

## 1-INTRODUCTION

Lanifibranor has shown efficacy on liver histology and on metabolic-immune markers of NASH in the phase 2b NATIVE study [1]. Adiponectin (ADP) is a pleiotropic adipokine which improves insulin resistance (IR), lipid metabolism, inflammation and fibrosis; low ADP levels are associated with cardiovascular disease and have also been reported in relation to NASH. We evaluated the correlation between response to lanifibranor therapy and ADP.

## 2-MATERIAL/METHODS

NATIVE evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients with non-cirrhotic NASH for 24 weeks of treatment. Paired samples for ADP analysis were available from 211 patients (72 on placebo, 66 and 73 on lanifibranor 800 and 1200 mg, respectively). ADP serum levels, markers of lipid and glucose metabolism, IR, inflammation, liver tests and hepatic steatosis by Continuous Attenuation Parameter (CAP) imaging were measured at baseline (BL) and end-of-treatment (EOT). ADP levels at BL were divided into low, medium and high (<5, 5 - 10 and >10 µg/mL, respectively). Increase in ADP at EOT was defined as unchanged, moderate and high (<1.5 fold, 1.5 - 4 fold and >4 fold change, respectively).

## 3-RESULTS

ADP levels at BL were low on average (mean 5.1, range 0.8 - 30.8 µg/mL, with 60% of low, 32% of medium and 8% of high values).

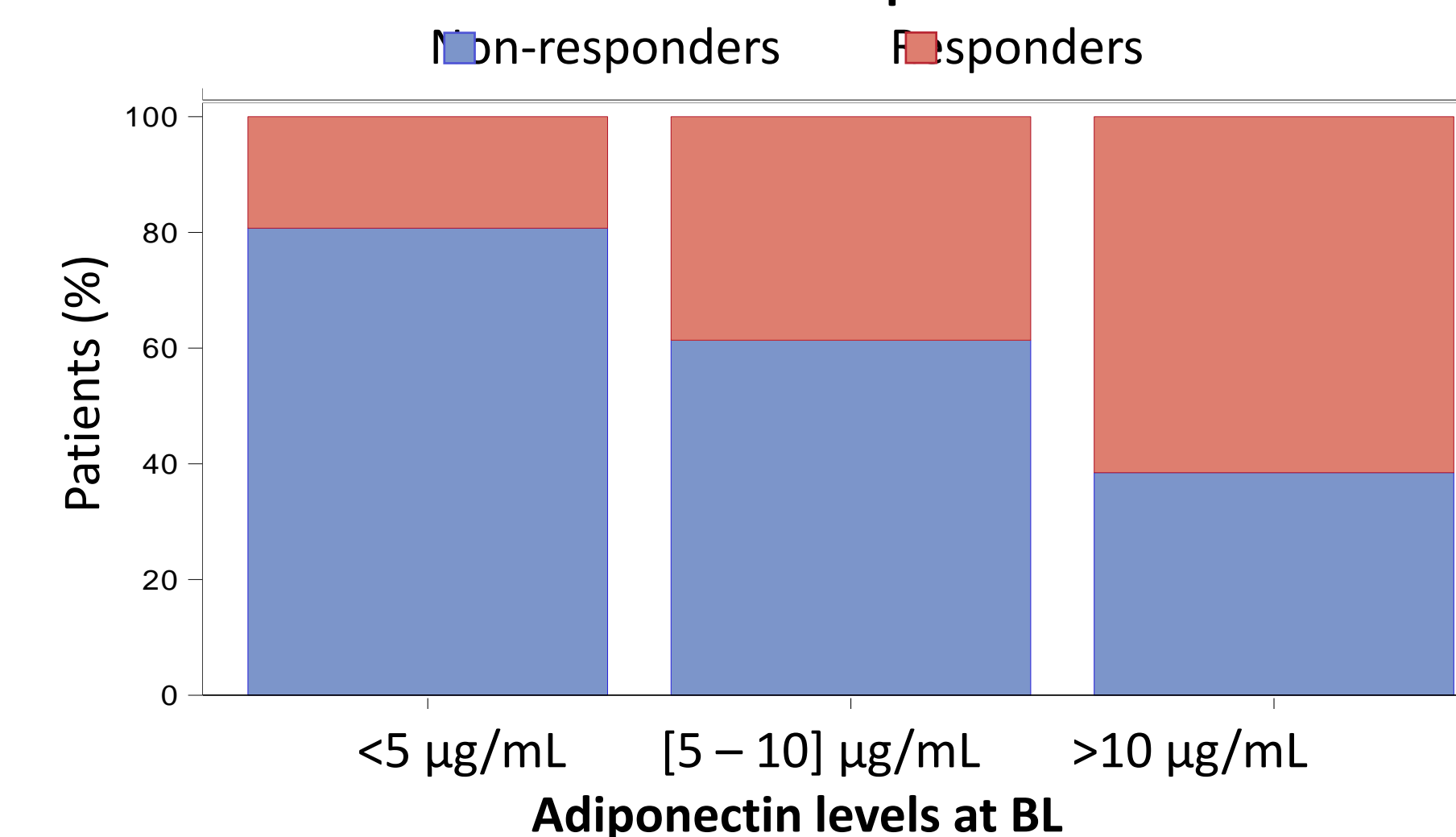
Adiponectin (µg/mL) at BL	Placebo	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor Pooled	Total
N	81	80	83	163	244
Mean (SD)	5.3 ± 4.2	5.0 ± 3.1	5.1 ± 3.2	5.1 ± 3.2	5.1 ± 3.5
Median	4.6	4.2	4.4	4.3	4.5
[Min ; Max]	1.2; 30.8	1.3; 22.3	0.8; 14.7	0.8; 22.3	0.8; 30.8
<5 µg/mL	48 (59%)	49 (61%)	50 (60%)	99 (61%)	147 (60%)
[5 - 10] µg/mL	27 (33%)	28 (35%)	23 (28%)	51 (31%)	78 (32%)
>10 µg/mL	6 (7%)	3 (4%)	10 (12%)	13 (8%)	19 (8%)

