Normalization of liver fat by efruxifermin is associated with improved liver, adipose tissue, and whole-body metabolic health

Erik J Tillman, PhD

Associate Director, Translational Biology & Pharmacology

Akero Therapeutics

August 10th, 2022

Disclosures

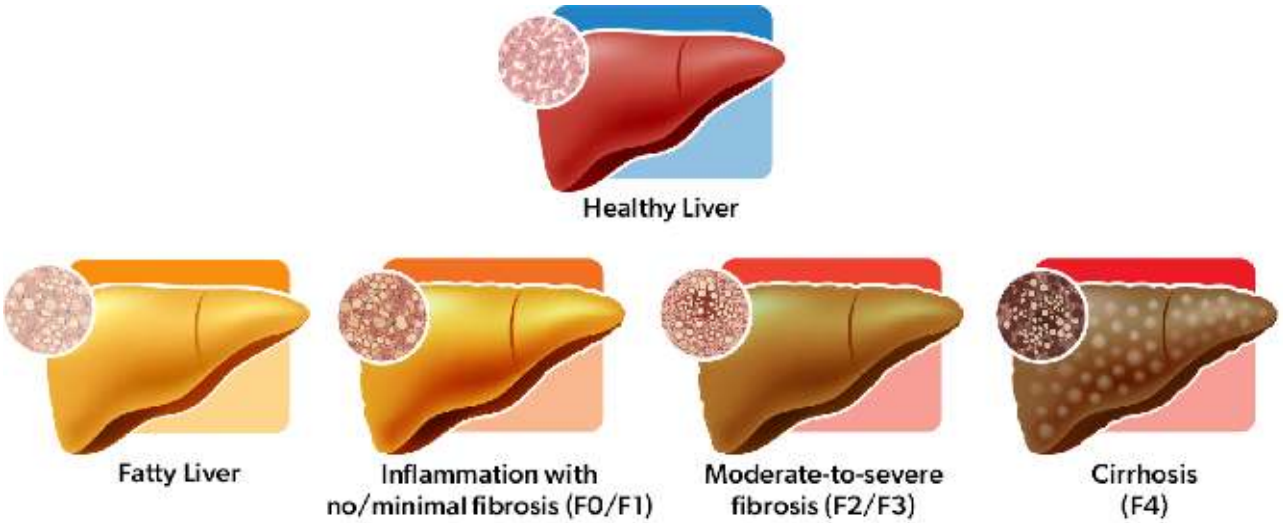
Akero Therapeutics: employee, shareholder

