Efruxifermin (EFX), a long-acting FGF21 analog as a therapy for NASH

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Disclosures

Akero Therapeutics: employee, shareholder

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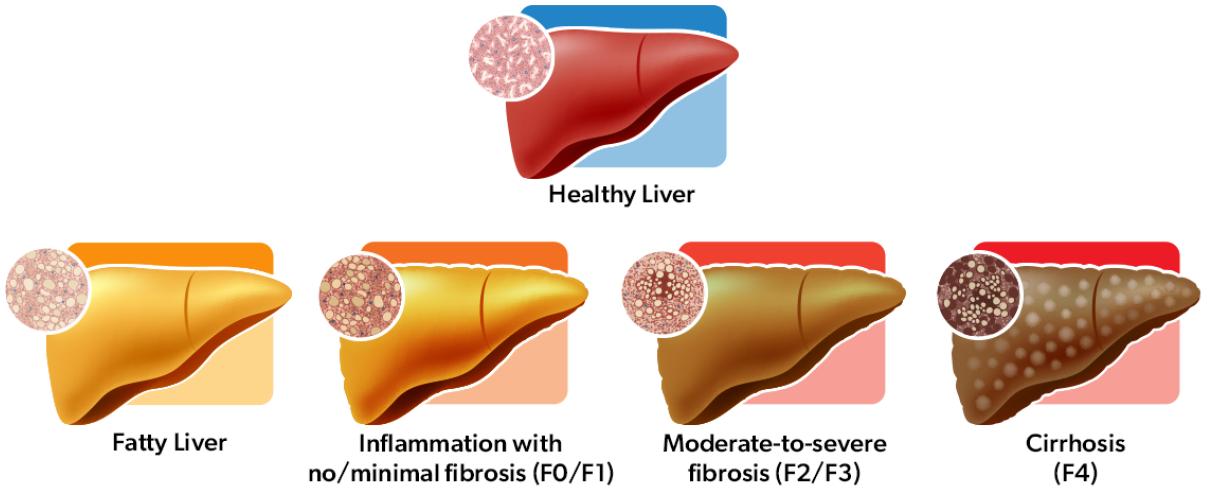
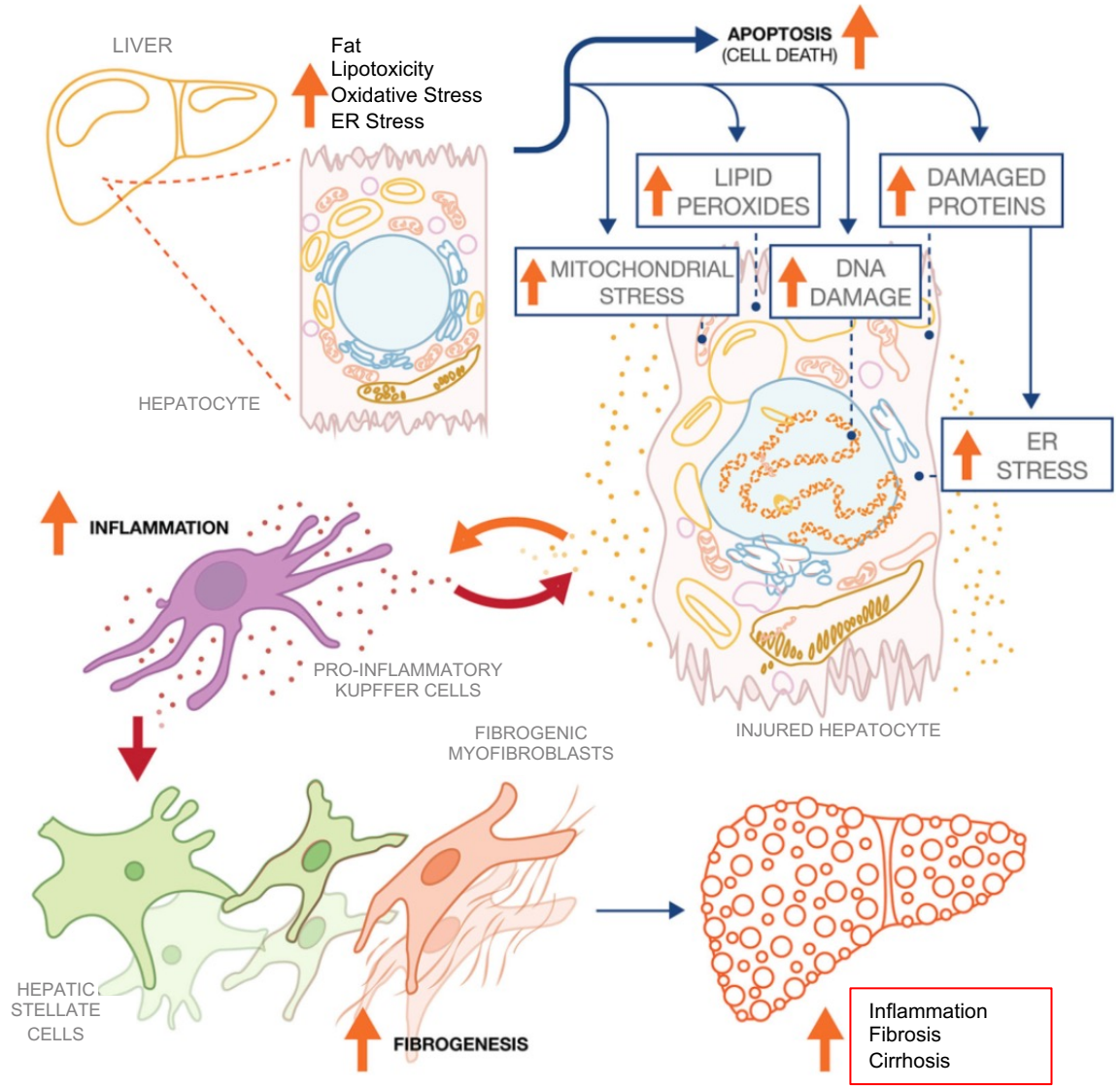
» Lipotoxicity in hepatocytes drives NASH pathology and progression



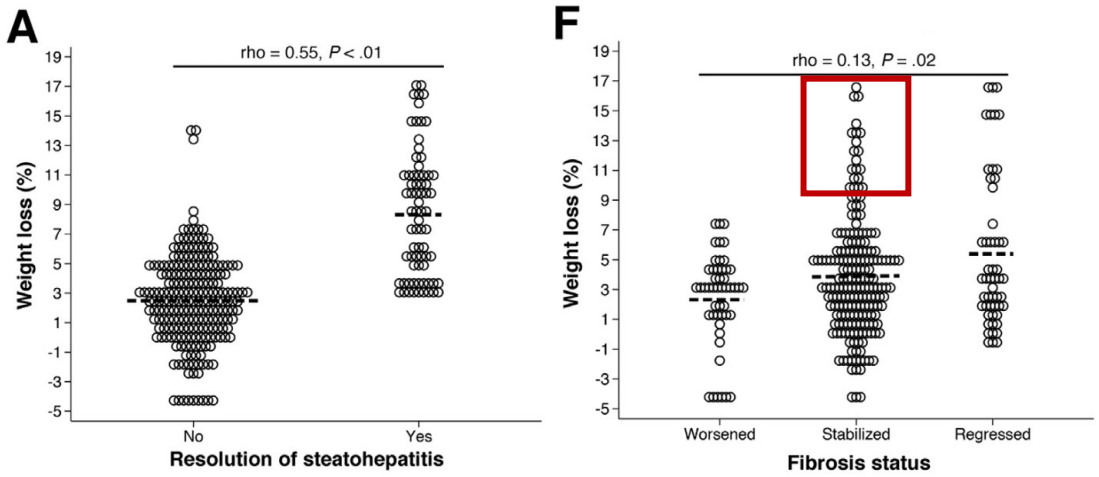


Tillman, E. J. & Rolph, T. (2020) *Front Endocrinol* **11**, 601290

Removing lipotoxic fat in hepatocytes via weight loss resolves steatohepatitis within a year, but fibrosis regression takes ≥5 years

