Identification of biomarkers of histological response in patients with non-cirrhotic NASH treated with lanifibranor

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INTRODUCTION

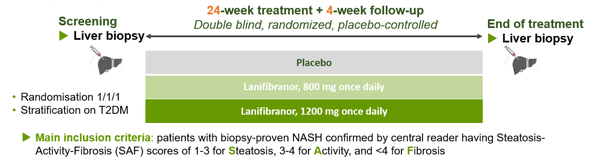
The pan-PPAR agonist lanifibranor is a promising investigational compound that has shown therapeutic efficacy on both NASH resolution and fibrosis improvement in the phase 2b NATIVE study (*Francque SM et al 2021*). The primary efficacy endpoint was ≥ 2 points decrease of the SAF Activity score, which assesses lobular inflammation and ballooning separately from steatosis. Secondary endpoints included 'NASH resolution and fibrosis improvement' (E1) and 'NASH resolution without worsening of fibrosis' (E2) according to NASH-CRN.

AIM

The aim of this project was to identify biological signatures of histological responders of E1 and E2 in non-cirrhotic NASH patients treated with lanifibranor, based on serum biomarkers.

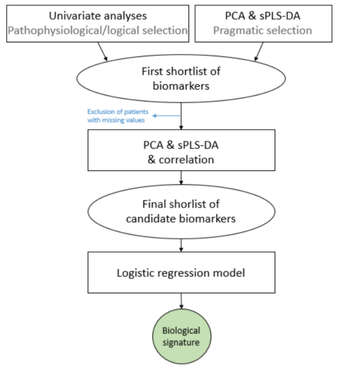
METHOD

NATIVE evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients with non-cirrhotic NASH for a treatment duration of 24 weeks. Liver biopsy was obtained at baseline and at the end of treatment (EOT).



Patients receiving lanifibranor 800 or 1200 mg/d were pooled and those with end-of-treatment (EOT) liver biopsies were selected (N=142).

A panel of more than 70 biomarkers related to metabolism, inflammation, tissue injury and fibrosis were evaluated by assessing baseline, absolute and relative changes at EOT.
Biomarker selection was done using classical univariate analysis, principal component analysis (PCA) and sparse partial least-square discriminant analysis (sPLS-DA), and combined in scores by logistic regression.



RESULTS (1/2)

	NASH resolution and fibrosis improvement (E1) N=142	NASH resolution and no worsening of fibrosis (E2) N=142
Responders	42 (30%)	63 (44%)
Non-responders	100 (70%)	79 (56%)

Predictive markers of E1:

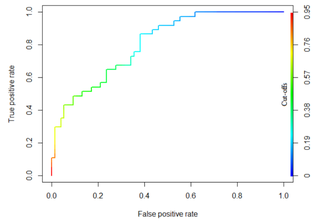
From all the markers tested, the pipeline for signature development identified 4 independent predictors of E1 that were combined in the E1-score:

- Baseline adiponectin
- Baseline ferritin
- Relative change of MMP9 at EOT
- Relative change of transferrin at EOT

Performance to predict histological response E1

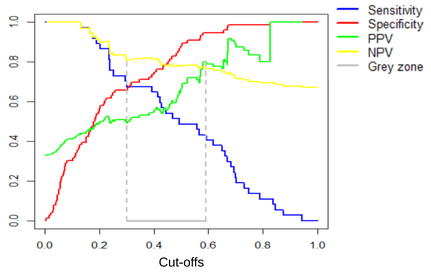
Combining these 4 parameters, the E1-score provided AUROC of 0.81±0.08 for predicting E1 response, with a Brier score of 0.17. 632+ bootstrap internal validation confirmed AUROC of 0.80±0.10 and a Brier score of 0.17.

ROC curve



Negative predictive value (NPV) threshold was 0.299 (rule-out with 80% NPV, corresponding sensitivity Se: 70%).
Positive predictive value (PPV) threshold was 0.592 (rule-in with 80% PPV, corresponding specificity Sp: 95%).

Se, Sp, PPV, NPV and grey zone by cut-offs



Using these thresholds, 72% of patients were classified as responders or non-responders with E1-score, of whom 81% were confirmed histologically, leaving only 28% patients in the grey zone between the two thresholds.

80% NPV threshold	**0.299**
- Rate of patients in refusal zone (%)	54%
- Sensitivity (%)	70%
80% PPV threshold	**0.592**
- Rate of patients in acceptation zone (%)	18%
- Specificity (%)	95%
Rate of patients in grey zone (%)	**28%**
Non-invasive Diagnostic Effectiveness (%)	**81%**

RESULTS (2/2)

Predictive markers of E2:

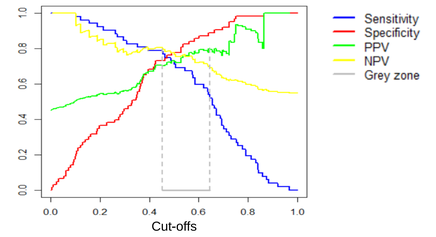
From all the markers tested, the pipeline for signature development identified 4 independent predictors of E2 that were combined in the E2-score :

- Baseline CK18 M65,
- Absolute change of hyaluronic acid at EOT
- Relative change of fructosamine at EOT
- Relative change of ALT at EOT

Performance to predict histological response E2

The E2-score provided AUROC of 0.80±0.08 and a Brier score of 0.18 for E2 response (.632+ bootstrap: AUROC 0.78±0.08, Brier score 0.21).
PV thresholds were 0.453 (80% NPV, corresponding 79% sensitivity) and 0.646 (80% PPV, corresponding 89% specificity).

Se, Sp, PPV, NPV and grey zone by cut-offs



Using these thresholds, 80% of patients were classified as responders or non-responders with E2-score, leaving only 20% patients in the grey zone between the two thresholds.

80% NPV threshold	**0.453**
- Rate of patients in refusal zone (%)	50%
- Sensitivity (%)	79%
80% PPV threshold	**0.646**
- Rate of patients in acceptation zone (%)	30%
- Specificity (%)	89%
Rate of patients in grey zone (%)	**20%**
Non-invasive Diagnostic Effectiveness (%)	**80%**

CONCLUSIONS

In this exploratory assessment, combined biomarker signatures allowed non-invasively identification of histological response under lanifibranor treatment in NASH with good diagnostic performance. These findings support utilising a similar approach in a larger sample size (*NATiV3*).

REFERENCES

S.M. Francque et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *N Engl J Med 2021;385:1547-58.*

NATiV3, A Phase 3 Study Evaluating Long-term Efficacy and Safety of Lanifibranor in Adult Patients With NASH and Fibrosis F2/F3 Stages of Fibrosis, *ClinicalTrials.gov identifier NCT04849728.*

CONTACT INFORMATION

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