Comparative Modulation of Adiponectin Across Select Therapeutics in Clinical Development for MASH with Fibrosis Identifies Lanifibranor as a Differentiated Metabolic Modulator.

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1-INTRODUCTION

Adiponectin (ADP) regulates lipid oxidation, insulin sensitivity, inflammation and fibrogenesis. Low circulating levels of adiponectin are linked to increased insulin resistance, cardiovascular risk and correlate with MASH histologic severity. Activation of PPAR pathways is known to restore adipose-tissue function and increase circulating adiponectin. In the phase 2b NATIVE study, lanifibranor produced a dose-dependent increase in circulating adiponectin together with improvements in histologic MASH resolution and fibrosis regression.

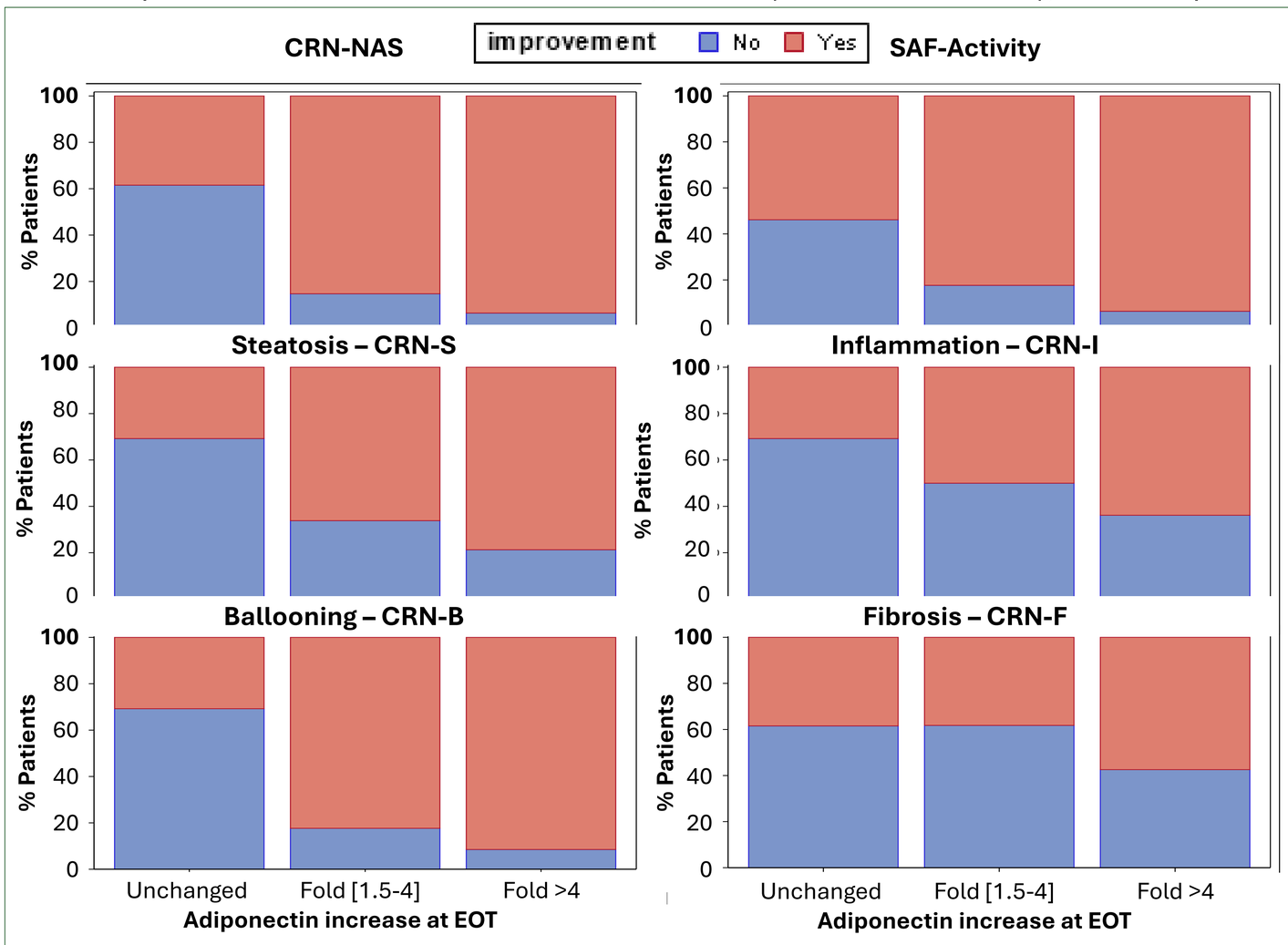
2-Material/Methods

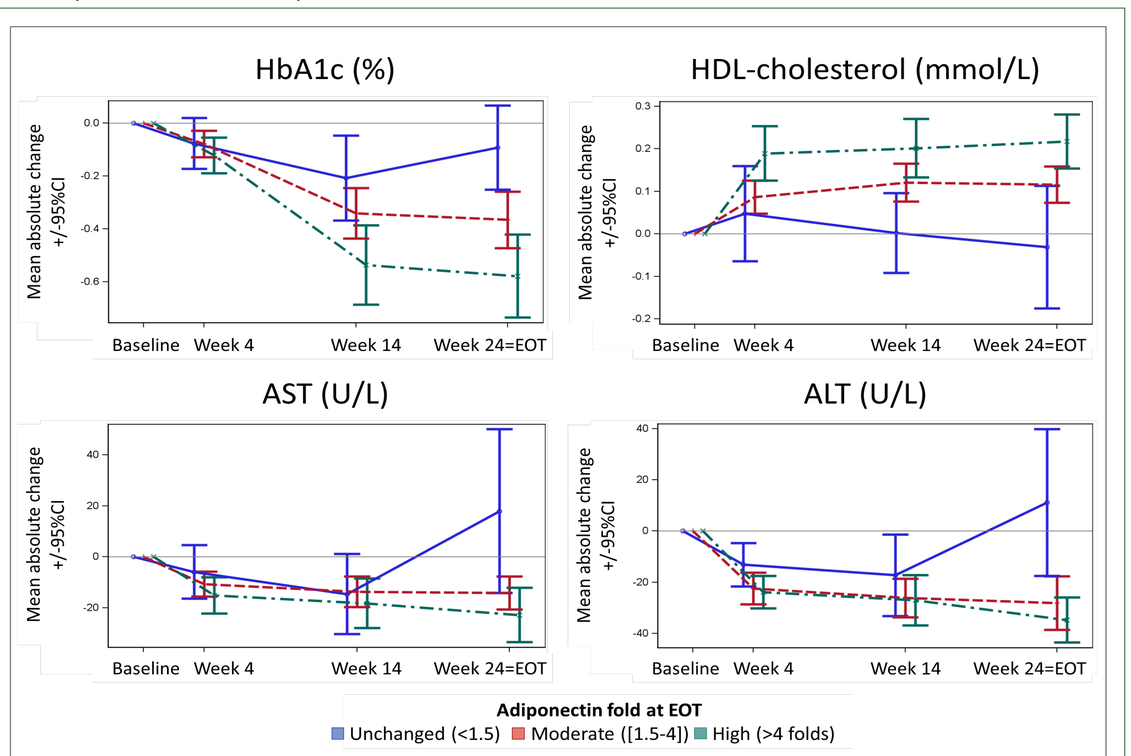
NATIVE evaluated lanifibranor 800 and 1200 mg/day versus placebo in 247 patients with non-cirrhotic MASH for 24 weeks of treatment. ADP serum levels, markers of lipid and glucose metabolism, Insulin Resistance (IR), inflammation, liver chemistries and hepatic steatosis by Continuous Attenuation Parameter (CAP) were also measured at baseline (BL) and end-of-treatment (EOT). ADP increase at EOT was defined as unchanged, moderate and high (<1.5-fold, 1.5-4-fold and >4-fold change). Data from late-stage therapeutics in MASH were collected from publications.

3-RESULTS

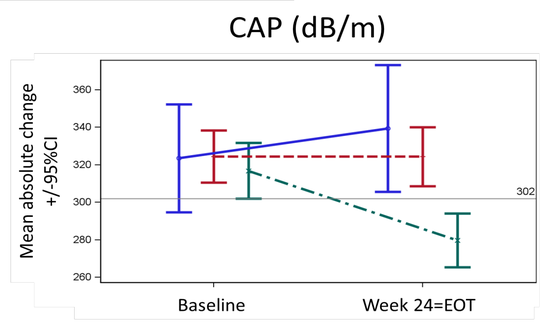
	Lanifibranor (NATIVE) 24 weeks[1]		Resmetirom (MAESTRO-NASH) 52 weeks[2]		Efruxifermin (HARMONY) 24 weeks[3]		Pegozafermin (ENLIVEN) 24 weeks[4]		