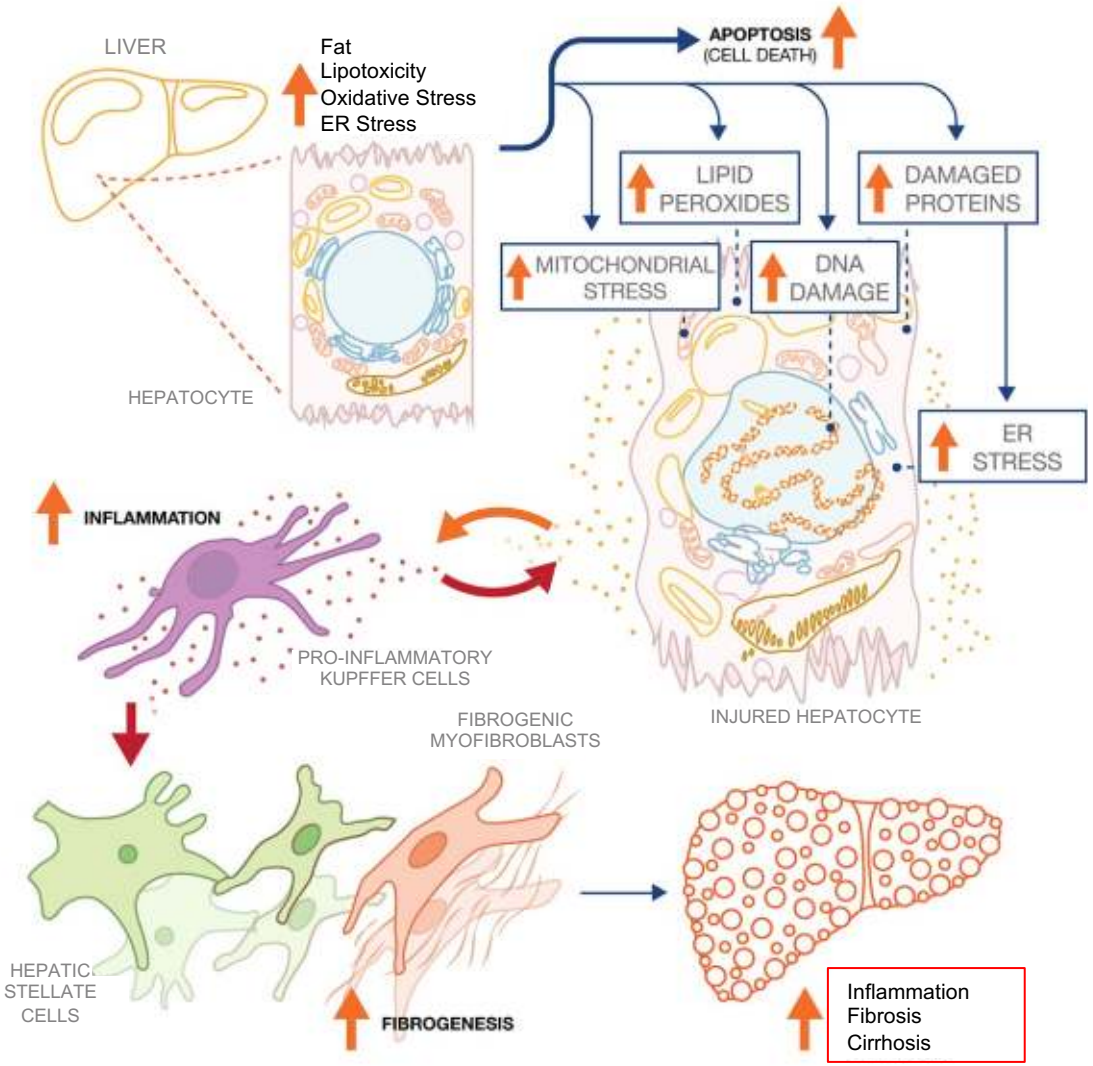
Safe Harbor

This presentation may contain “forward-looking statements” of Akero Therapeutics, Inc. (“we,” “us,” “our,” “Akero” or the “Company”) within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to current beliefs, expectations and assumptions regarding: the future of our business; future plans and strategies, including our expectations around the therapeutic potential and clinical benefits of Efruxifermin (“EFX”); our development plans for EFX, including our belief in the unique potential of EFX as a foundational NASH therapy; our preclinical and clinical results, including our safety/tolerability, laboratory measures and paired biopsy data from our Phase 2a BALANCED study; the potential benefits resulting from the PRIME and Fast Track designations of EFX; the Phase 2b HARMONY and SYMMETRY studies, including expected timing to complete enrollment, report preliminary results, and other related milestones; the availability of a new drug product formulation to support Phase 3 clinical trials; risks related to the competitive landscape; expectations regarding the Company’s use of capital, expenses and other future financial results; and the potential impact of COVID-19 on strategy, our employees, supply chain, future operations and clinical trials. Words such as, but not limited to, “look forward to,” “believe,” “expect,” “anticipate,” “estimate,” “intend,” “plan,” “would,” “should” and “could,” and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in our most recent annual report on Form 10-K filed with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties, and other important factors in our other subsequent filings with the Securities and Exchange Commission. All information in this presentation is as of the date hereof, and we undertake no duty to update this information unless required by law.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company’s own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

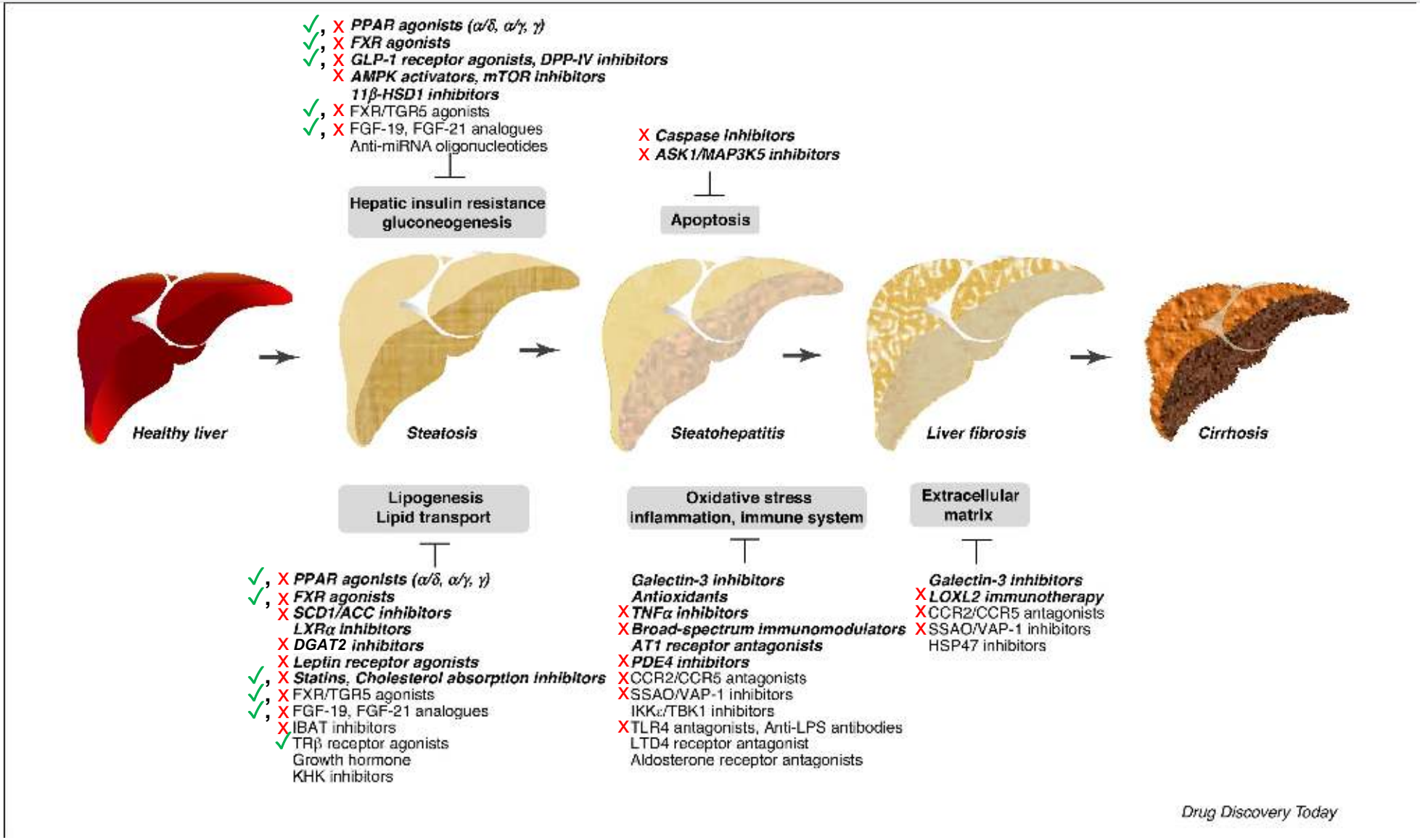
Lipotoxicity in hepatocytes drives NASH pathology and progression





