Liver forum 12
Effects of pegbelfermin on NIT's for NASH in a Phase 2b study: Falcon-1

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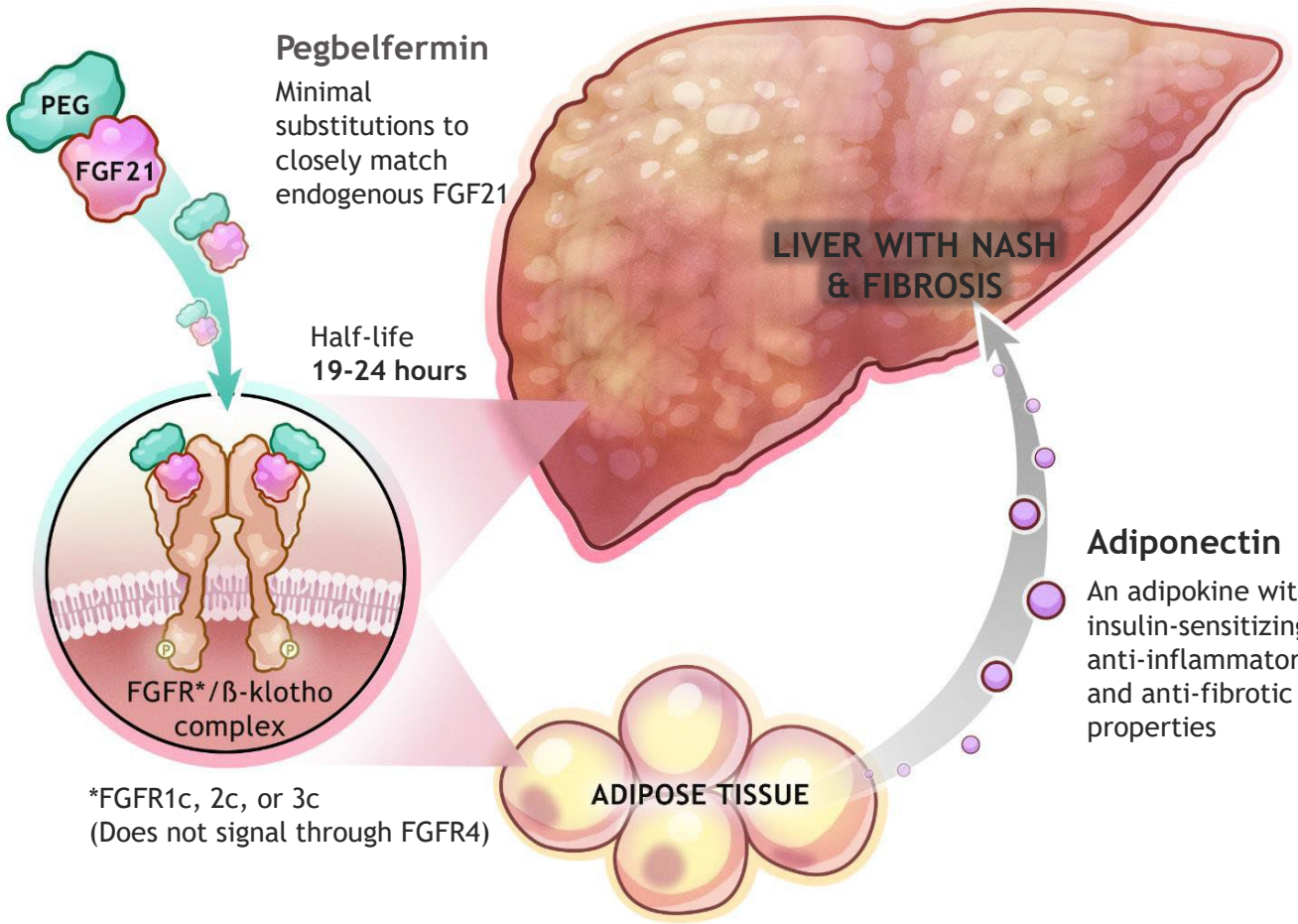
Anne Minnich

Bristol Myers Squibb™

Pegbelfermin (PGBF)

PGBF is a PEGylated, recombinant human FGF21 analog with a prolonged half-life, supporting weekly dosing



METABOLIC EFFECTS

INCREASES adiponectin, insulin sensitivity, and improves lipid parameters (HDL, LDL, and triglycerides)

ANTI-NASH EFFECTS

DECREASES liver fat, hepatic injury, inflammation, and hepatocyte ballooning

ANTI-FIBROTIC EFFECTS

DECREASES fibrogenesis (PRO-C3) and improves liver fibrosis

FGF21, fibroblast growth factor 21; FGFR, fibroblast growth factor receptor; PEG, polyethylene glycol polymer; PRO-C3, N-terminal type III collagen propeptide.