Dose	800mg	1200mg	80mg	100mg	28mg	50mg	15mg	30mg	44mg
Absolute change from BL at EOT µg/ml	+ 11.95 (8.97 to14.94)[$]	+ 17.12 (14.29 to 19.96)[$]	+ 0.86 (0.19)*	+ 1.1 (0.19)*	+ 1.4 (0.34)[£]	+ 3.0 (0.34)[£]	+ 1.1 (0.7)[£]	+ 1.1 (0.3)[£]	+ 1.2 (0.4)[£]
Placebo	-0.35 (-3.20 to 2.50)		- 0.1 (0.18)		+ 0.28 (0.32)		- 0.6 (0.4)		

[$] Least Square Mean, 95% confidence intervals; *Mean (Standard Deviation); [£] Least Square Mean (Standard Error)





Mean CAP values improved from 317 at BL to 280 dB/m at EOT in patients with >4 fold ADP increase, and 73% of them were below the threshold of 302 dB/m at EOT[5].



In the NATIVE study, degree of adiponectin increase correlated with improvement of CRN-NAS and SAF-Activity scores as well as with individual components (steatosis, inflammation, ballooning) and cardiometabolic parameters.

4-CONCLUSION

Among MASH therapeutics in clinical development, lanifibranor induces the largest reported increase in ADP, with substantial changes that correlate with histologic improvement in both MASH activity and fibrosis[6]. This relationship aligns mechanistically with pan-PPAR-mediated restoration of adipose tissue function and enhanced hepatic and muscle insulin sensitivity. Importantly, these increases also correlate with improvements in cardiometabolic parameters (e.g., HbA1c, HDL, and hepatic steatosis)[6], supporting ADP as a systemic biomarker of metabolic normalization. Together, these findings support the potential of lanifibranor as a differentiated therapy capable of addressing both intrahepatic and extrahepatic complications of MASH through multi-pathway PPAR engagement.

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