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

Investigational mechanisms acting on single steps underlying NASH pathogenesis have met with limited success

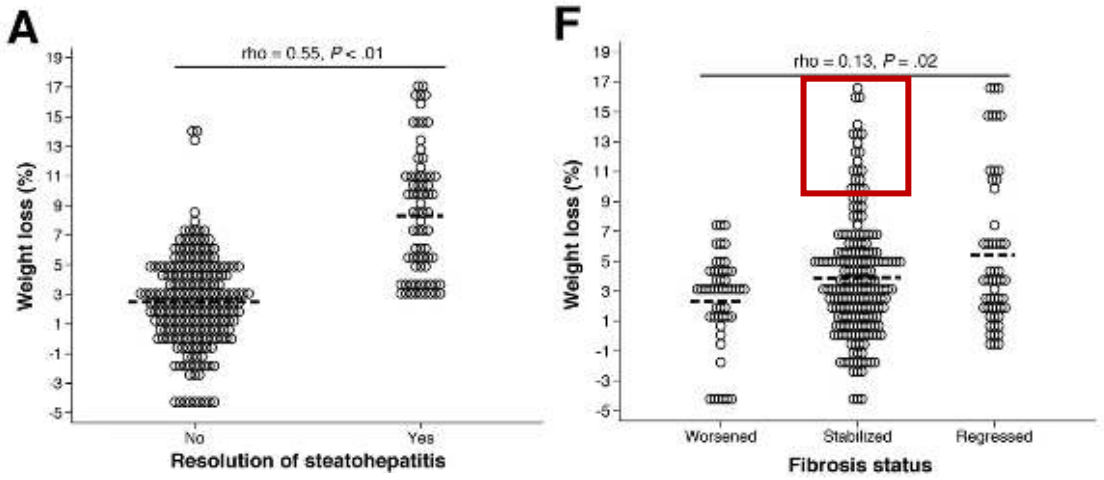


Adapted from Hansen, H. H. *et al.* (2017) *Drug Discov Today* 22:1707–1718

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]

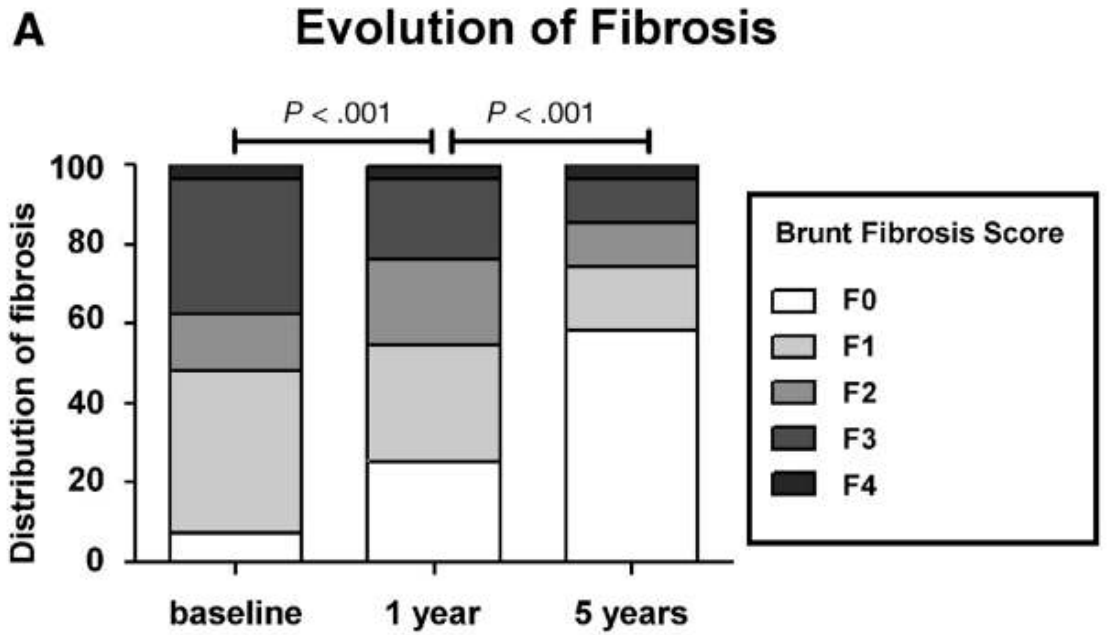


55% of patients who lost ≥10% of body weight *did not* achieve fibrosis improvement at 52 weeks