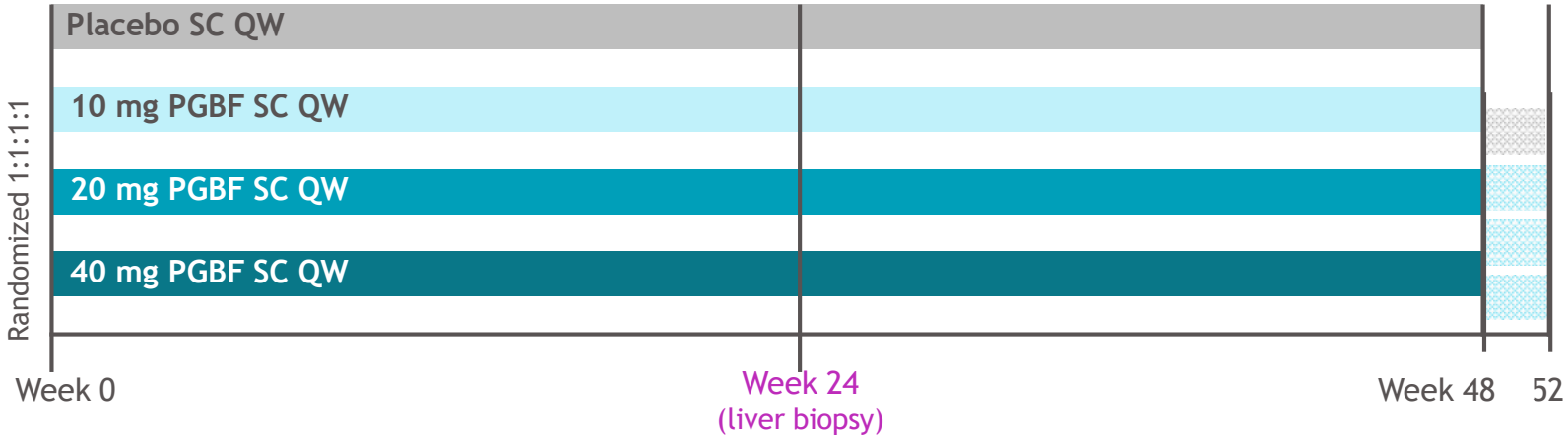
1. Sanyal A, et al. *Lancet*. 2018;392(10165):2705-2717; 2. Charles ED, et al. *Obesity*. 2019;27:41-49; 3. Verzijl C, et al. *Expert Opinion on Investigational Drugs*. 2020;29(2):125-133; 4. Sonoda J, et al. *Horm Mol Biol Clin Investig*. 2017;30(2):1-13; 5. Kurosu H, et al. *J Biol Chem*. 2007;282(37):26687-26695; 6. Ornitz D and Itoh N. *WIRES Dev Biol*. 2015;4:215-266; 7. Achari A and Jain S. *Int J Mol Sci*. 2017;18:1-17.

FALCON 1 Study Design

NCT03486899:
US and Japan

NASH & bridging fibrosis (NASH CRN stage 3)

N = 197



Patient stratification:

- **All patients:** US vs Japan
- **US patients only:** T2DM (yes vs no); NAS (> 5 vs ≤ 5)

Key inclusion criteria

- Aged 18–75 years
- Liver biopsy performed within 6 months of screening
- Biopsy-proven NASH with a score of ≥ 1 for each NAS component and NASH CRN stage 3 liver fibrosis assessed by central reader
- Anti-diabetic, -obesity, or -dyslipidemic regimens permitted if stable for ≥ 12 weeks (6 weeks for statins)
- Vitamin E doses ≥ 800 IU/day permitted if initiated before the qualifying liver biopsy and if stable for ≥ 26 weeks

Key exclusion criteria

- Other causes of liver disease
- Current or past history of hepatocellular carcinoma
- Current or past evidence of hepatic decompensation or liver transplantation

Primary endpoint (week 24)
≥ 1 stage improvement in fibrosis, without worsening of NASH **or** NASH improvement without worsening of fibrosis

Secondary endpoints (week 24)
NASH CRN fibrosis score improvement, modified Ishak score improvement, any decrease in CPA, NASH resolution without worsening of fibrosis, NASH resolution, ≥ 1 stage improvement in NASH CRN fibrosis score without NASH worsening, NASH improvement, progression to cirrhosis

