

Effect of pegbelfermin on NASH and fibrosis-related biomarkers and correlation with histological response in the FALCON 1 trial

Elizabeth A. Brown, Anne Minnich, Arun J. Sanyal, Rohit Loomba, Shuyan Du, John Schwarz, Richard L. Ehman, Morten Karsdal, Diana J. Leeming, Giovanni Cizza, Edgar D. Charles

Table of contents

Fig. S1.....2

Fig. S2.....3

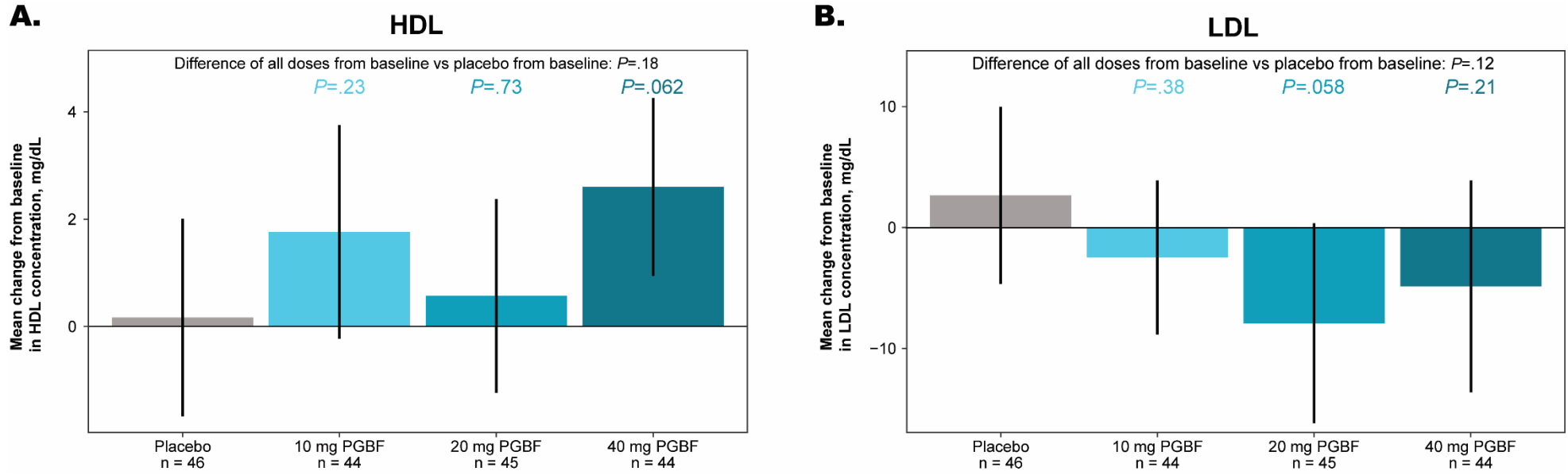
Fig. S3.....4

Fig. S4.....7

Table S1.....9

Supplementary reference..... 11