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1] Ana Torres-Gonzalez,[1] Bienvenido Gra-Oramas,[3] Licet Gonzalez-Fabian,[3] Scott L. Friedman,[4] Moises Diago,[5] and Manuel Romero-Gomez[2]

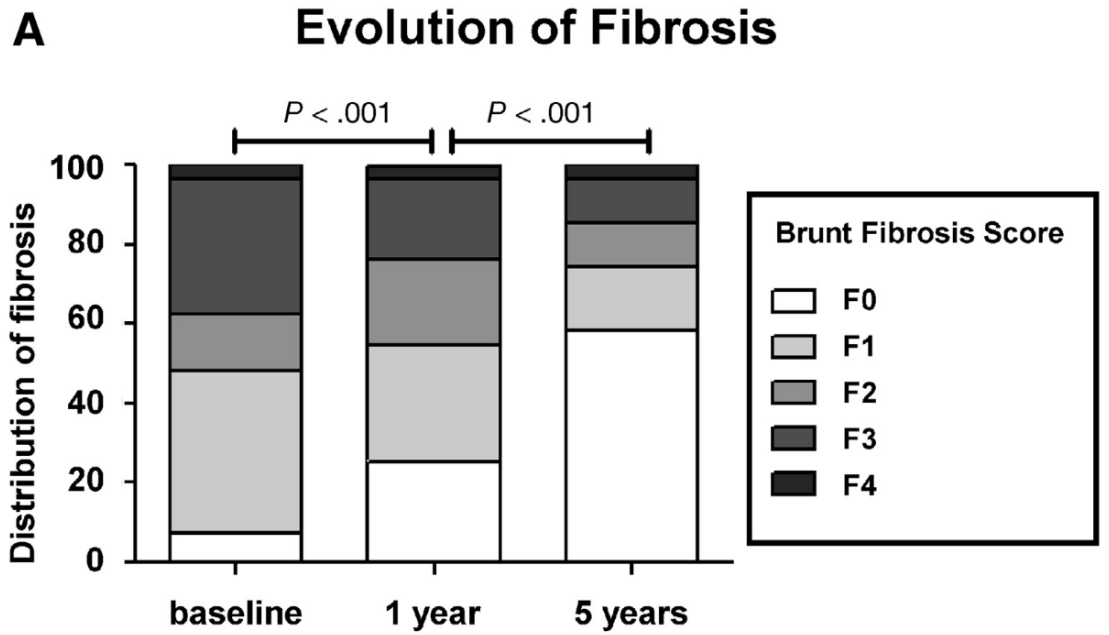


55% of patients who lost ≥10% of body weight *did not* achieve fibrosis improvement at 52 weeks

Vilar-Gomez, E et al (2015) *Gastroenterol* 149:367-78

Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis

Guillaume Lassailly,[1,2] Robert Caiazzo,[3,4] Line-Carolle Ntandja-Wandji,[1] Viviane Gnemmi,[5] Gregory Baud,[3,4] Helene Verkindt,[3] Massih Ningarhari,[1,2] Alexandre Louvet,[1,2] Emmanuelle Leteurtre,[5] Violeta Raverdy,[3,4] Sébastien Dharancy,[1,2] François Pattou,[3,4] and Philippe Mathurin[1,2]



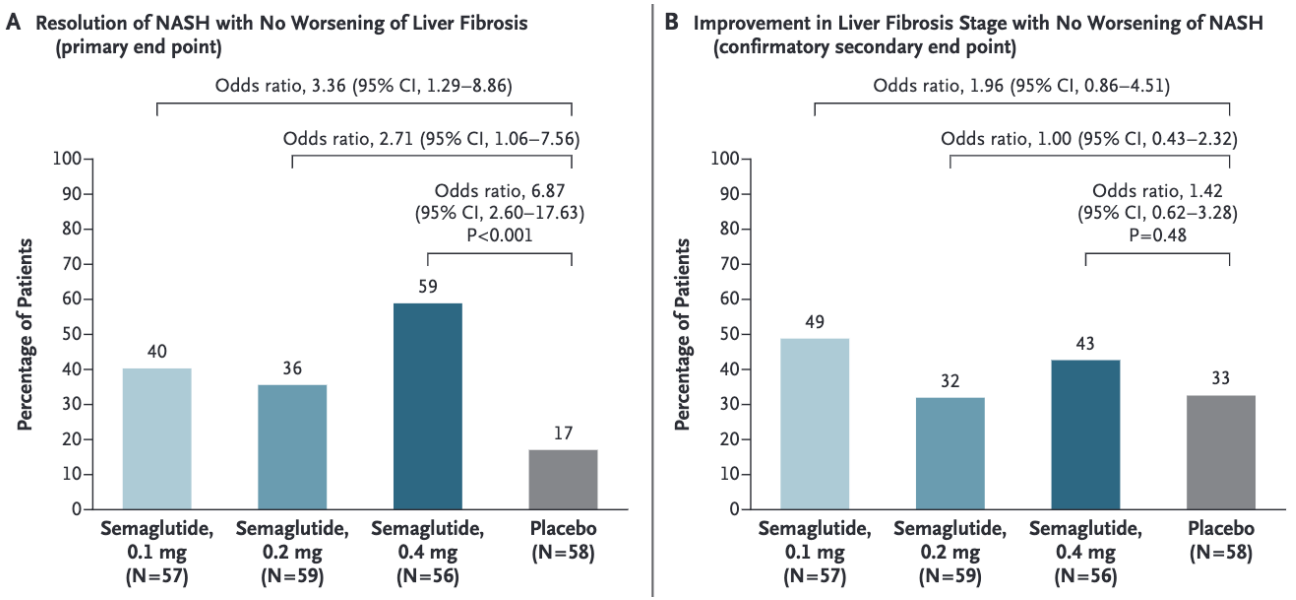
Lassailly, G. *et al.* (2020) *Gastroenterol* 159:1290-1301.e5

Pharmacology-driven reduction in lipotoxic fat in hepatocytes and improvement in glycemic control stabilizes but does not significantly improve fibrosis