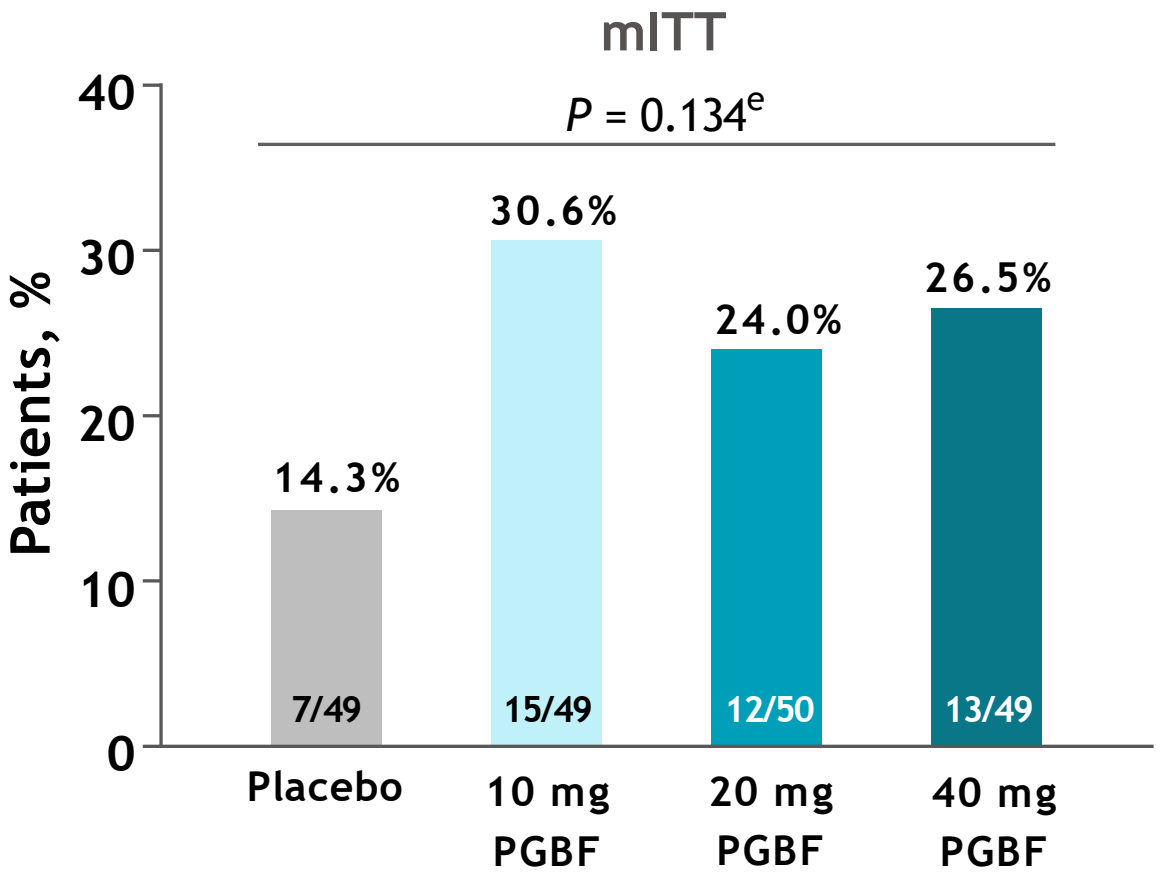
Key exploratory endpoints HFF (MRI-PDFF) and liver stiffness (MRE) at weeks 24 and 48, NAS, biomarkers through week 52 (ALT, PRO-C3, lipids, adiponectin), metabolic assessments

Safety endpoints
TEAEs

ALT, alanine aminotransferase; CPA, collagen proportionate area; HFF, hepatic fat fraction; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; PGBF, pegbelfermin; PRO-C3, N-terminal type III collagen propeptide; QW, once weekly; SC, subcutaneous; T2DM, type-2 diabetes mellitus; TEAE, treatment-emergent adverse event.

Primary Endpoint

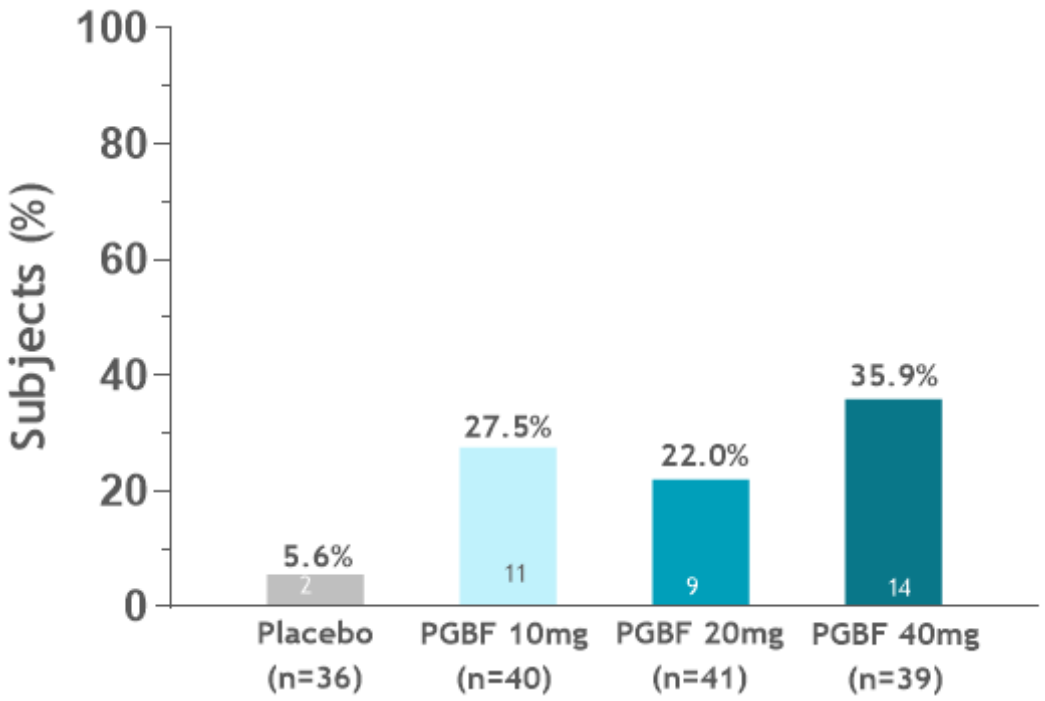
At Week 24: ≥ 1 stage improvement in fibrosis[a] without worsening of NASH[b] **OR**
NASH improvement[c] without worsening of fibrosis[d]