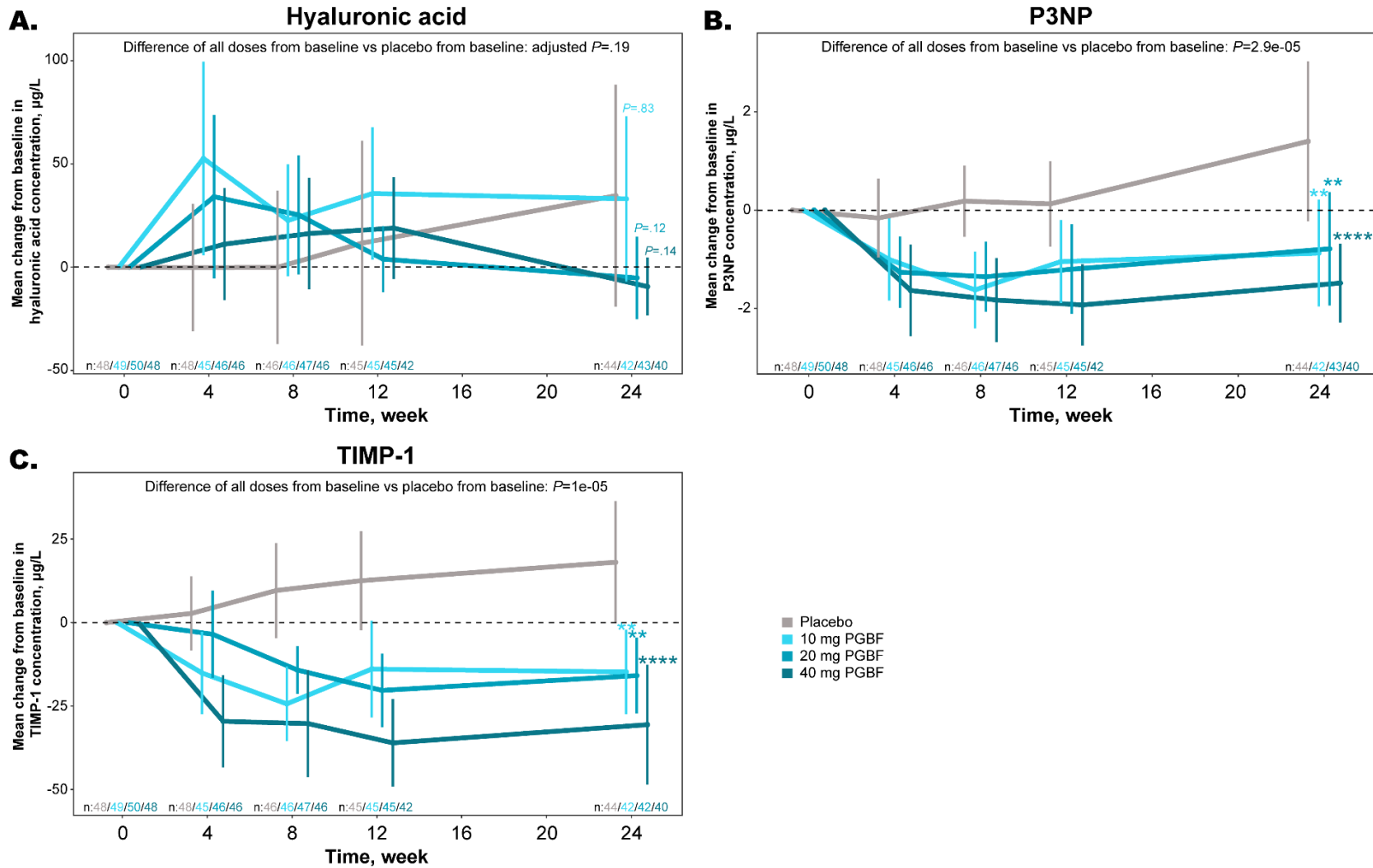
Fig. S1. Mean absolute change from baseline to week 24 in HDL and LDL



Mean change from baseline \pm 95% CI at week 24 is shown. Linear mixed models were fit for each biomarker over time; the difference of each treated arm, and all treated pooled, from baseline compared to placebo from baseline were calculated with P values corrected for multiple testing across all tests and biomarkers using the Benjamini-Hochberg procedure.

