# Effect of the panPPAR agonist lanifibranor on plasma biomarkers of liver necro-inflammation and fibrosis in non-cirrhotic NASH patients: additional results of the NATIVE Phase 2b trial.

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## 1-INTRODUCTION

Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with anti-inflammatory and anti-fibrotic effects in pre-clinical models of NASH. 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 the effects of lanifibranor on plasma biomarkers of liver necro-inflammation and fibrosis measured during the NATIVE trial.

### 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 |
|---|---|---|
| Full Analysis Set (FAS)=Safety set | 247 | Patients randomized having received at least one dose of lanifibranor/placebo |

## 2-Material/Methods

Blood samples were taken at baseline and week 24. The following biomarkers were measured: the collagen neo-epitope Pro-C3 (Nordic Bioscience using ELISA), MMP2 and TIMP1 (BARC using Mesoscale and CMIA, respectively), Hs-CRP and ferritin (BARC using turbidimetry and ECLIA, respectively) and CK18-M30 (BARC using ELISA). For each biomarker, the patients with values available pre-treatment (baseline) and post-treatment (week 24) were considered. The two doses of lanifibranor were pooled in the treatment group. Mean values at baseline and week 24, mean absolute change, mean and median relative changes from baseline at week 24 were described in the placebo and treatment groups. Relative changes in treatment group vs. placebo were compared using Student's t-test or Wilcoxon signed rank test.

## 3-RESULTS

### Main histological secondary endpoints

FAS (N=247)*

Statistically significant / Non-statistically significant

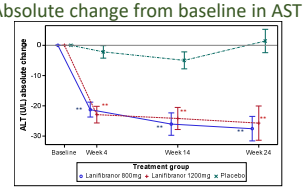
| | Placebo (N = 81) | Lanifibranor 800 mg (N = 83) | Lanifibranor 1200 mg (N = 83) |
|---|---|---|---|
| Resolution of NASH and no worsening of fibrosis[1] | 19% | 33% (0.043) | 45% (<0.001) |
| Improvement of fibrosis by at least one stage and no worsening of NASH[2] | 24% | 28% (0.530) | 42% (0.011) |
| Resolution of NASH and improvement of fibrosis[3] | 7% | 21% (0.017) | 31% (<0.001) |

Similar results in the PP population, Consistent response in diabetic and non-diabetic patients, See Poster LP9

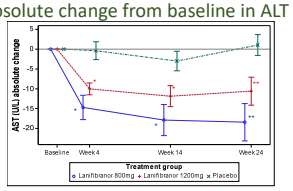
- (1) Resolution of NASH with no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline;
- (2) Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24;
- (3) Resolution of NASH and improvement of fibrosis at week 24: NAS-I = 0 or 1, NAS-B = 0 and an improvement of NAS-F ≥ 1 stage
- P-values -values were calculated using Cochran Mantel Haenszel test to assess lanifibranor's effect versus placebo, stratified on T2DM status
- * Missing biopsies are considered Non-responders

### Effect of lanifibranor in liver enzymes in FAS (n=247)

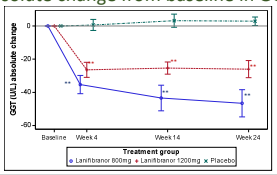
Absolute change from baseline in AST




Absolute change from baseline in ALT




Absolute change from baseline in GGT




▶ Statistically significant decrease of ALT, AST and GGT in both lanifibranor dose groups observed beginning after 4 weeks

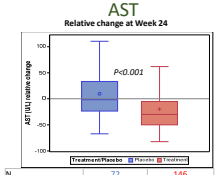
* p<0.01 **p<0.001

### Baseline and week 24 table

| | Placebo | | | | | Lanifibranor | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | | Week 24 | | | Baseline | | Week 24 | |
| | N | Mean ± SD | Median | Mean ± SD | Median | N | Mean ± SD | Median | Mean ± SD | Median |
| AST (U/L) | 72 | 41.5 ± 22.2 | 35.0 | 42.5 ± 25.6 | 37.5 | 146 | 48.5 ± 34.7 | 39.5 | 34.0 ± 29.3 | 26.5 |
| ALT (U/L) | 72 | 54.4 ± 31.1 | 43.5 | 55.8 ± 38.7 | 42.0 | 146 | 63.2 ± 41.7 | 52.0 | 36.6 ± 34.6 | 25.5 |
| ALT/AST ratio | 72 | 1.36 ± 0.45 | 1.3 | 1.33 ± 0.45 | 1.3 | 146 | 1.36 ± 0.46 | 1.3 | 1.05 ± 0.39 | 1.0 |
| PRO-C3 (ug/L) | 69 | 15.8 ± 8.2 | 13.2 | 15.4 ± 8.7 | 11.9 | 137 | 17.5 ± 9.2 | 14.9 | 14.5 ± 5.8 | 12.8 |
| PRO-C3 (ug/L) > 14 ug/L at baseline | 28 | 23.1 ± 8.2 | 21.0 | 22.0 ± 10.1 | 19.1 | 79 | 22.0 ± 9.8 | 18.3 | 16.4 ± 6.0 | 14.6 |
| TIMP1/MMP2 ratio | 66 | 3.5 ± 1.3 | 3.2 | 3.4 ± 0.9 | 3.3 | 135 | 3.4 ± 1.0 | 3.3 | 2.7 ± 0.9 | 2.6 |
| Cytokeratin M30 (pmol/L) | 69 | 701.6 ± 509.0 | 571.6 | 710.0 ± 562.3 | 589.0 | 135 | 954.9 ± 809.5 | 729.1 | 564.7 ± 576.4 | 352.2 |
| Ferritin (µg/L) | 73 | 267.0 ± 240.3 | 205.0 | 263.2 ± 259.4 | 183.0 | 145 | 240.4 ± 241.5 | 179.0 | 167.6 ± 174.6 | 115.0 |
| Hs-CRP (mg/L) - High Sensitivity | 72 | 4.1 ± 4.4 | 3.2 | 4.6 ± 5.6 | 3.0 | 146 | 5.1 ± 5.7 | 3.2 | 3.3 ± 4.0 | 2.0 |