### Contact information:

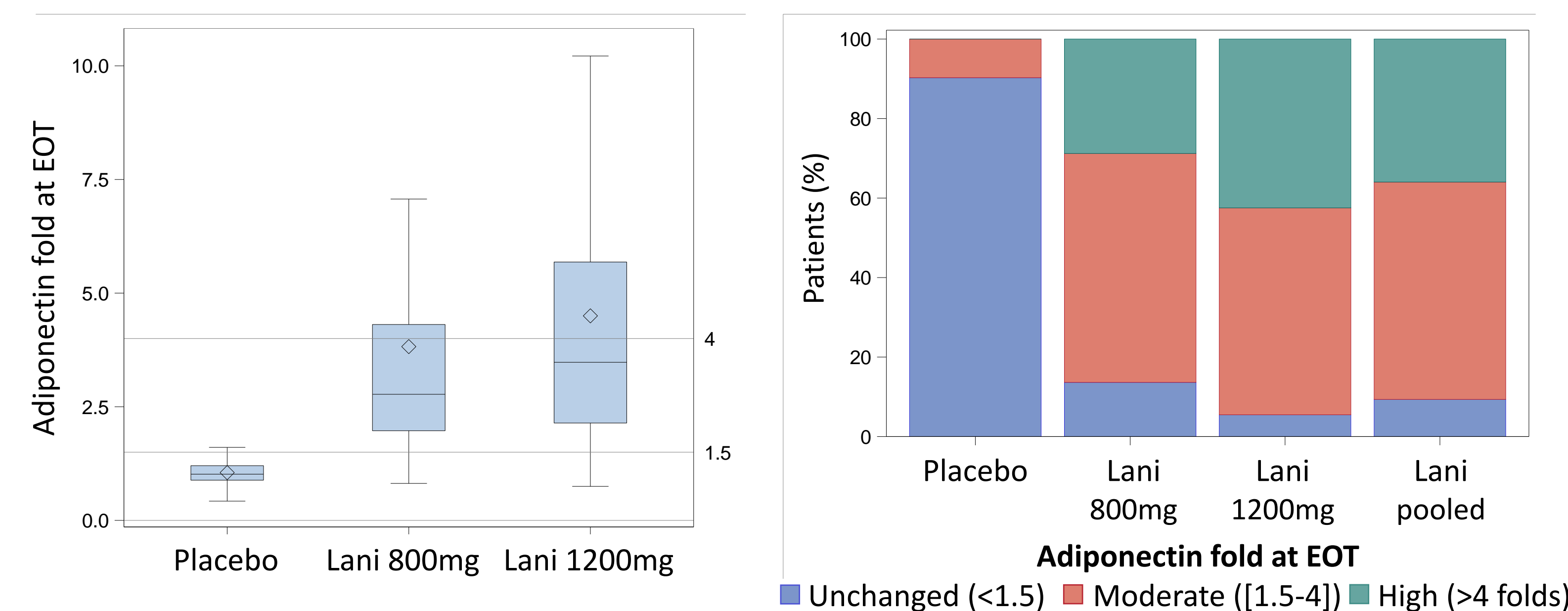
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In the pooled data of both lanifibranor arms, ADP levels at BL showed a positive correlation with histological response “resolution of NASH and improvement of fibrosis”.