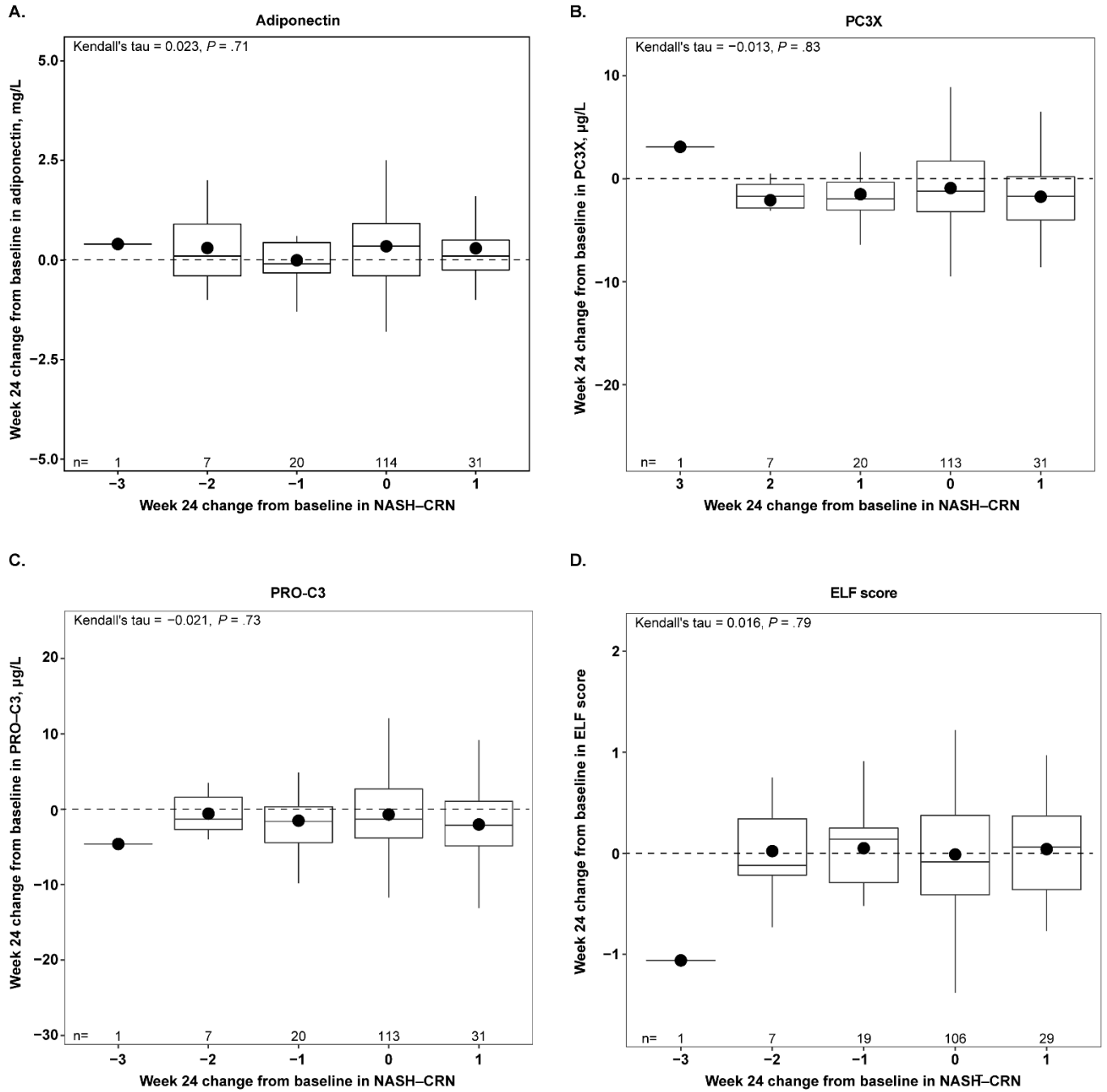
HDL, high-density lipoprotein; LDL, low-density lipoprotein; PGBF, pegbelfermin.

Fig. S2. Mean absolute change from baseline in ELF score components

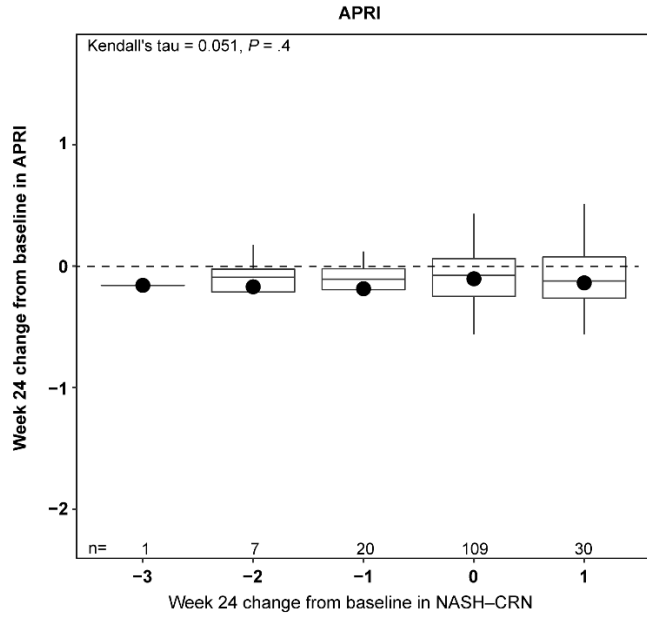


Mean change from baseline at each measured timepoint \pm 95% CI is shown. Linear mixed models were fit for each biomarker over time; the difference of each treated arm, and all treated pooled, from baseline compared to placebo from baseline were calculated with P values corrected for multiple testing across all tests and biomarkers using the Benjamini-Hochberg procedure. * $P \leq .05$; ** $P \leq .01$, *** $P \leq .001$, **** $P \leq .0001$. ELF, enhanced liver fibrosis; P3NP, procollagen-3 N-terminal propeptide; PGBF, pegbelfermin; TIMP-1, tissue inhibitor of metalloproteinases type 1.