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]



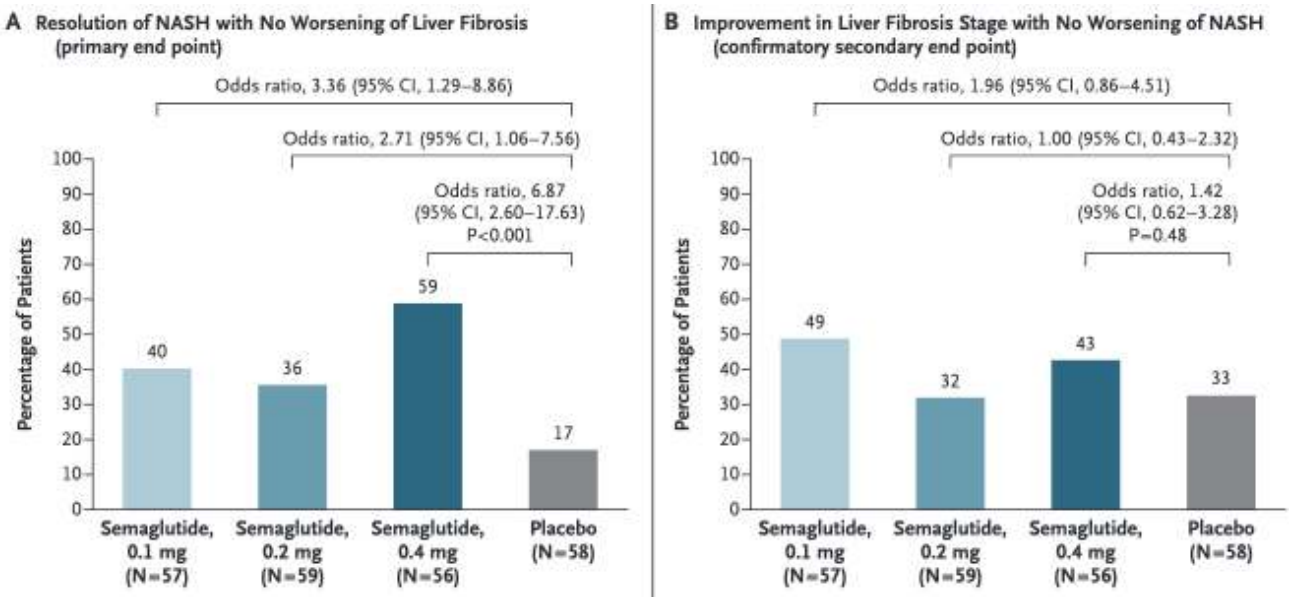
Lassailly, G. *et al.* (2020) *Gastroenterol* 159:1290-1301.e5

Pharmacology-driven reduction in lipotoxic fat in hepatocytes improved steatohepatitis but did not improve fibrosis