Resolution of NASH and improvement of fibrosis

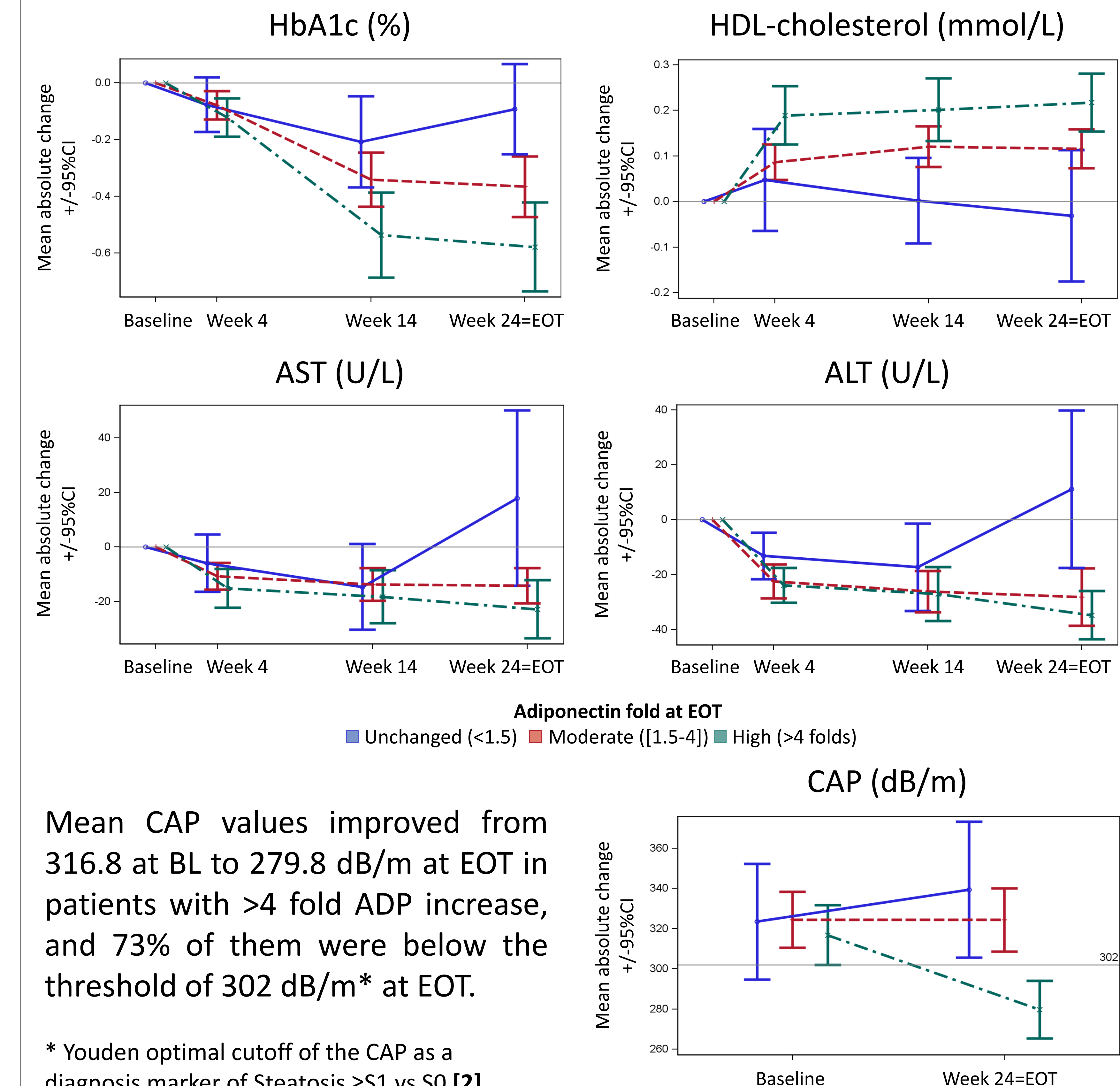


Lanifibranor therapy resulted in a dose-dependent response in ADP levels; at EOT, 91% of patients in the pooled lanifibranor arm had a moderate (55%) or high (36%) increase; in contrast, under placebo only 10% of patients had a moderate, and none a high increase.



In the pooled data of both lanifibranor arms, degree of increase of ADP levels correlated with improvement in glycemic control (fasting glucose, Hb1Ac), IR (insulin levels, HOMA-IR), lipid metabolism (decrease in total serum triglycerides and APO-B, increase in HDL-cholesterol), liver tests (ALT, AST) and systemic inflammation (hs-CRP), with generally a more pronounced effect size for high than for moderate ADP increase.

Absolute change at EOT (mean ± SD)	Adiponectin fold at EOT		
	Unchanged <1.5 folds	Moderate [1.5 - 4] folds	High >4 folds