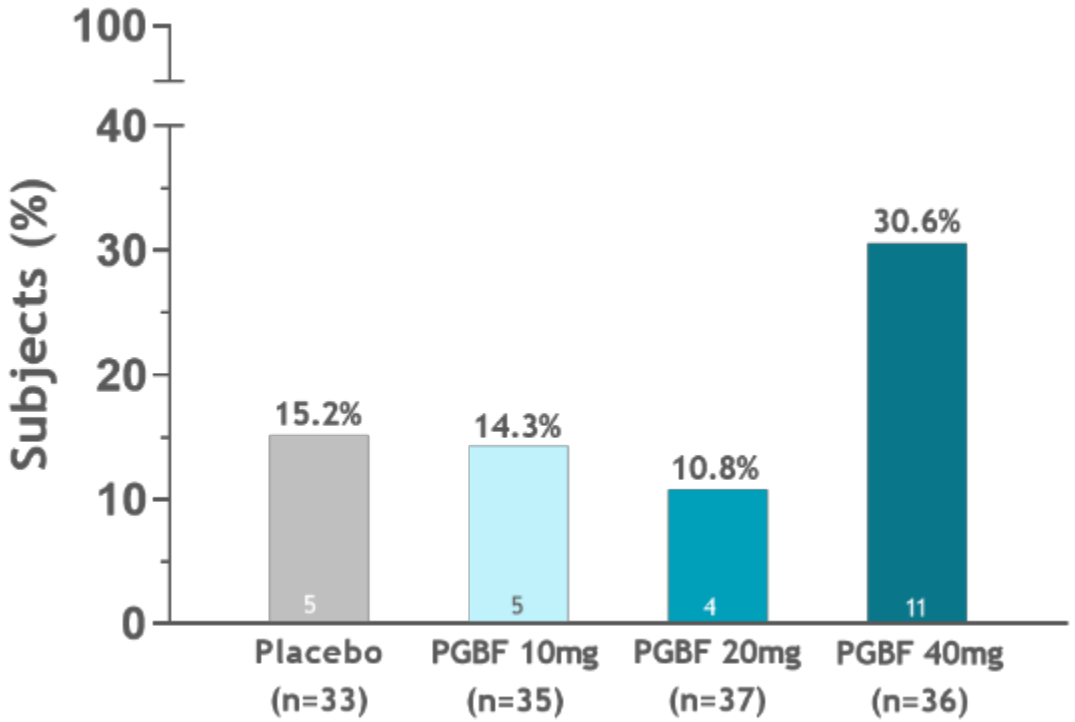
[a]Improvement of fibrosis = ≥ 1 stage decrease in NASH CRN fibrosis score; [b]Worsening of NASH = increase in NAS by ≥ 1 point; [c]NASH improvement = ≥ 2 point decrease in NAS with contribution from > 1 NAS component; [d]Worsening of fibrosis = ≥ 1 stage increase in NASH CRN fibrosis score; [e]Cochran-Armitage trend test across proportions of responders in the treatment groups at a 1-sided 0.05 level of significance provided at least 80% power if 160 patients were randomized 1:1:1:1. mITT, modified intent-to-treat; NASH, nonalcoholic steatohepatitis; PGBF, pegbelfermin.