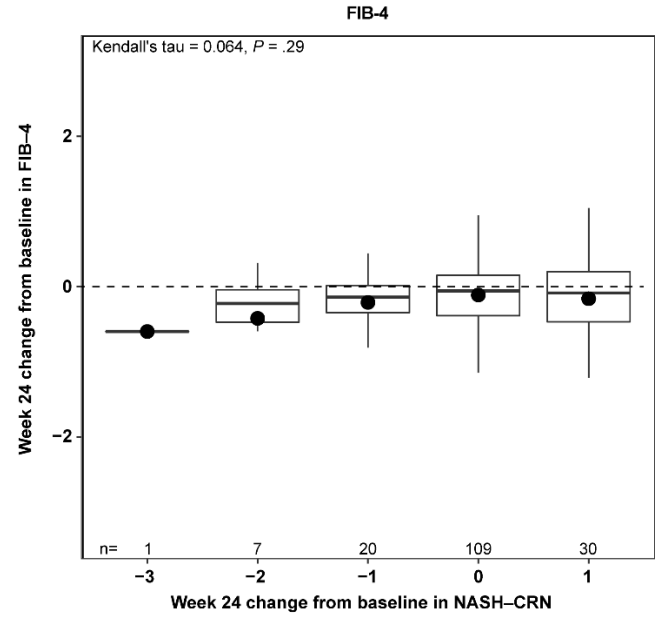
Fig. S3. Correlative analysis between week 24 biomarker changes and week 24 NASH CRN fibrosis stage changes



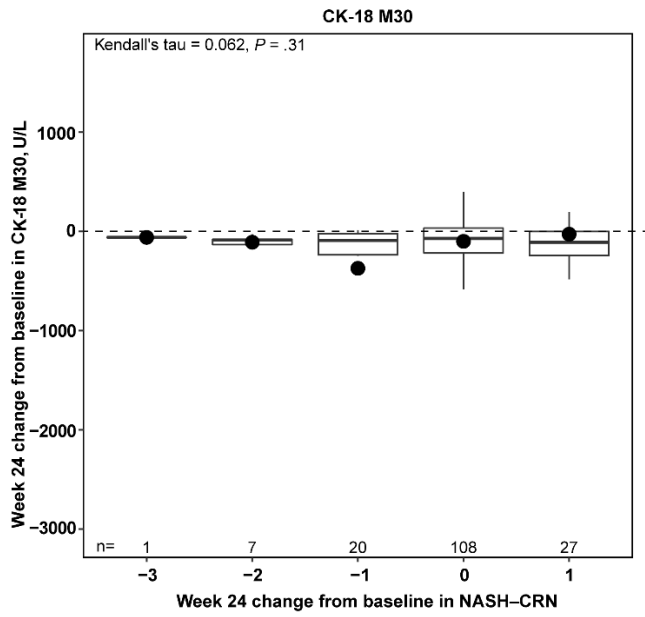
E.



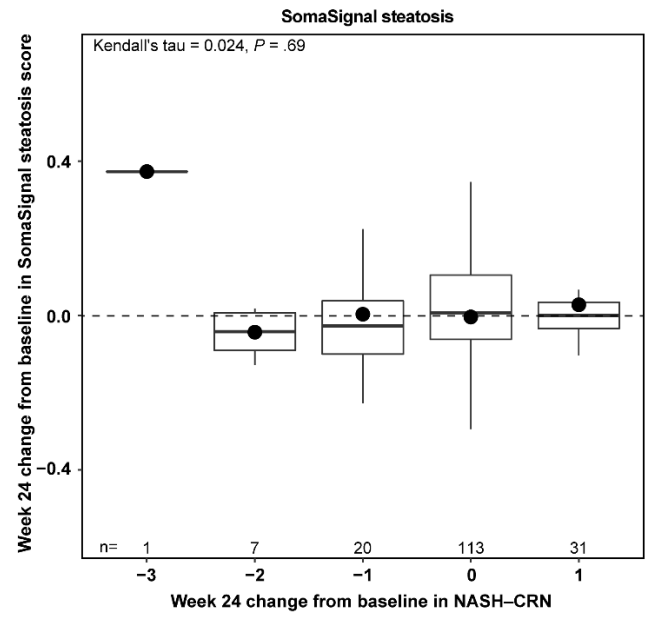
F.