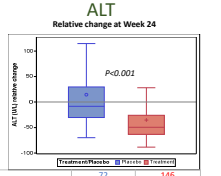
### Effect of lanifibranor in plasma liver enzyme and biomarkers

AST — Relative change at Week 24



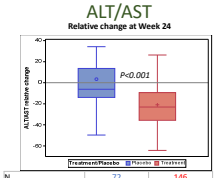

| | Placebo | Treatment |
|---|---|---|
| N | 72 | 146 |
| Mean % change ± SD | 9.70 ± 48.72 | -19.81 ± 56.42 |
| Median % change | -1.8 | -29.9 |
| Min ; Max | [-67.2 ; 161.5] | [-82.4 ; 439.1] |

ALT — Relative change at Week 24



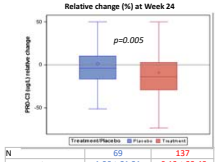

| | Placebo | Treatment |
|---|---|---|
| N | 72 | 146 |
| Mean % change ± SD | 14.48 ± 106.21 | -35.36 ± 62.66 |
| Median % change | -8.2 | -49.6 |
| Min ; Max | [-70.1 ; 808.3] | [-88.6 ; 565.8] |

ALT/AST — Relative change at Week 24



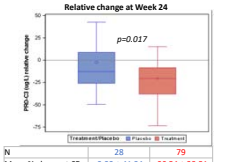

| | Placebo | Treatment |
|---|---|---|
| N | 72 | 146 |
| Mean % change ± SD | 3.37 ± 52.54 | -21.01 ± 21.39 |
| Median % change | -6.2 | -23.2 |
| Min ; Max | [-62.5; 390.5 | [-64.4; 46.9 |

Pro-C3 — Relative change (%) at Week 24



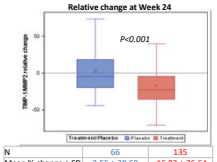

| | Placebo | Treatment |
|---|---|---|
| N | 69 | 137 |
| Mean % change ± SD | 1.06 ± 31.21 | -9.12 ± 33.48 |
| Median % change | -4.1 | -13.9 |
| Min ; Max | [-51.2 ; 168.2] | [-73.5 ; 137.3] |

Pro-C3 >14 at baseline — Relative change at Week 24



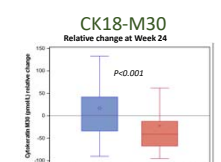

| | Placebo | Treatment |
|---|---|---|
| N | 28 | 79 |
| Mean % change ± SD | -2.33 ± 41.84 | -20.54 ± 28.51 |
| Median % change | -12.8 | -20.5 |
| Min ; Max | [-49.5 ; 168.2] | [-73.5 ; 136.8] |
| Patients at week 24 with Pro-C3<=14µg/l | N=5 (18%) | N=36 (46%) |
| Patients at week 24 with Pro-C3 > 14µg/l | N=23 (82%) | N=43 (54%) |

TIMP-1/MMP-2 — Relative change at Week 24



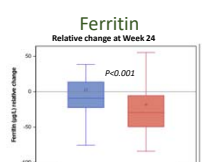

| | Placebo | Treatment |
|---|---|---|
| N | 66 | 135 |
| Mean % change ± SD | 2.55 ± 30.68 | -16.82 ± 26.64 |
| Median % change | -4.6 | -22.5 |
| Min ; Max | [-43.8 ; 87.4] | [-70.4 ; 97.1] |

CK18-M30 — Relative change at Week 24



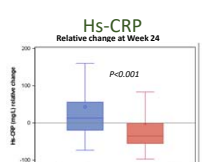

| | Placebo | Treatment |
|---|---|---|
| N | 69 | 135 |
| Mean % change ± SD | 16.85 ± 80.56 | -22.15 ± 71.78 |
| Median % change | 0.5 | -41.1 |
| Min ; Max | [-90.4 ; 351.1] | [-95.8 ; 327.0] |

Ferritin — Relative change at Week 24




| | Placebo | Treatment |
|---|---|---|
| N | 73 | 145 |
| Mean % change ± SD | 2.44 ± 47.69 | -17.95 ± 53.73 |
| Median % change | -9.1 | -29.4 |
| Min ; Max | [-75.6 ; 165.0] | [-84.1 ; 257.1] |

Hs-CRP — Relative change at Week 24




| | Placebo | Treatment |
|---|---|---|
| N | 72 | 146 |
| Mean % change ± SD | 43.07 ± 127.20 | -2.87 ± 165.05 |
| Median % change | 13.0 | -35.5 |
| Min ; Max | [-73.6 ; 687.5] | [-97.4 ; 1730.0] |

## 4-CONCLUSION

Consistent with the histological data from the NATIVE study showing a decrease in the activity and fibrosis of the SAF score, the plasma markers of inflammation - ferritin and Hs-CRP, apoptosis - CK18-M30, and fibrosis - Pro-C3, TMP1/MMP2, all show a statistically significant reduction in the lanifibranor treatment group compared to the placebo group.

## Contact information

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