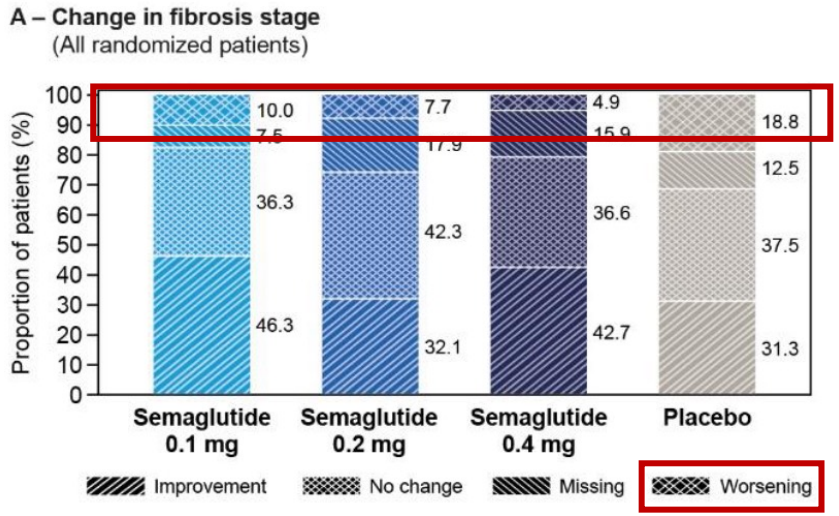
ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*



Body weight — %	−4.84	−8.91	−12.51	−0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	−0.63	−1.07	−1.15	−0.01

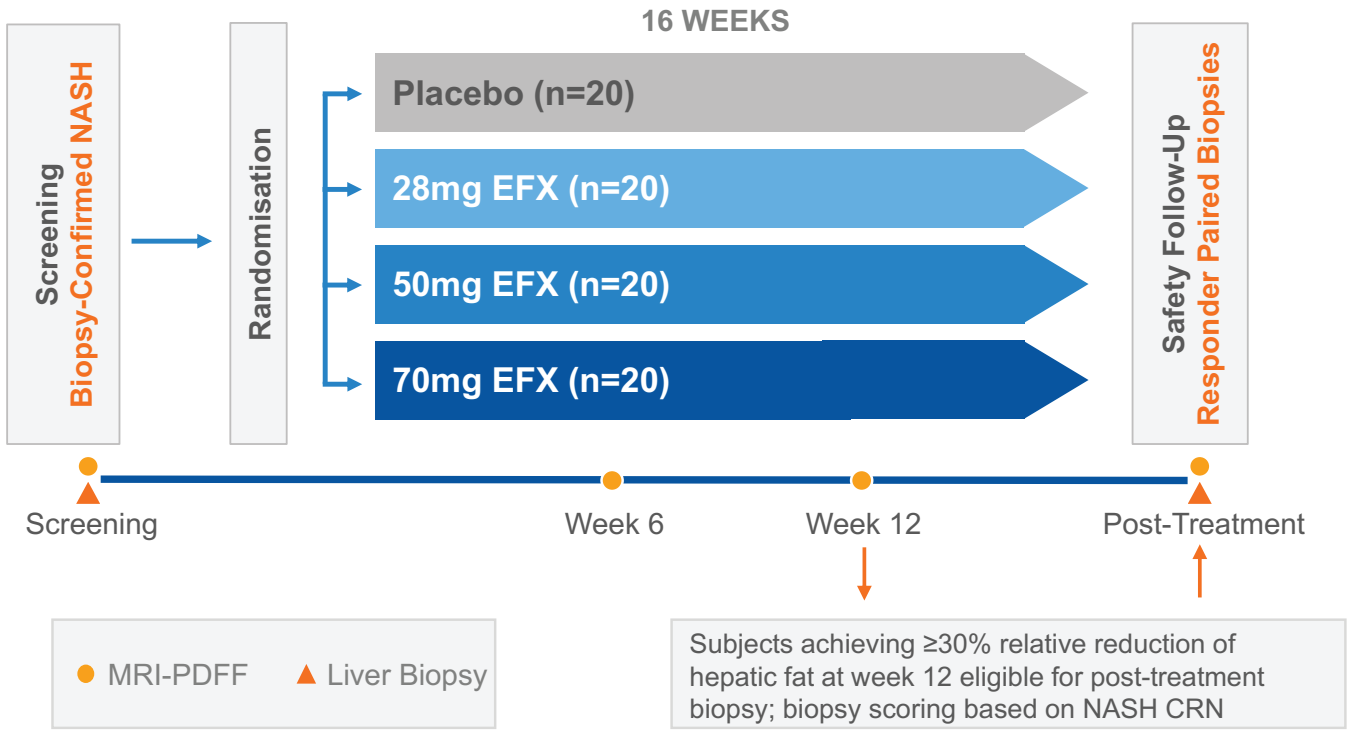


semaglutide *did not* improve liver fibrosis in patients with NASH cirrhosis after 48 weeks

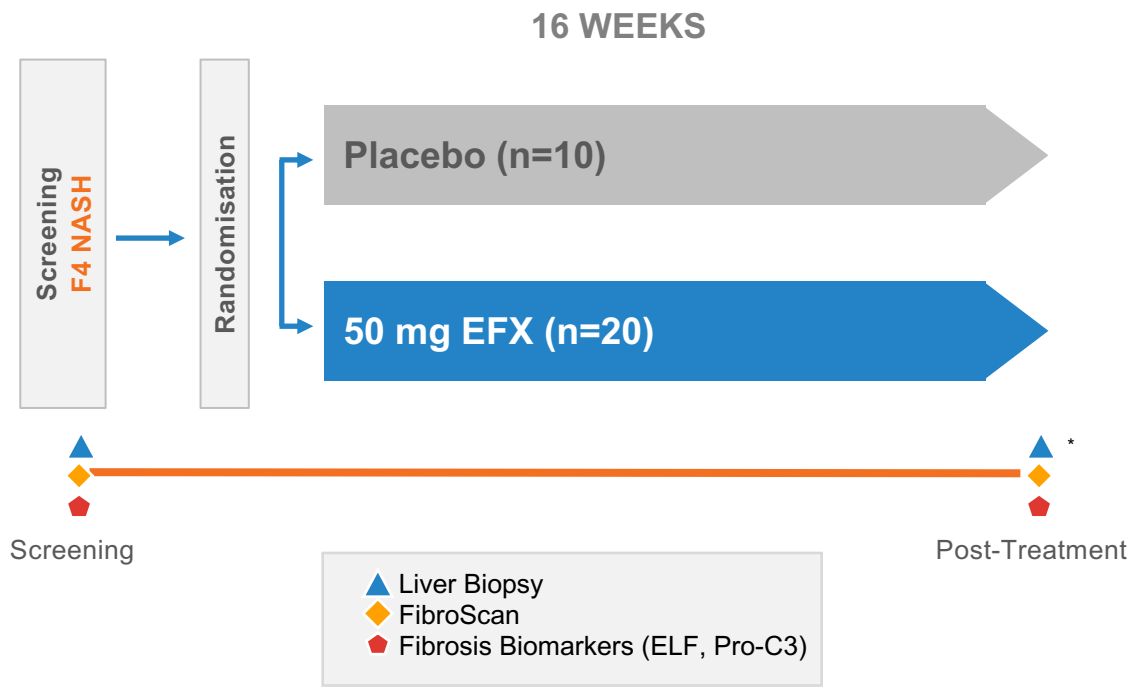
Newsome, PN et al (2020) *New Engl J Med* 384:1113-24

Ph2a BALANCED study evaluated efruxifermin (EFX), an Fc-FGF21 analog, in two cohorts: *"Main Study"* (F1-F3, moderate-to-advanced fibrosis) and *"Cohort C"* (F4, compensated cirrhosis)

