Improvements in MACK-3, a diagnostic test for active metabolic dysfunction-associated steatohepatitis, parallel response to lanifibranor therapy

Contact information
Dr. MP COOREMAN:
Michael.COOREMAN@inventivapharma.com

Michael P. Cooreman[1], Sven M. Francque[2], Philippe Huot-Marchand[3], Lucile Dzen[3], Martine Baudin[3], Jean-Louis Junien[3], Pierre Broqua[3], Manal F. Abdelmalek[4], Jerome Boursier[5]

[1]Inventiva, New York, United States; [2]University Hospital Antwerp, Edegem; [3]Inventiva, Daix, France; [4]Mayo Clinic, Rochester, United States; [5]CHU Angers, Angers, France

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Introduction

The pan-PPAR agonist lanifibranor has shown efficacy on histological 'MASH resolution and fibrosis improvement' and on non-invasive markers of cardiometabolic health (CMH), MASH activity and fibrosis (including MACK-3, adiponectin and Pro-C3) in the NATIVE phase 2b study.[1,2]

MACK-3 has been validated against histology as a diagnostic marker for active MASH with fibrosis. Its components (AST, HOMA-IR, and CK-18) reflect the spectrum of MASH biology. [3]

We therefore evaluated the correlation of MACK-3 response with improvement of liver histology and CMH markers with treatment.

Method

NATIVE evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients with noncirrhotic MASH for 24 weeks of treatment.

MACK-3, liver histology, adiponectin, and pro-C3 (as a marker of fibrogenesis) were evaluated at baseline and at end of treatment (EOT).

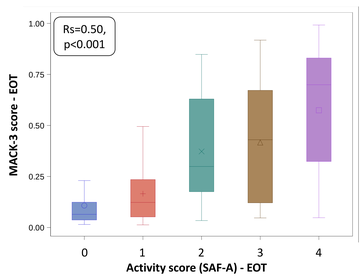
Correlations between MACK-3 and adiponectin, Pro-C3 and histological components according to NASH-CRN and SAF activity (SAF-A) scoring were assessed using Spearman's rank (Rs) among all randomized patients at baseline and at EOT.

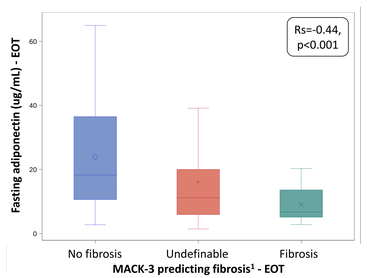
Change in MACK-3 between histological responders and non-responders in the pooled lanifibranor arms were compared using Wilcoxon test.

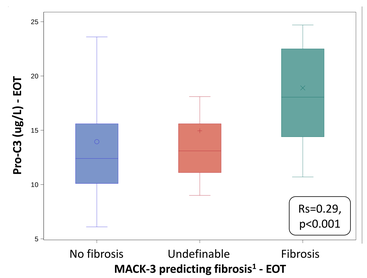
Results

At baseline, MACK-3 correlated with histological fibrosis stage (Spearman Rs=0.25, p<0.001), disease activity (CRN-NAS: Rs=0.22, p<0.001; SAF-A: Rs=0.16, p=0.015) and circulating biomarkers (adiponectin: Rs=-0.18, p=0.006; Pro-C3: Rs=0.50, p<0.001).

At EOT, among lanifibranor-treated patients, MACK-3 still correlated with histological fibrosis stage (Rs=0.23, p=0.01), disease activity (CRN-NAS: Rs=0.54, p<0.001; SAF-A: Rs=0.50, p<0.001) and circulating markers (adiponectin: Rs=-0.44, p<0.001; Pro-C3: Rs=0.29, p<0.001).