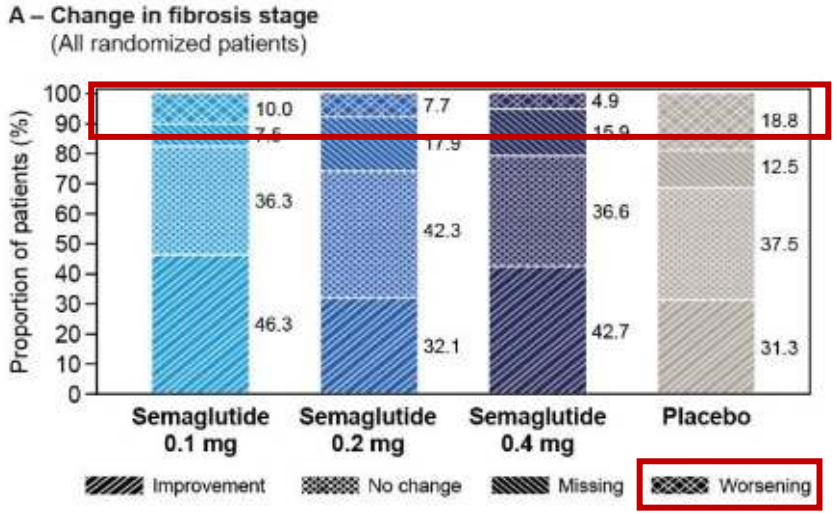
ORIGINAL ARTICLE

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

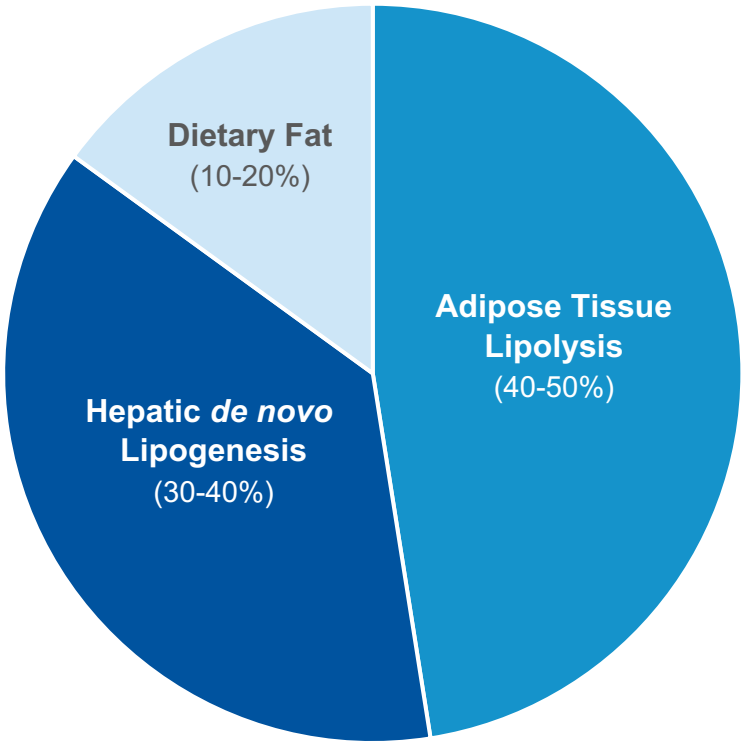


semaglutide did not improve liver fibrosis in patients with NASH cirrhosis after 48 weeks

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

NASH pathophysiology highlights the need for a multi-pronged therapeutic approach to resolve hepatic and extra-hepatic complications

Sources of Hepatic Fat Flowing into and Through Liver for NASH Patients



Lambert, JE *et al.* (2014) *Gastroenterology* 146(3): 726-35

NASH treatment should aim to:

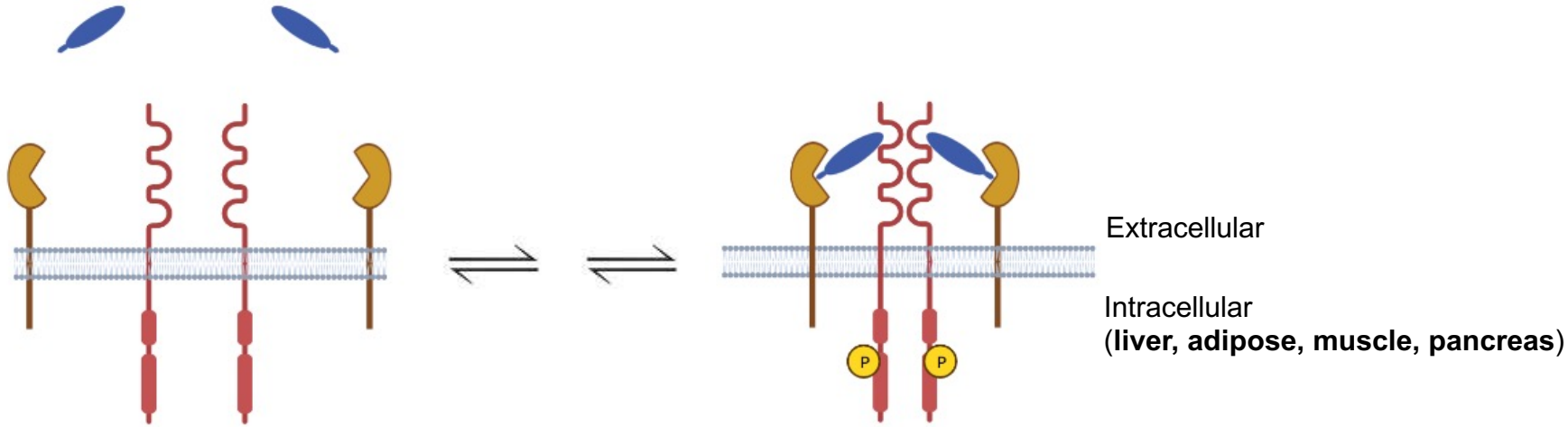
1. Reduce lipotoxic burden on liver,
2. By leveraging improvements in whole-body metabolism,
3. While accelerating fibrosis regression

FGF21: an endocrine metabolic regulator and autocrine/paracrine mediator of protective stress response pathways

FGF21 (from **liver, adipose, muscle**)

β-Klotho

FGFR1c/2c/3c



- Low protein, high carbohydrate, or ketogenic diets induce FGF21
- ER stress and oxidative stress induce FGF21 *in vitro* and *in vivo*
- Hepatic stressors (alcohol, fructose, acetaminophen) induce FGF21 *in vivo*
- FGF21 up-regulates pathways associated with protecting against these cell and tissue stressors, and suppresses induction of pro-apoptotic pathways