Glucose (mmol/L)	0.20 ± 0.79	-0.83 ± 1.33	-1.01 ± 1.63
Insulin (pmol/L)	-17.3 ± 64.3	-115.4 ± 207.4	-177.8 ± 342.1
HOMA-IR	-0.50 ± 3.04	-5.70 ± 10.53	-9.17 ± 20.13
Triglycerides (mmol/L)	-0.23 ± 0.62	-0.36 ± 0.96	-0.59 ± 0.51
Apolipoprotein B (APO-B) (mg/dL)	-3 ± 24	-9 ± 17	-19 ± 22
High-sensitivity C Reactive Protein (hs-CRP) (mg/L)	1.02 ± 6.63	-1.73 ± 5.60	-2.90 ± 4.82



## 4-CONCLUSION

Patients with non-cirrhotic NASH had low ADP levels. Treatment with the pan-PPAR agonist lanifibranor significantly increased ADP levels, and this increase correlated with an improvement of a broad panel of markers of hepatic and cardiometabolic health.

### References:

- [1] S.M. Francque and al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *N Engl J Med.* 2021;385:1547-58.
- [2] P.J. Eddowes and al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2019 May;156(6):1717-1730. doi: 10.1053/j.gastro.2019.01.042. Epub 2019 Jan 25. PMID: 30689971