Exploratory Endpoints: Imaging measures of steatosis and fibrosis week 24

MRI-PDFF, ≥30% Relative Reduction from Baseline

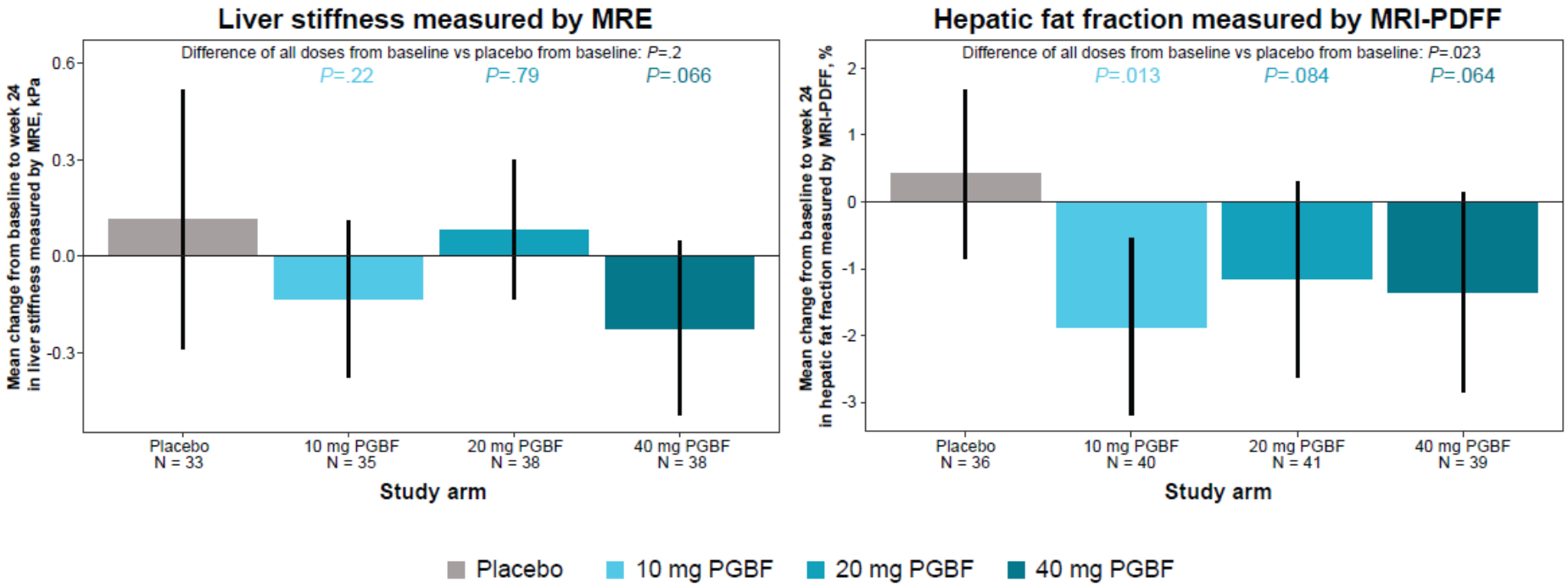


MRE, ≥15% Relative Reduction from Baseline



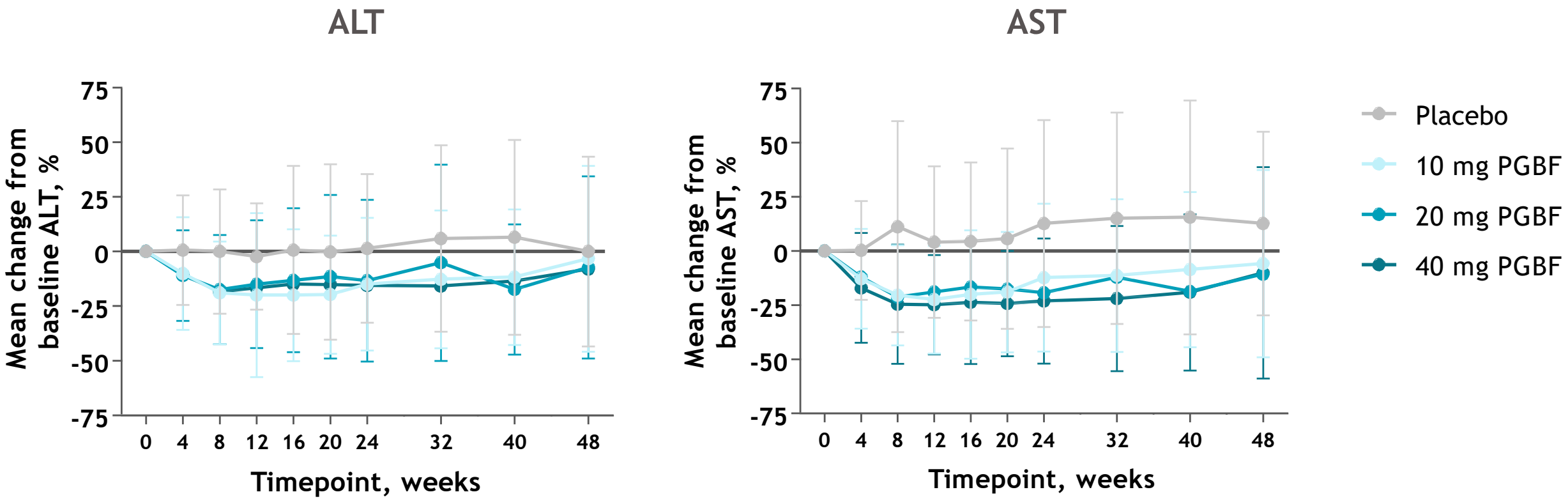
Completer analysis. MRE, magnetic resonance elastography; PGBF, pegbelfermin; .