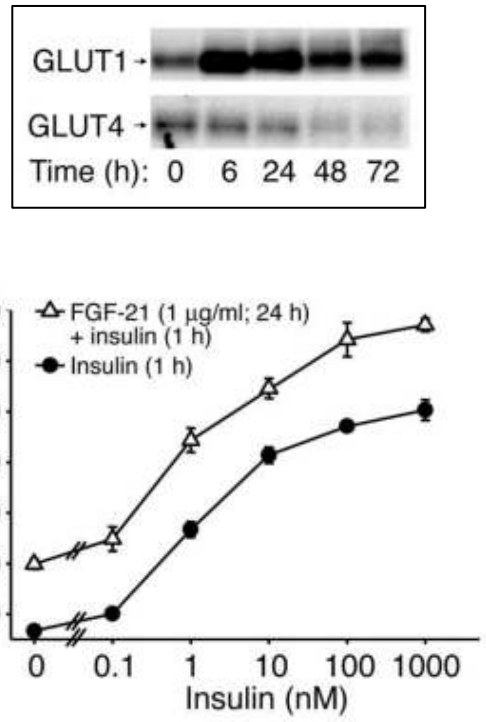
[1]Jiang S *et al.* (2014) *J Biol Chem* 289:29751-65.
[2]Wang X *et al.* (2016) *Cell Metab* 60:977-89.
[3]Desai BN *et al.* (2017) *Mol Metab* 6:1395-1406.
[4]Fisher FM *et al.* (2017) *Mol Metab* 6:14-21.
[5]Ye D *et al.* (2014) *Hepatology* 60:977-89.
[6]Laeger T *et al.* (2014) *J Clin Invest* 124:3913-22.

Created with BioRender.com

How might FGF21 act to protect the liver in NASH fibrosis?

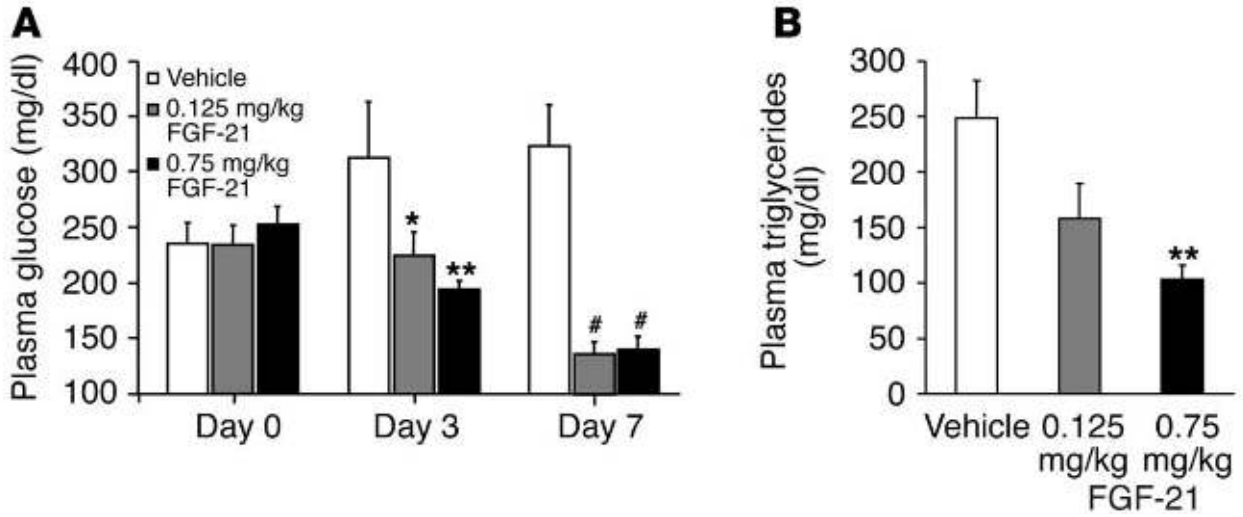
1) Endocrine role: partitions energy away from liver to adipose by increasing insulin sensitivity and suppressing DNL, reducing fat flux to liver

FGF21 potentiates insulin-dependent glucose uptake via GLUT1 upregulation[1]



3T3-L1 adipocytes

FGF21 significantly reduced plasma glucose and triglycerides in *ob/ob* mice[1]