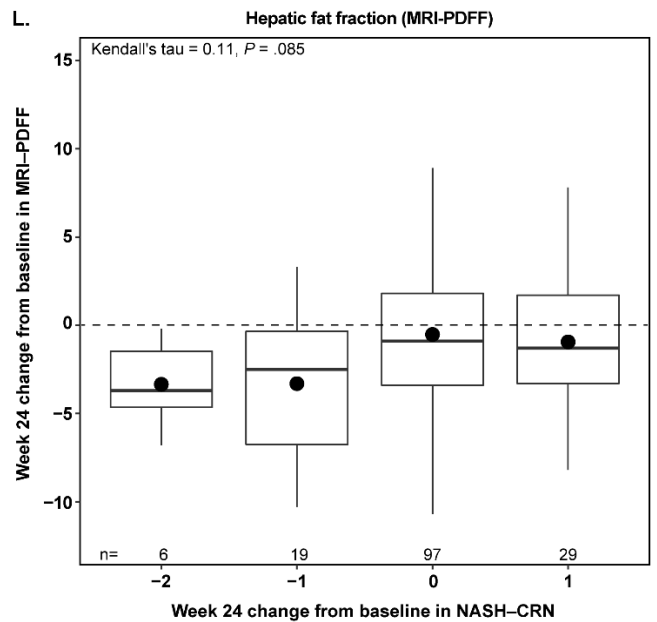
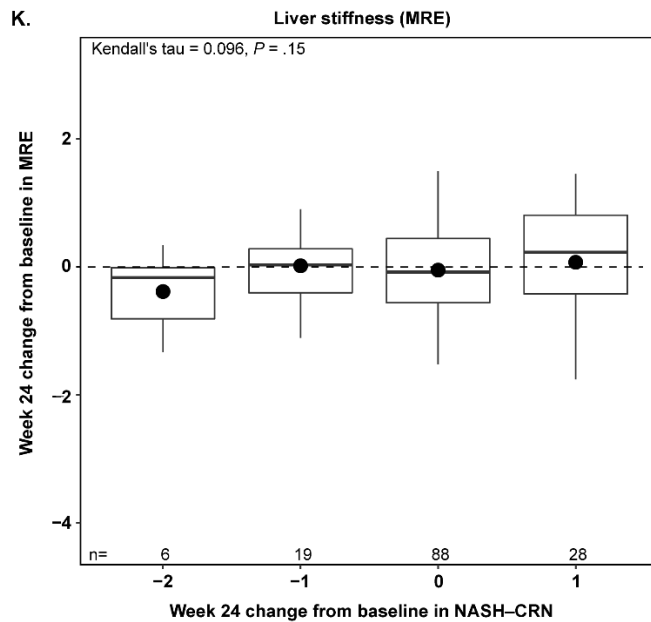
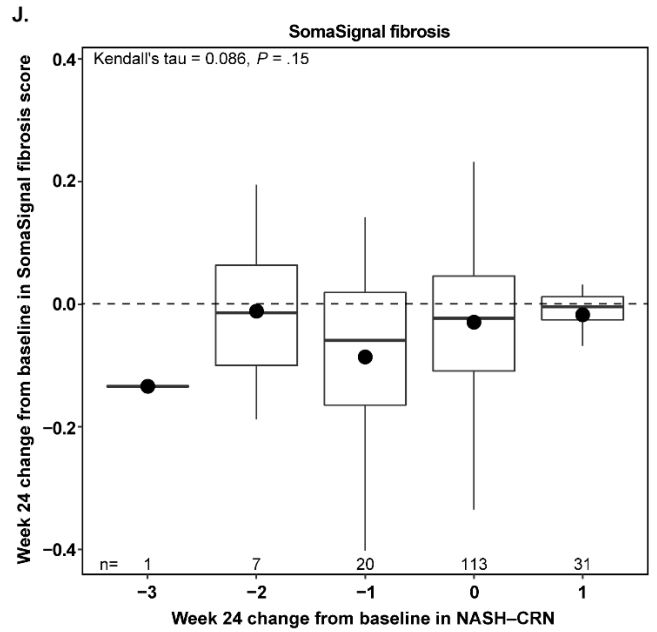
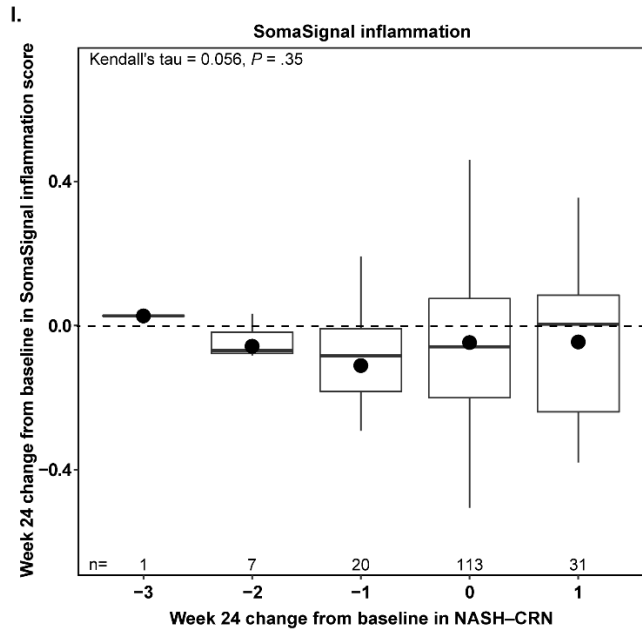