Main Study

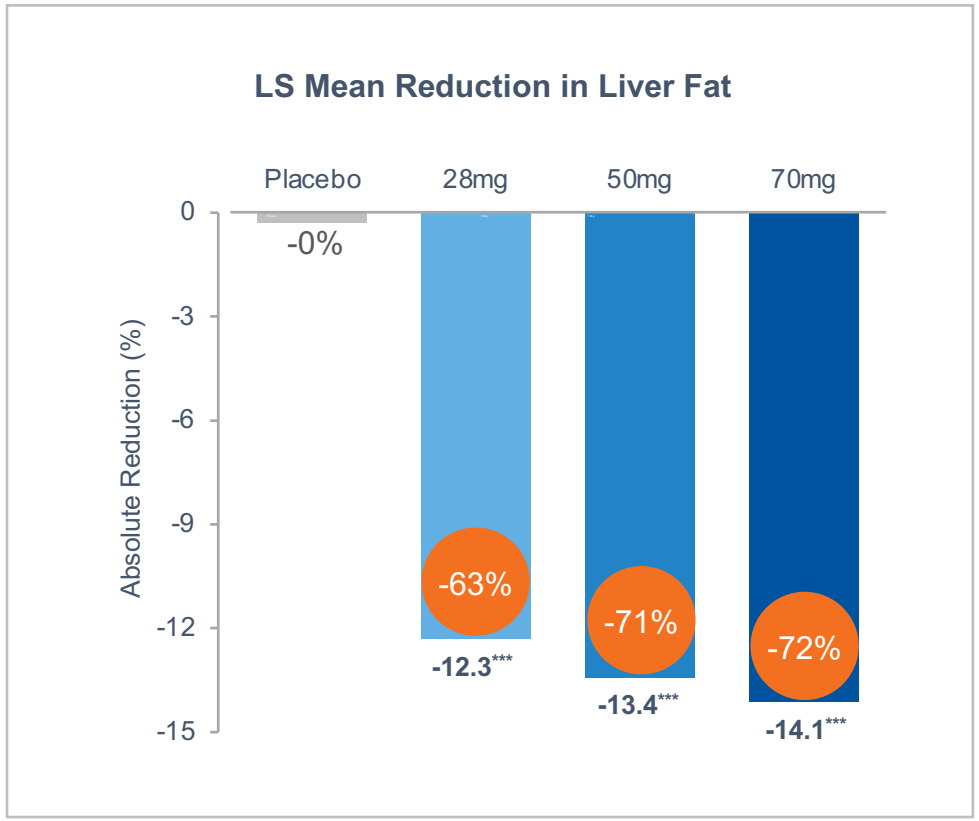


Cohort C



Harrison, SA et al (2021) *Nat Med* **27**, 1262–1271.

EFX reduced lipotoxic liver fat substantially, such that LFC was normalized (≤5%) in almost half of treated patients within 12 weeks



*** p<0.001, versus placebo (ANCOVA)

Proportion of Patients Achieving Fat Reduction Thresholds

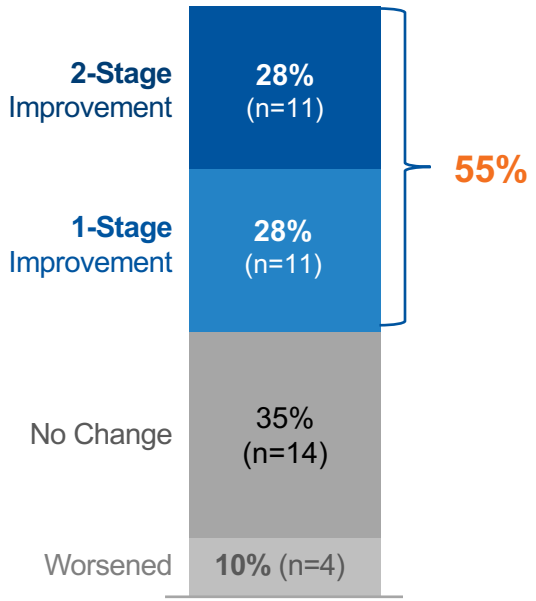
Endpoint	Placebo (N=20)	28mg (N=16)	50mg (N=17)	70mg (N=15)
Relative Reduction in Liver Fat				
≥30%	10%	100%**	100%***	100%***
≥50%	5%	69%**	100%***	93%***
≥70%	5%	50%*	53%**	80%***
Normalization of Liver Fat Content				
≤5%	5%	25%*	53%**	67%***

* p<0.05, ** p<0.01, *** p<0.001, versus placebo (ANCOVA)

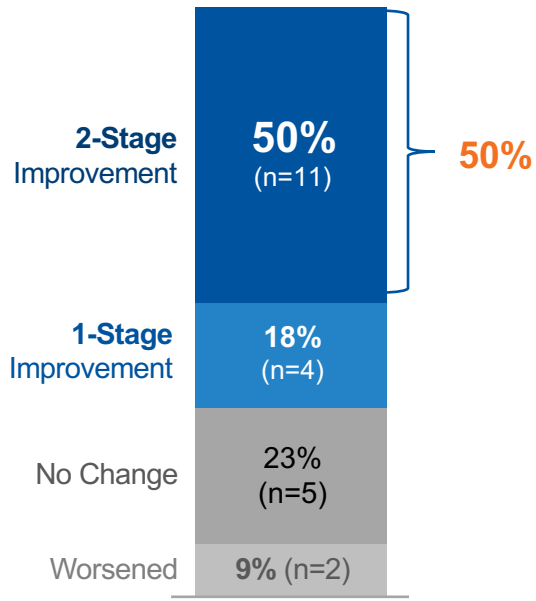
Harrison, SA et al (2021) *Nat Med* **27**, 1262–1271.

Fibrosis improved by ≥1 stage in half of pair-biopsied F1-F3 patients, and by 2 stages in half of F2-F3 patients, after just 16 weeks of EFX treatment

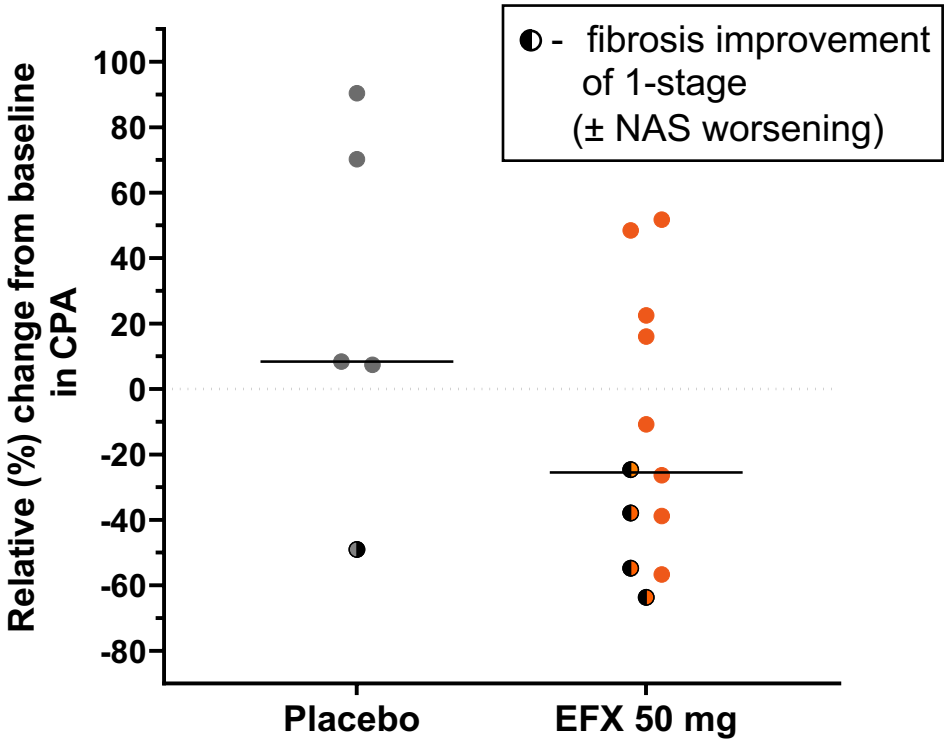
Fibrosis Change in EFX-Treated Patients with Baseline F1-F3 Fibrosis (n=40)