Noninvasive imaging assessments of hepatic steatosis and stiffness week 24



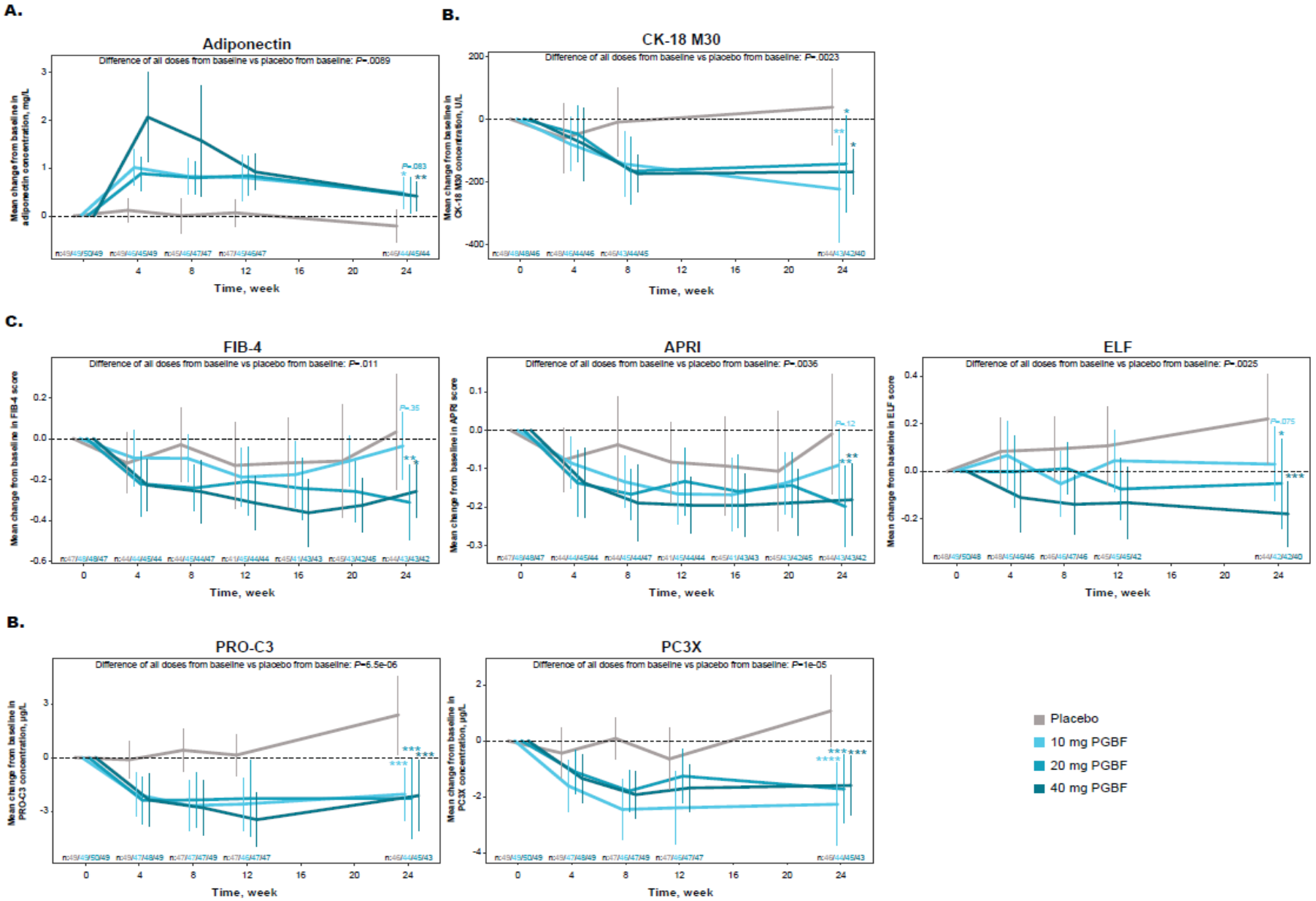
Baselines ~ 4.3 and 13.2, resp

Exploratory Endpoints: Biomarkers of Liver Injury

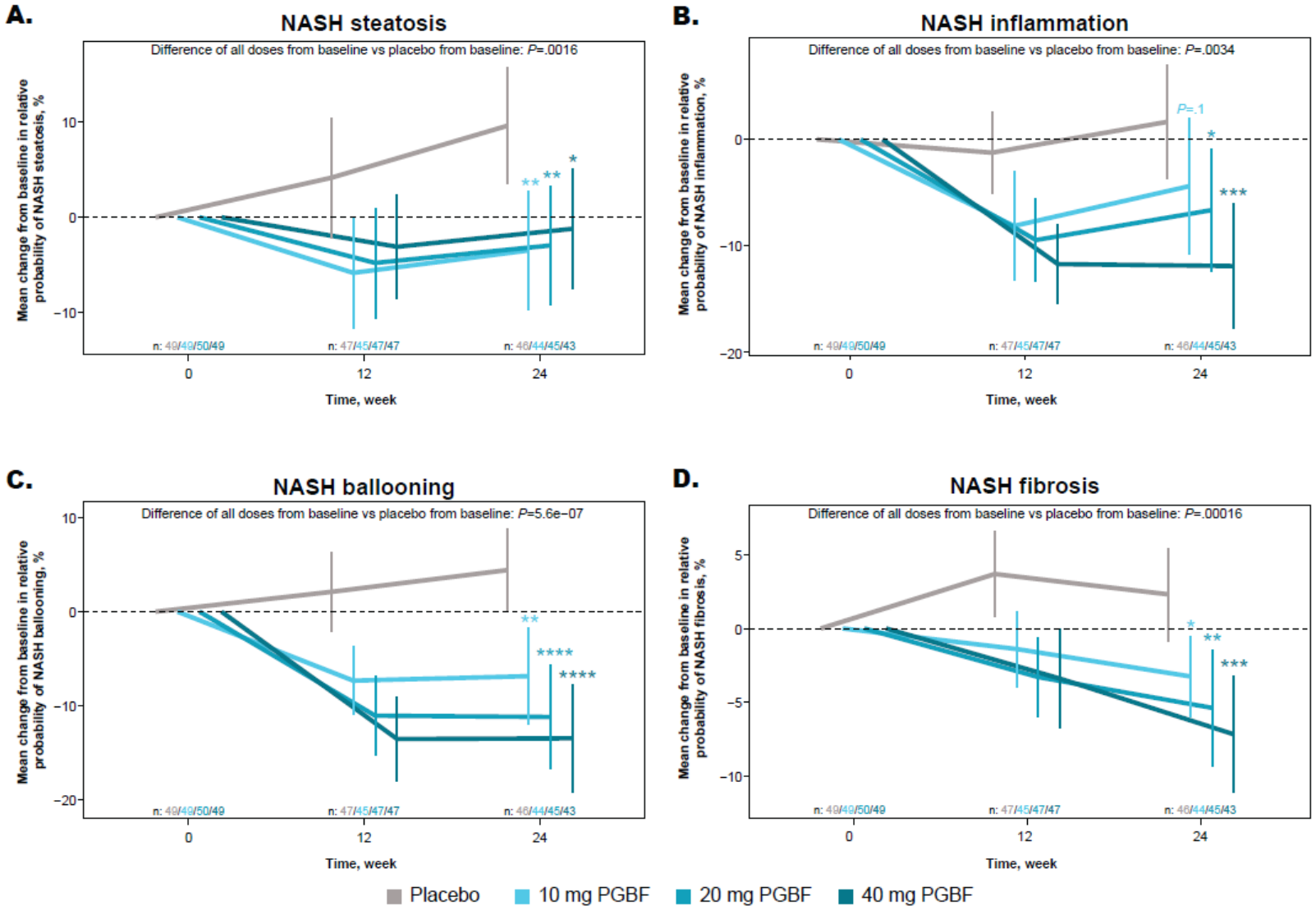