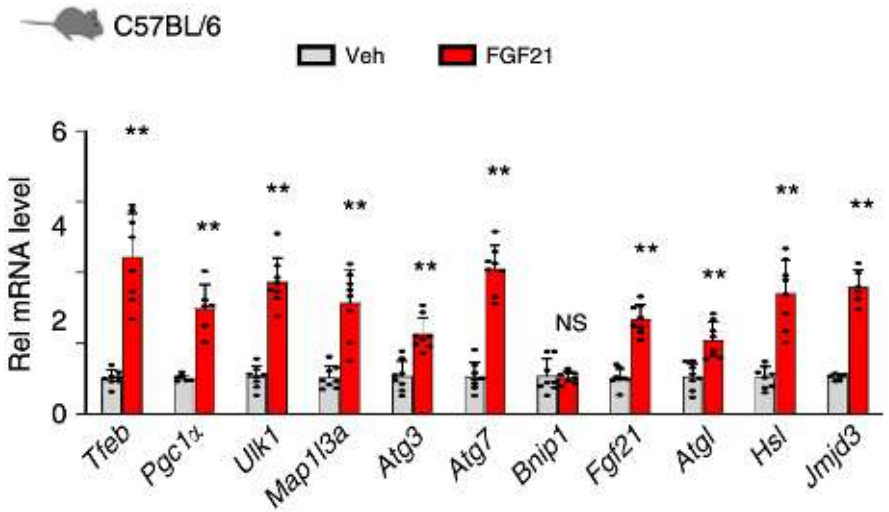


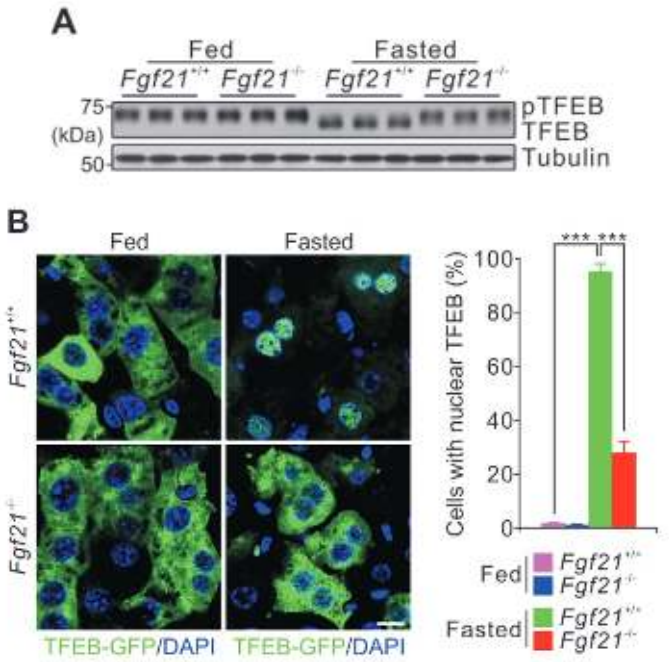
1. ***Reduce lipotoxic burden on liver,***
2. ***By leveraging improvements in whole-body metabolism…***

1. Kharitonenkov, A. *et al.* FGF-21 as a novel metabolic regulator. *J Clin Invest* **115**, 1627–1635 (2005).

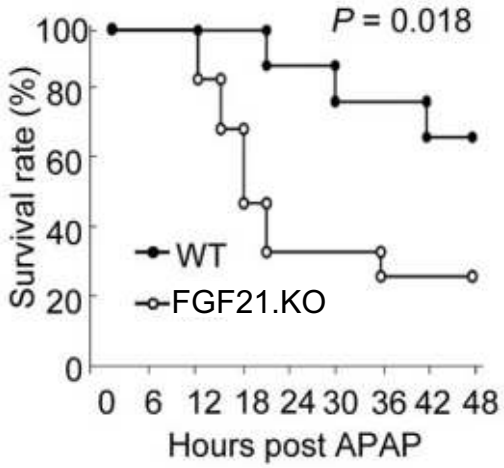
2) Paracrine/autocrine role: induces stress response pathways that protect against lipotoxicity and reduce drivers of inflammation

FGF21 induces autophagy via TFEB





FGF21 protects against APAP-mediated liver toxicity



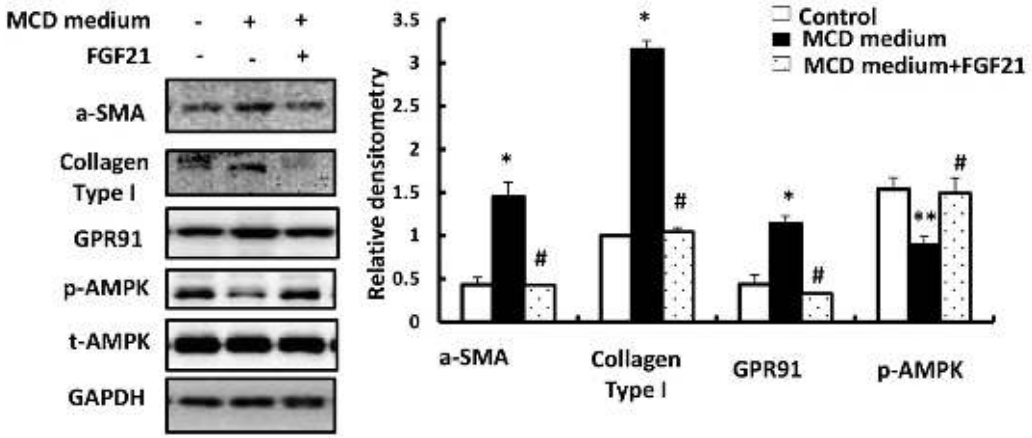
Byun *et al.* (2020) *Nat Commun* 11:807