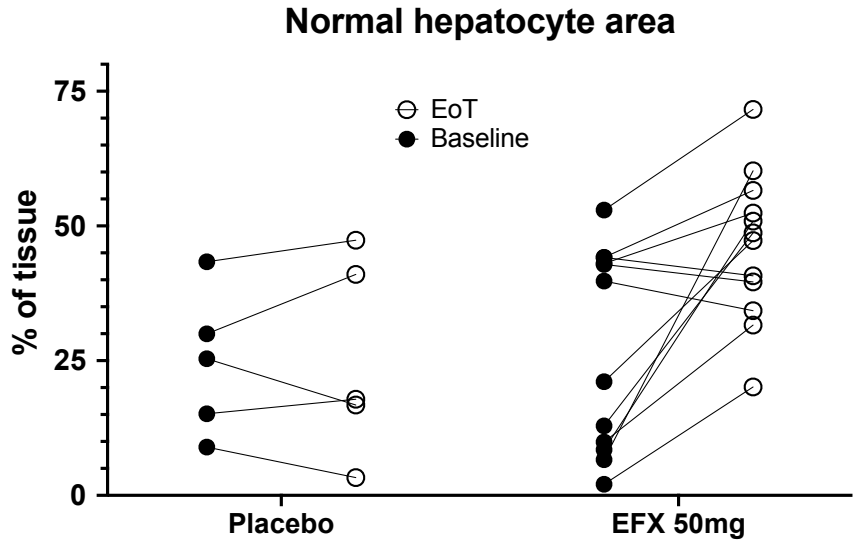
Fibrosis Change in EFX-Treated Patients with Baseline F2 or F3 Fibrosis (n=22)

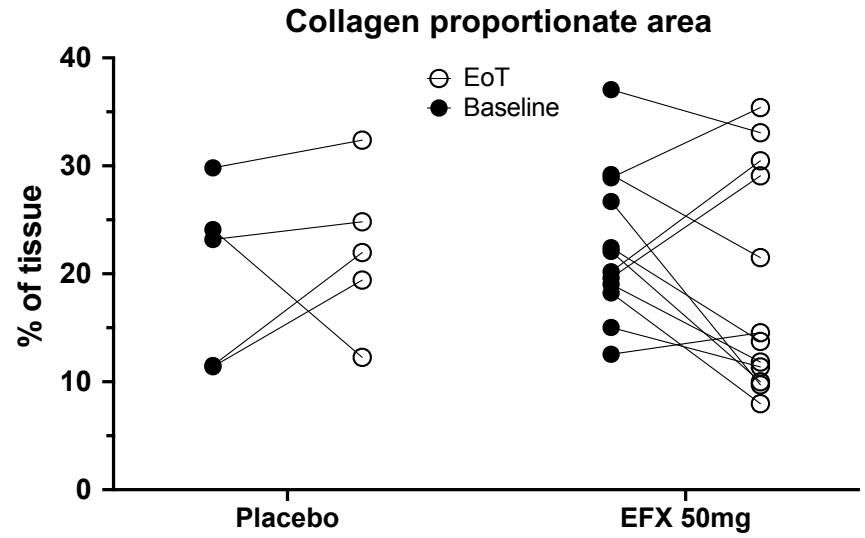


In patients with compensated cirrhosis, EFX reduced fibrotic area and increased normal hepatocyte area, as scored by AI-based method (*PathAI*)



Median (IQR) Relative (%) Change in Collagen Proportionate Area from Baseline	
Placebo	EFX 50 mg
+8.4% (-20.8%, 80.3%)	**-25.5%** (-50.8%, 20.8%)





In patients with F1-F3 NASH, EFX consistently reduced Pro-C3 below the threshold associated with increased risk of ≥F2 fibrosis in NASH patients