G.



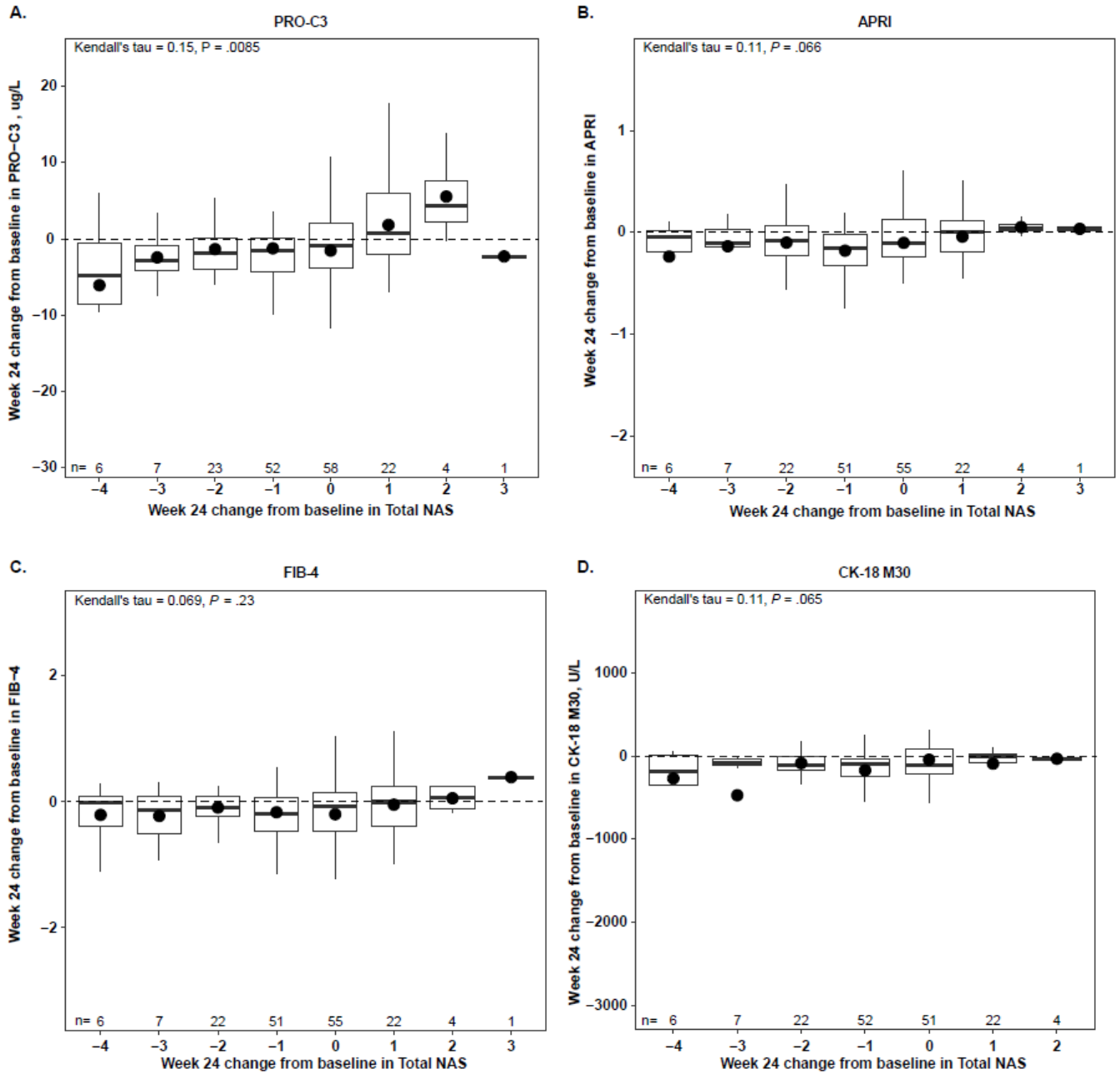
H.