ALT, alanine aminotransferase; AST, aspartate aminotransferase; PGBF, pegbelfermin.

PGBF modulates blood biomarkers of liver injury and fibrosis

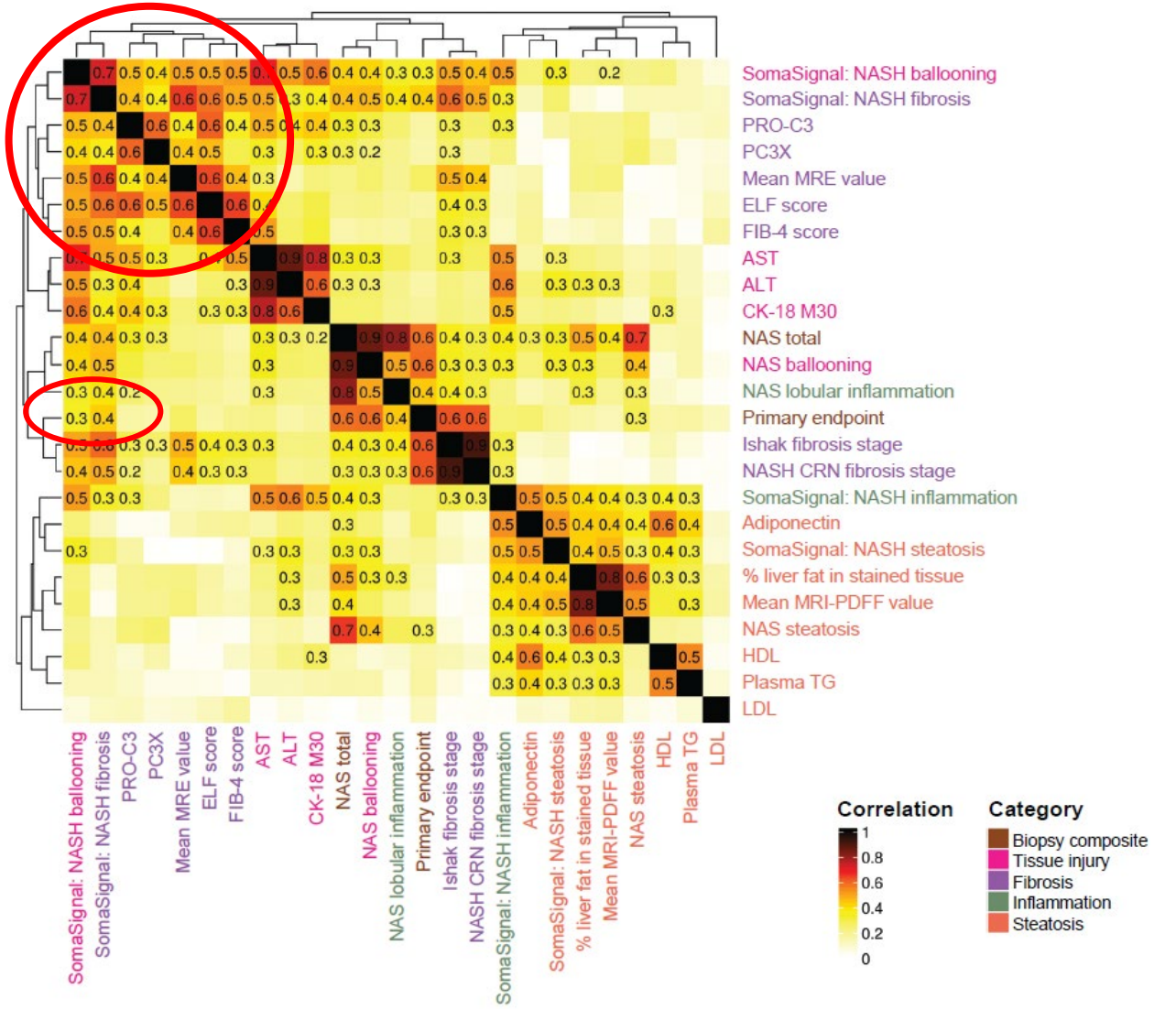


Somasignal NASH bundle



Clustering of correlation coefficients for biomarkers and histological assessments