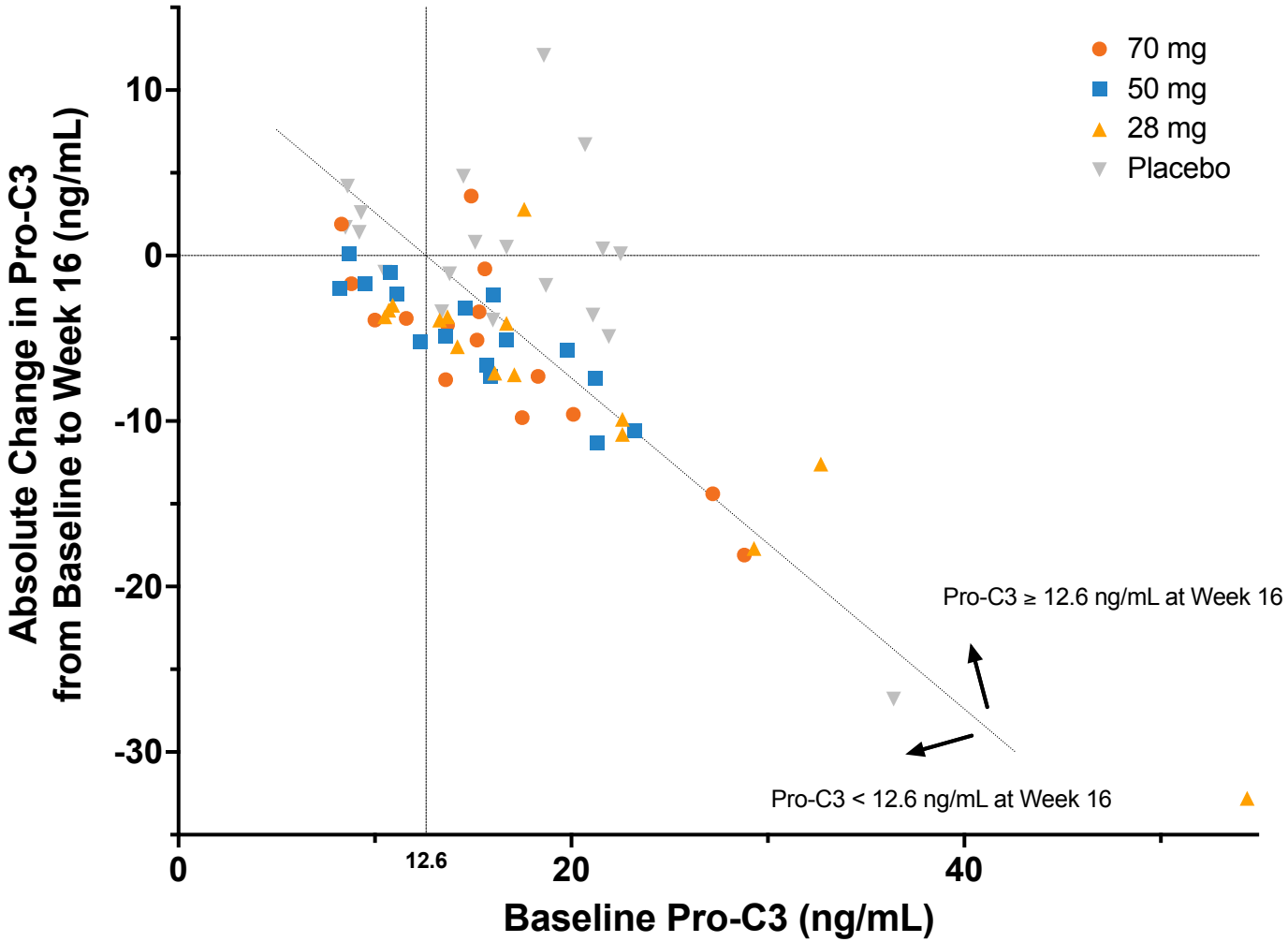


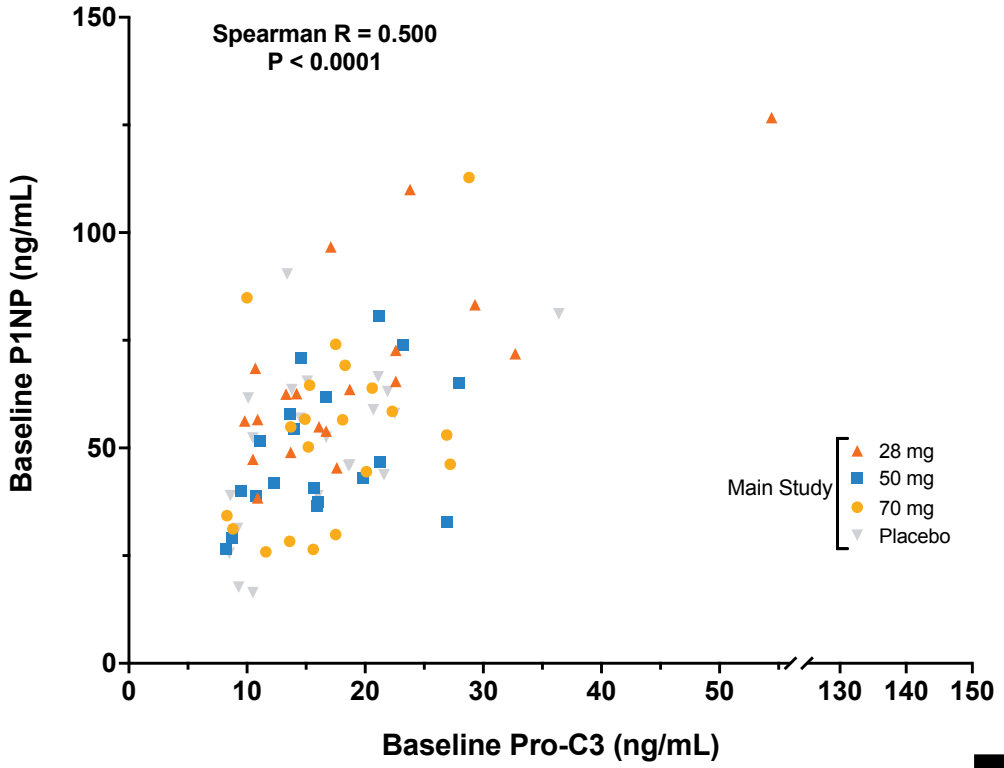
Table 4. Ability of PRO-C3 to distinguish between relevant subgroups of NAFLD/NASH patients.

	AUC [95% CI]	Cut-off [95% CI]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p* value
F ≥2	0.83 [0.77–0.88]	12.6 [12.0–14.8]	63.0	91.2	95.4	46.0	<0.0001
F ≥3	0.79 [0.73–0.85]	12.7 [10.9–15.3]	73.6	75.0	72.9	75.7	<0.0001
Fibrotic NASH	0.75 [0.68–0.81]	12.6 [10.5–15.5]	67.5	72.5	74.3	65.5	<0.0001

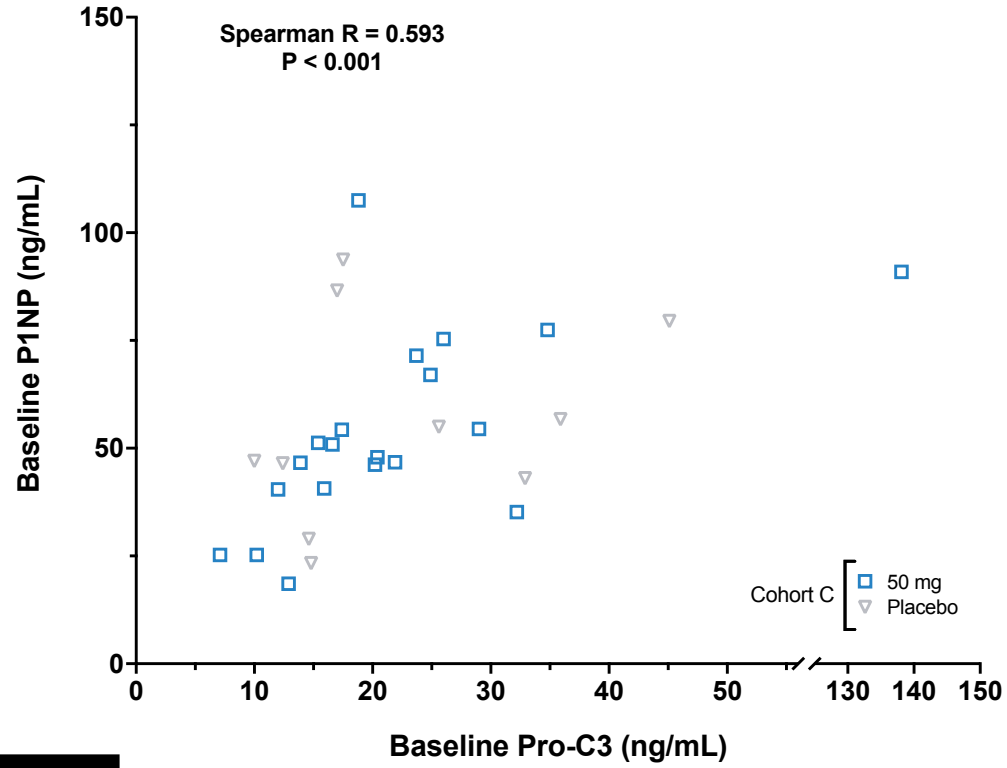
Erhardtsen, E *et al.* (2021) *JHEP reports* 3:100317

Synthesis of two major components of ECM in soft-tissue fibrosis, type-I and -III collagen, are correlated at baseline, particularly in patients with advanced fibrosis-to-cirrhosis

F1-F3 NASH (Main Study)