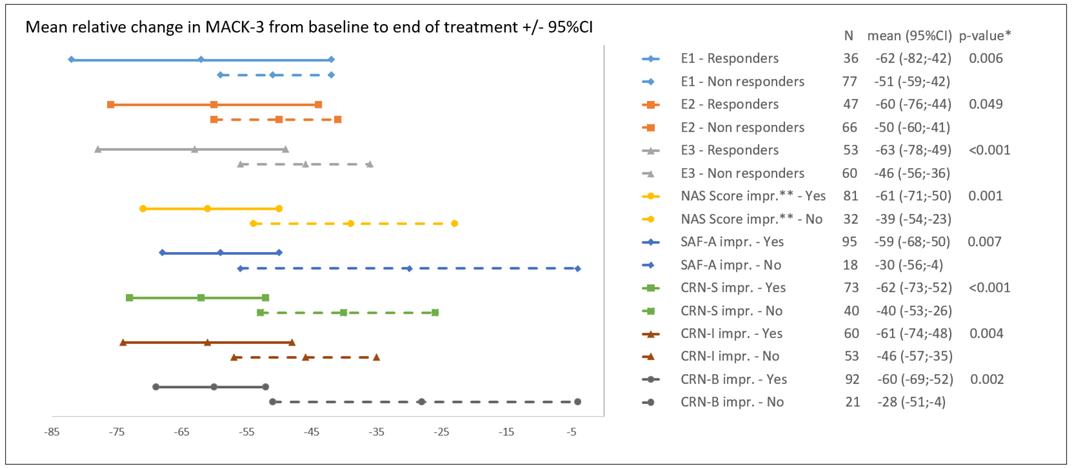






Decrease in MACK-3 value at EOT from baseline was significantly higher among lanifibranor-treated histological responders vs non-responders for 'MASH resolution and fibrosis improvement' (E1; -62% vs -51%, p=0.006), for 'Fibrosis improvement without worsening of MASH' (E2; -60% vs -50%, p=0.05), and for 'MASH resolution without fibrosis worsening' (E3; -63% vs -46%, p<0.001).

Similar results were observed for improvement of CRN-NAS of at least 2 points (-61% vs -39%, p=0.001), SAF-A (-59% vs -30%, p=0.007), and individual liver lesions: steatosis (-62% vs -40%, p<0.001), CRN-lobular inflammation (-61% vs -46%, p=0.004), and CRN-ballooning (-60% vs -28%, p=0.002).



	N	mean (95%CI)	p-value*
E1 - Responders	36	-62 (-82;-42)	0.006
E1 - Non responders	77	-51 (-59;-42)	
E2 - Responders	47	-60 (-76;-44)	0.049
E2 - Non responders	66	-50 (-60;-41)	
E3 - Responders	53	-63 (-78;-49)	<0.001
E3 - Non responders	60	-46 (-56;-36)	
NAS Score impr.** - Yes	81	-61 (-71;-50)	0.001
NAS Score impr.** - No	32	-39 (-54;-23)	
SAF-A impr. - Yes	95	-59 (-68;-50)	0.007
SAF-A impr. - No	18	-30 (-56;-4)	
CRN-S impr. - Yes	73	-62 (-73;-52)	<0.001
CRN-S impr. - No	40	-40 (-53;-26)	
CRN-I impr. - Yes	60	-61 (-74;-48)	0.004
CRN-I impr. - No	53	-46 (-57;-35)	
CRN-B impr. - Yes	92	-60 (-69;-52)	0.002
CRN-B impr. - No	21	-28 (-51;-4)	

** p-values from Wilcoxon tests comparing responders/improvers versus non responders/no improvers; ** NAS score impr. = improvement in CRN-NAS of at least 2 points; CI=confidence interval, impr.=improvement, N=number of patients*

With lanifibranor, decrease in MACK-3 score at EOT from baseline was also correlated with adiponectin increase (Rs=-0.48, p<0.001) and Pro-C3 decrease (Rs=0.23, p=0.01).

Conclusions

MACK-3 is a practical diagnostic algorithm for fibrotic MASH that also shows good correlation with improvement of histological disease activity and fibrosis, as well as with improvement of non-invasive biomarkers following therapy with lanifibranor, and thus warrants further study as a potential marker for evaluation of treatment response.

Acknowledgement

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References

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Michael Cooreman
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