THE PANPPAR AGONIST LANIFIBRANOR INDUCES BOTH RESOLUTION OF NASH AND REGRESSION OF FIBROSIS AFTER 24 WEEKS OF TREATMENT IN NON-CIRRHOTIC NASH: RESULTS OF THE NATIVE PHASE 2b TRIAL

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Background: In NASH, disease progression results from a complex interplay of intra- and extra-hepatic processes encompassing metabolic (adipose tissue dysfunction, insulin resistance), inflammatory and fibrogenic pathways. Successful treatment most likely needs a multi-targeted approach. Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors with key regulatory functions in metabolism, inflammation and fibrogenesis. Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with a broader and superior efficacy over single and dual PPAR agonists in various pre-clinical models.

Methods: NATIVE (NCT03008070) was a phase 2b double-blind randomised-controlled trial of lanifibranor in patients with biopsy proven, non-cirrhotic, highly active NASH (a SAF Activity score of 3-4). Patients were randomised 1:1:1 to receive once daily placebo, 800 or 1200 mg of lanifibranor for 24 weeks. The primary endpoint was a ≥2 point reduction in SAF Activity score. Secondary endpoints were NASH resolution and fibrosis regression.

Results: 247 patients were randomised: mean age 54y, mean BMI 32.9 kg/m^2, 42% males, 42% diabetes, 76% F2/F3 and 73% NAFLD Activity Score (NASH CRN) ≥6. Lanifibranor met the primary endpoint at 1200 mg/day and also all key secondary endpoints including: NASH resolution without worsening of fibrosis and regression of ≥1 stage of fibrosis without worsening of NASH (Table). The combined endpoint of resolution of NASH plus regression of fibrosis was also significantly met for both treatment arms. Both doses significantly and sustainably improved liver enzymes starting at week 4. In diabetics, both doses significantly reduced HbA1c by > 0.5%. Both doses also equally and significantly increased HDL cholesterol and decreased serum triglycerides. Lanifibranor showed a favourable safety profile with a low drop-out rate (<5%) of for adverse events comparable to placebo. A mean weight increase of 2.4 and 2.7 kg in the 800 and 1200 mg arms respectively was noted, compared to no significant weight change on placebo.

Conclusion: In this large Phase 2b trial of patients with active NASH, lanifibranor, a panPPAR agonist, significantly improved key histological endpoints as well as glycaemic control and lipid profile after only 24 weeks of treatment. Most notably, lanifibranor also met the combined endpoint of resolution of NASH and concomitant regression of fibrosis. The favourable safety profile further places lanifibranor as a promising drug for NASH treatment.

Intention to Treat Population	Placebo N=81	800 mg N=83	1200 mg N=83
Reduction of 2 points of the SAF Activity score with no worsening of fibrosis (%, p value)	27%	41% (NS)	49% (S**)
Resolution of NASH with no worsening of fibrosis (%, p value)	19%	33% (S*)	45% (S***)
Improvement of fibrosis with no worsening of NASH (%, p value)	24%	28% (NS)	42% (S**)
Resolution of NASH and improvement of fibrosis (%, p value)	7%	21% (S*)	31% (S***)

S*: p<0.05, S**: p<0.01, S***: P<0.001