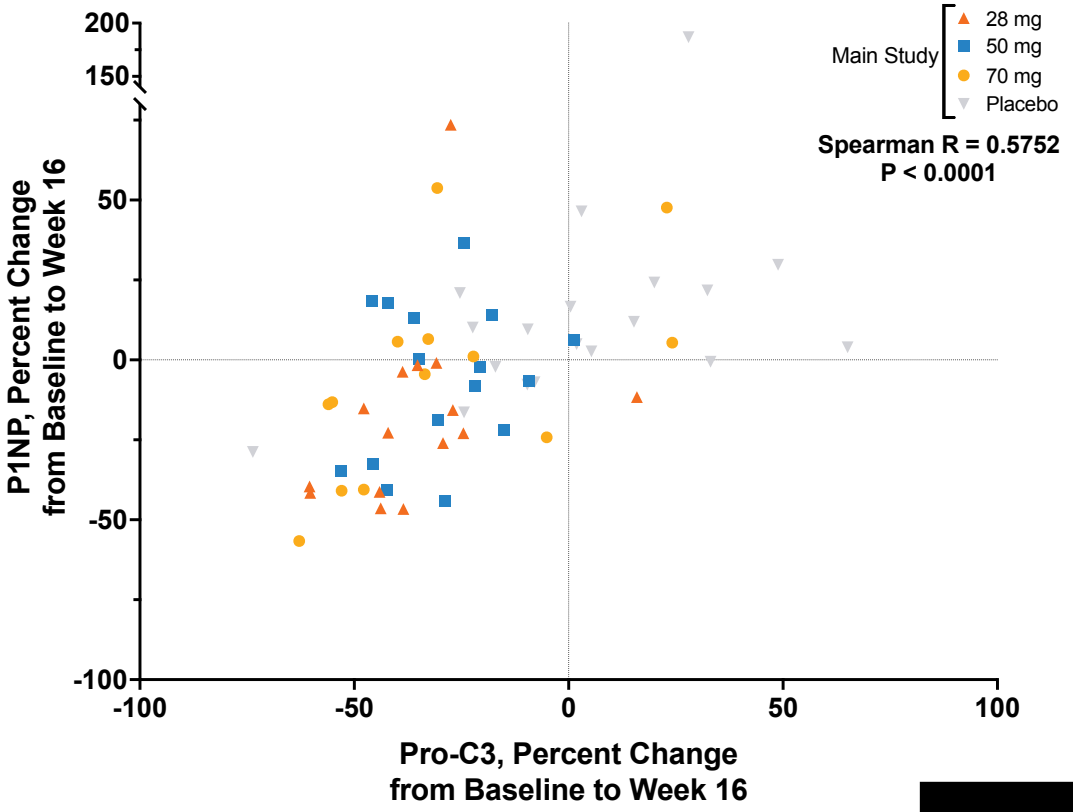
F4 NASH (Cohort C)



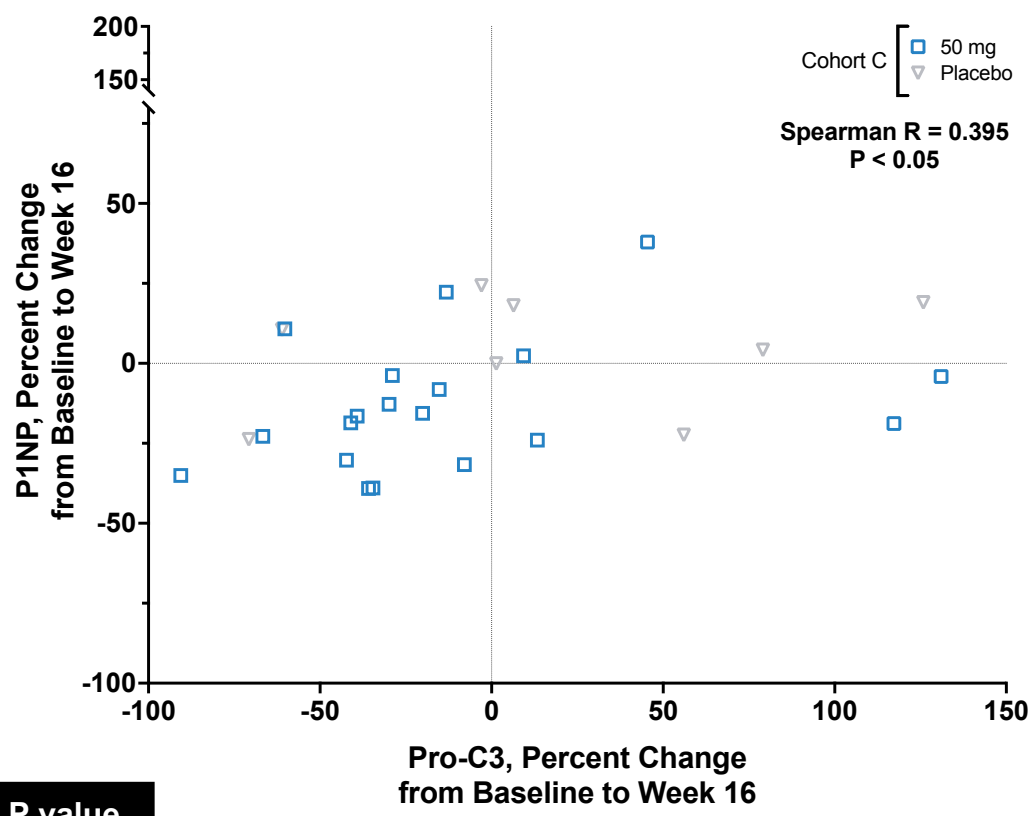
	Spearman R	P value
F1	0.256	>0.1
F2	0.612	<0.01
F3	0.566	<0.01
F4	0.644	<0.001

Across all patients (F1-F4) in BALANCED, EFX appears to reduce synthesis of collagen-I and collagen-III synthesis in a concerted fashion

F1-F3 NASH (Main Study)