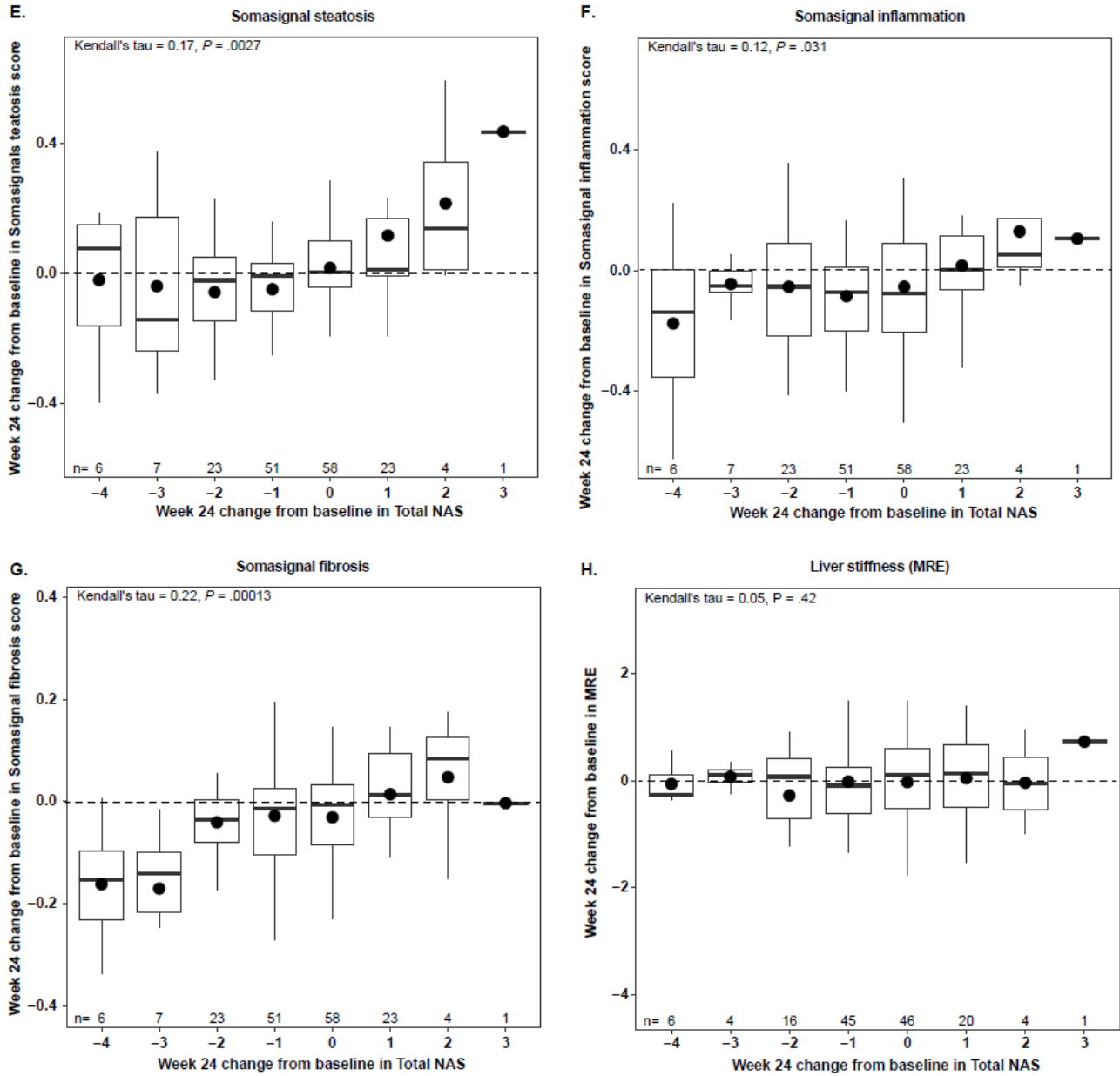




Plots show mean (dots), median (bold line), IQR (top and bottom lines of box) and range excluding any outliers over 1.5x IQR (whiskers). APRI, aspartate aminotransferase-to-platelet ratio index; CK-18 M30, caspase-cleaved cytokeratin 18; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH CRN, nonalcoholic steatohepatitis clinical research network; PC3X, crosslinked ADAMTS-2-released N-terminal type III collagen propeptide; PRO-C3, monomeric ADAMTS-2-released N-terminal type III collagen propeptide.

Fig. S4. Correlative analysis between week 24 biomarker changes and week 24 total NAS changes





Plots show mean (dots), median (bold line), IQR (top and bottom lines of box) and range excluding any outliers over 1.5x IQR (whiskers). APRI, aspartate aminotransferase-to-platelet ratio index; CK-18 M30, caspase-cleaved cytokeratin 18; FIB-4, fibrosis-4; IQR, interquartile range; MRE, magnetic resonance elastography; NAS, nonalcoholic fatty liver disease activity score; PRO-C3, monomeric ADAMTS-2-released N-terminal type III collagen propeptide.

Table S1. SomaSignal scoring system¹

Test	Definition ^a	Protein Analytes
NASH ballooning	Predicted probability of NAS steatosis component score of 1, 2, or 3, as opposed to 0	<ol style="list-style-type: none"> 1. aldo-keto reductase family 1 member b10 2. prostaglandin reductase 1 3. adamts-like protein 2 cytotoxic t-lymphocyte protein 4 5. calponin-2
NASH lobular inflammation	Predicted probability of NAS lobular inflammation component score of 2 or 3, as opposed to 0 or 1	<ol style="list-style-type: none"> 1. aminoacylase-1 2. dolichyl-diphospho-oligosaccharide protein glycosyltransferase subunit 1 3. uncharacterized