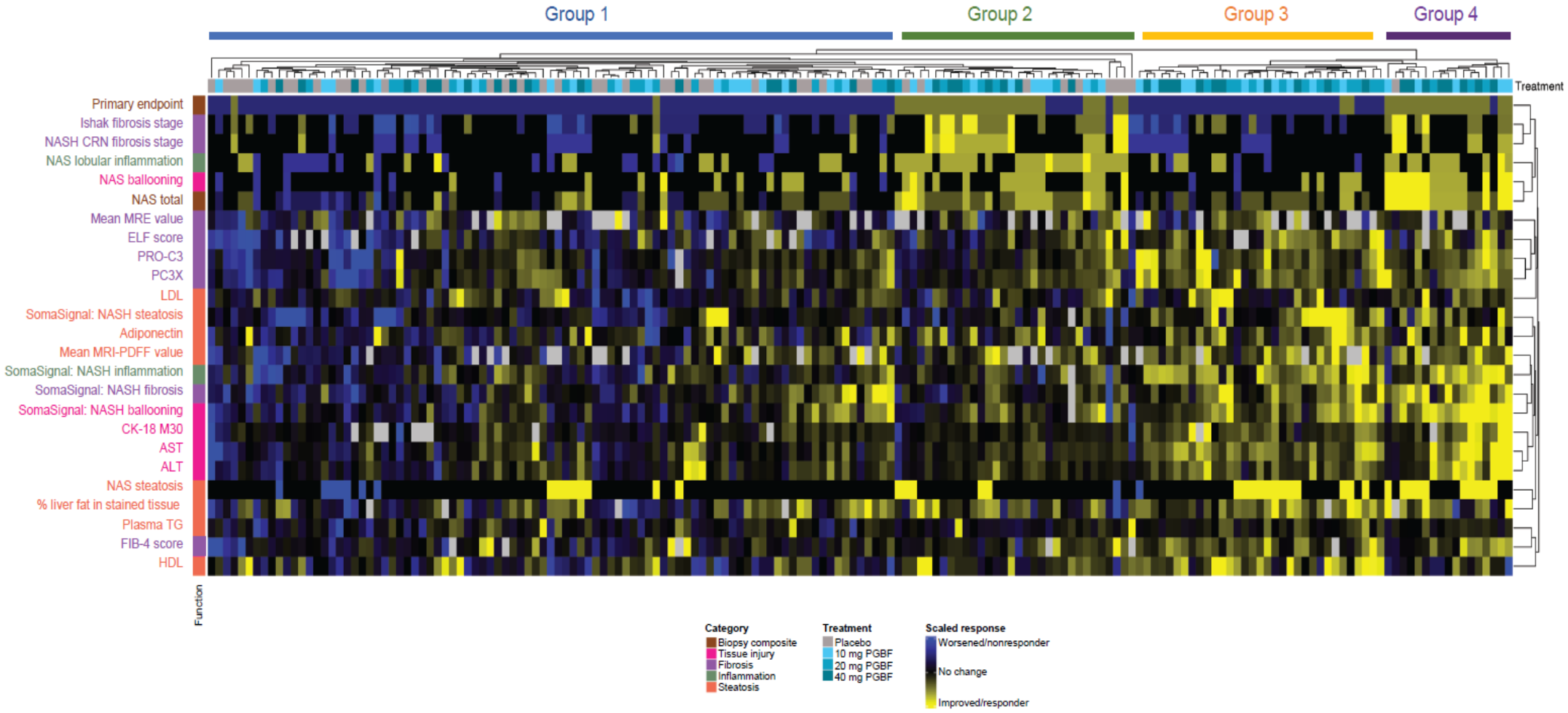
Pairwise week 24 correlation



Fibrosis NIT's cluster well together but not with the primary endpoint

Soma-NASH = only NIT to cluster with primary endpoint

Concordance analysis between primary endpoint and week 24 biomarker responses



Summary/Conclusions

- Despite Falcon 1 not meeting its primary endpoint, PGBF improved several diverse NASH-related PD biomarkers from baseline to week 24 in patients with NASH and stage 3 fibrosis
- PGBF demonstrated concordant and discordant effects on liver biopsy-based assessments of NASH and fibrosis and noninvasive assessments of metabolism, liver injury, and fibrosis
- The most distinctive correlation and concordance clustering was for antisteatotic effects, supporting primary MOA hypothesis for PGBF
- This trial is one of the first NASH clinical trials to use SomaSignal™ NASH Bundle and PC3X to monitor drug activity – these appear to be sensitive and relevant tests to reflect drug effects on hepatic histological features of NASH and advanced fibrosis
- Data suggest that combination of PGBF with a direct antifibrotic would improve performance in biopsy-related endpoints and overall efficacy
- *Possibly, greater consideration should be given to the overall totality of data when evaluating NASH drugs to limit the possibility of false negative conclusions.*

Acknowledgments

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- Elizabeth Brown
- Falcon Study participants