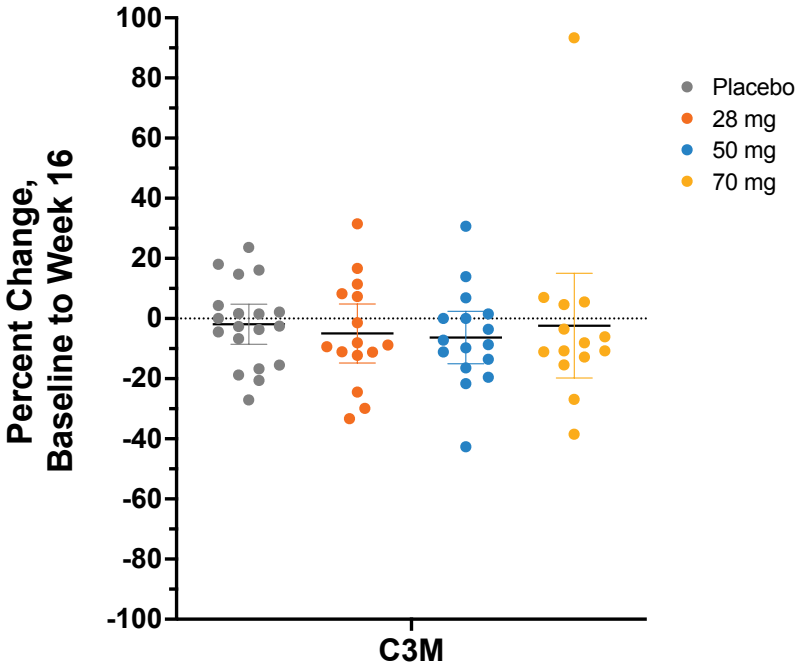


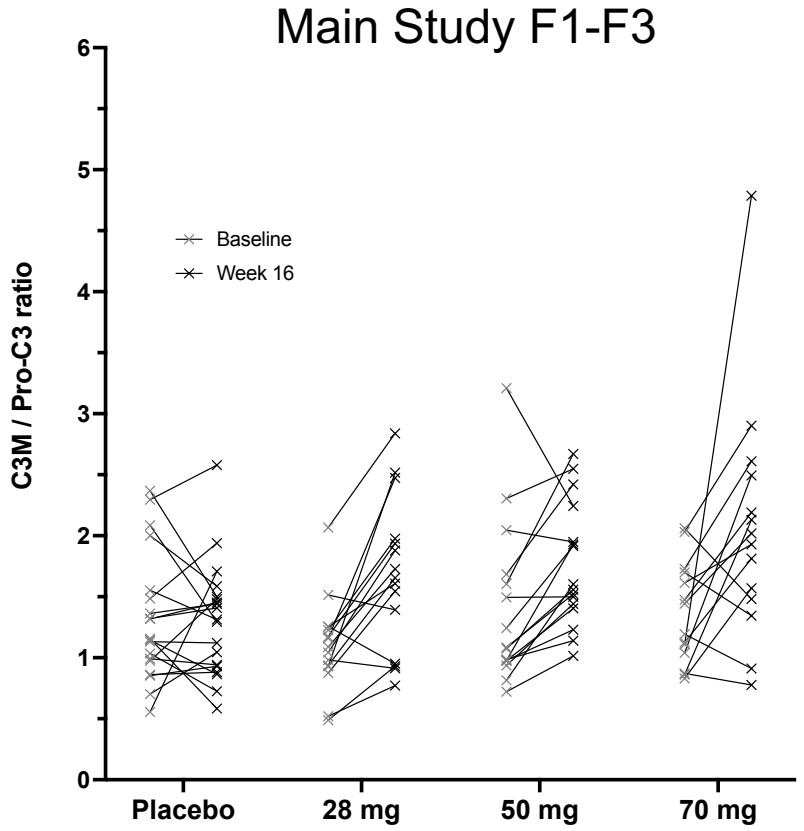
F4 NASH (Cohort C)

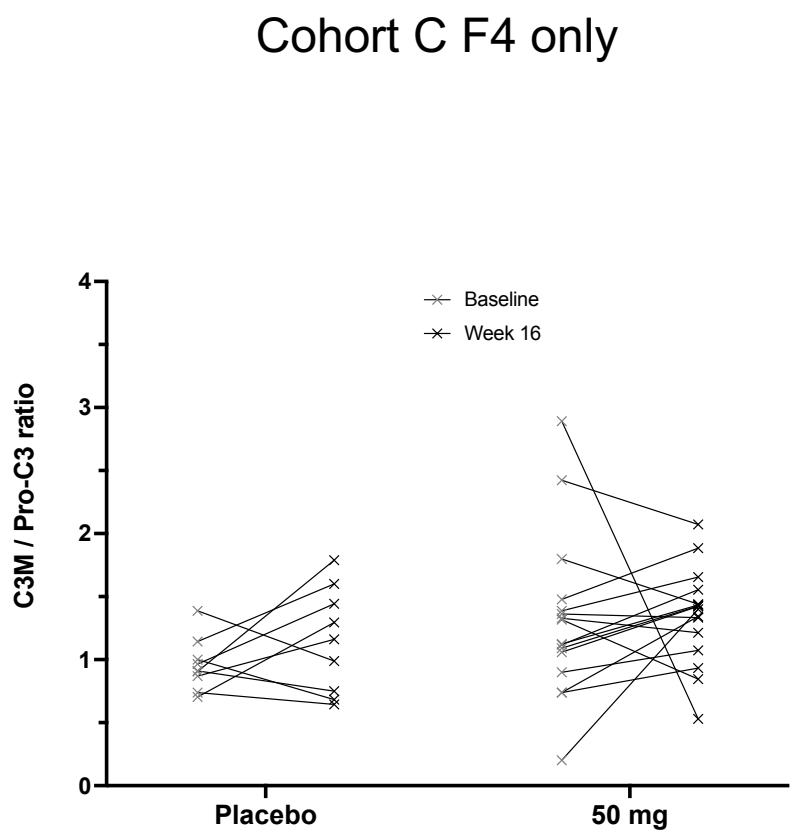


	Spearman R	P value
Main Study	0.575	<0.0001
Cohort C	0.395	<0.05
Combined	0.505	<0.0001

C3M, a marker of collagen-III degradation, likely increases relative to soft-tissue collagen mass, leading to a shift in balance of collagen turnover from synthesis to degradation







Antifibrotic activity of EFX in patients with NASH appears consistent with preclinical demonstration of FGF21's antifibrotic activity

- ER stress[1] and oxidative stress[2] induce FGF21 *in vitro*, and diverse hepatic stressors (alcohol[3], fructose[4], acetaminophen[5], protein restriction[6]) induce FGF21 *in vivo*
- FGF21 up-regulates pathways associated with protecting against these stressors,[1-6] as well as suppressing induction of pro-apoptotic pathways[1]

- FGF21 improves fibrosis independent of metabolic etiology:
  - Suppresses human, rat HSC activation and collagen expression *in vitro*[7,8,9]
  - Restores apoptosis and inhibits proliferation of activated rat HSC *in vitro*[9]
  - Inhibits fibrogenesis in chemically-induced liver fibrosis[8,9,10]
  - Protects the exocrine pancreas from cerulein-induced pancreatitis and fibrosis[11]
  - Protects airway epithelia from bleomycin-induced pulmonary fibrosis[12]
  - Protects the heart against oxidative damage, fibrosis, and cardiac dysfunction[13,14,15]

Presence and resolution of underlying metabolic insult is not required for antifibrotic activity of FGF21

[1]Jiang S *et al.* (2014) *J Biol Chem* 289:29751-65.
[2]Wang X *et al.* (2016) *Cell Metab* 60:977-89.
[3]Desai BN *et al.* (2017) *Mol Metab* 6:1395-1406.
[4]Fisher FM *et al.* (2017) *Mol Metab* 6:14-21.
[5]Ye D *et al.* (2014) *Hepatology* 60:977-89.
[6]Laeger T *et al.* (2014) *J Clin Invest* 124:3913-22.
[7]Le CT, *et al.* (2018) *PLoS ONE* 13: e0192146.
[8]Xu P, *et al.* (2017) *Toxicol Appl Pharmacol* 290:43-53.
[9]Meng F et al (2012) Mol Biol Rep 48: 7153-7163.
[10]Opoku YK *et al.* (2020) *EXCLI J* 19:567-81.
[11]Johnson CL, *et al.* (2009) *Gastroenterol* 137:1795-1804.
[12]Zhang S *et al.* (2018) *BioMed Pharmacother* 103:1516-25.
[13]Zhang X *et al.* (2019) *Heart Fail Rev* 24:1005-17.
[14]Planavila A *et al.* (2015) *Cardiovasc Res* 106:19-31
[15]Ma Y et al (2021) Int J Mol Sci 22: 12341.

Acknowledgments

- Patients with NASH fibrosis who participated in the BALANCED Main Study and Cohort C
- Physicians, investigators, and staff at Akero's clinical sites, including Dr. Stephen Harrison
- Dr. Cindy Behling, Pacific Rim Pathology: central read of liver biopsy slides
- Medpace and Akero clinical development team for design and conduct of BALANCED
- PathAI: digital pathology analysis
- Nordic Biosciences: measurement of markers of collagen turnover
- Erik Tillman: analysis and interpretation of the data presented