protein c1orf198 4. transcriptional repressor ctcf 5. serum amyloid a-2 protein 6. low affinity immunoglobulin gamma fc region receptor iii-b 7. adiponectin 8. thioredoxin reductase 1 9. maleylacetoacetate isomerase 10. tumor-associated calcium signal transducer 2 11. peptide yy 12. c-c motif chemokine 23 13. procollagen c-endopeptidase enhancer 2 14. low molecular weight phosphotyrosine protein phosphatase
NASH steatosis	Predicted probability of NAS steatosis component score of 1, 2, or 3, as opposed to 0	<ol style="list-style-type: none"> 1. insulin-like peptide insl5 2. fatty acid-binding protein 12 3. atp-dependent dna helicase q1 4. beta-glucuronidase 5. beta-hexosaminidase subunit beta 6. beta-ala-his dipeptidase 7. growth hormone variant 8. prostaglandin reductase 1 9. bpi fold-containing family b member 1

		<ul style="list-style-type: none"> 10. glutamate receptor ionotropic; delta-2 11. serine/threonine-protein kinase/ endoribonuclease ire1
NASH fibrosis	Predicted probability of NASH CRN fibrosis stage 2, 3, or 4, as opposed to 0 or 1	<ul style="list-style-type: none"> 1. adamts-like protein 2 2. complement component c7 3. neurofascin 4. collectin-11 5. vascular endothelial growth factor receptor 6. protein wnt-5 7. procollagen-lysine; 2-oxoglutarate 5-dioxygenase 3 8. fc receptor-like protein 3

^aFor all tests, a probability score of $\geq 50\%$ is predictive of the specified scoring or staging.
 NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

Supplementary reference

1. Ostroff R, Alexander L, Williams S. A liquid liver biopsy: Serum protein patterns of liver steatosis, inflammation, hepatocyte ballooning and fibrosis in NAFLD and NASH [abstract]. Presented at AASLD 2020. Abstract LP11.