantly more likely to be fibrosis improvers than non-improvers for lanifibranor 1200 mg, but not for 800 mg and placebo.

4-CONCLUSION

With lanifibranor 800 or 1200 mg, NASH resolution and improvement in ballooned hepatocytes are associated with improvement in hepatic fibrosis. These analyses support a biologically link between NASH resolution and fibrosis. The specific pathogenic link between ballooned hepatocytes and fibrosis warrants further investigation.

Contact information

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