Chen *et al.* (2017) *Cell Res* 27:748-63

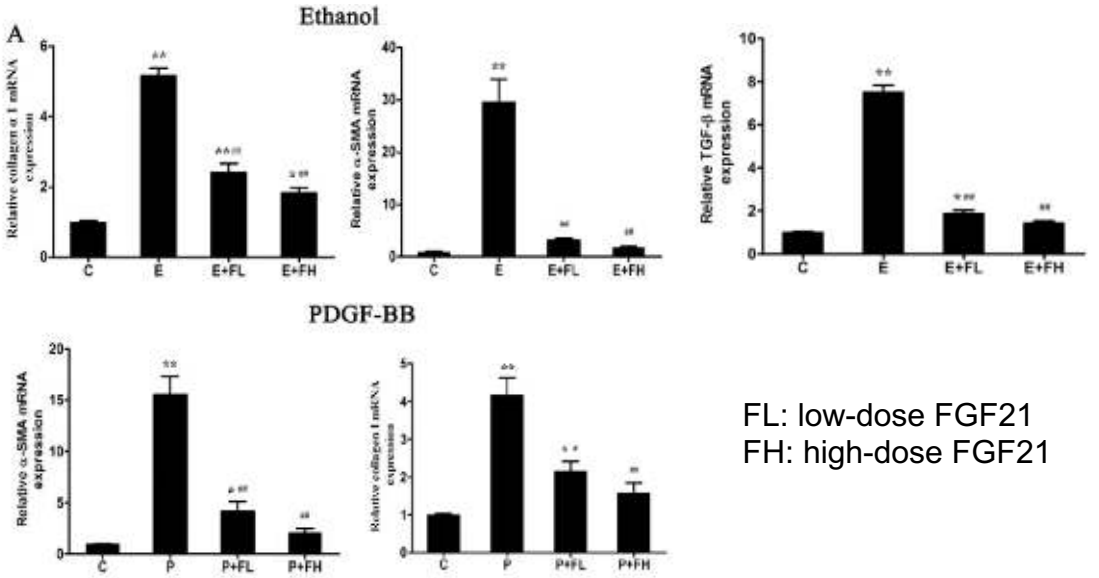
Ye *et al.* (2014) *Hepatol* 60:977-89

3) Suppresses fibrosis: reduces HSC activation and fibrogenic gene expression, and induces apoptosis *in vitro*

FGF21 suppresses fibrogenic gene expression in, and activation of, (LX-2) HSCs in methionine/choline-deficient medium[1]



FGF21 suppresses fibrogenic gene expression in HSCs induced by ethanol or PDGF[2]



FL: low-dose FGF21
FH: high-dose FGF21

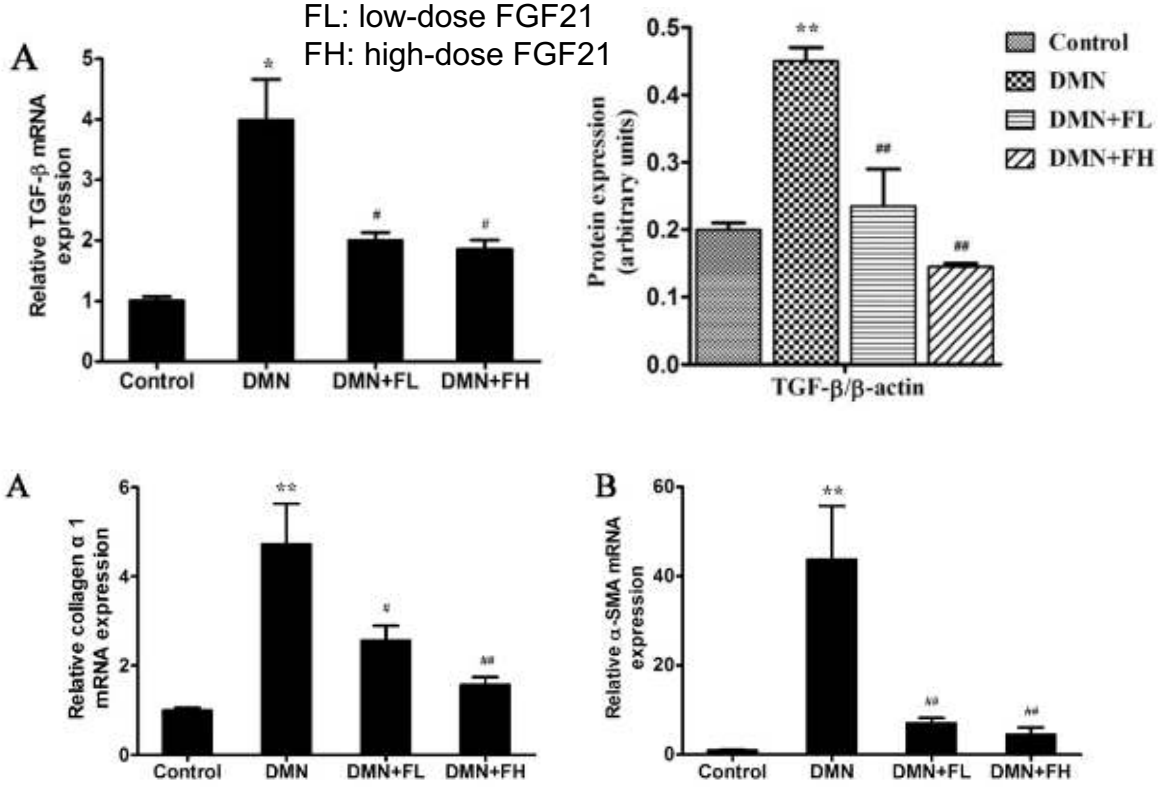
1. Le, C. T., *et al*. (2018) *Plos One* **13**, e0192146;

2. Xu, P. *et al.* (2016). *Toxicol Appl Pharm* **290**, 43–53;

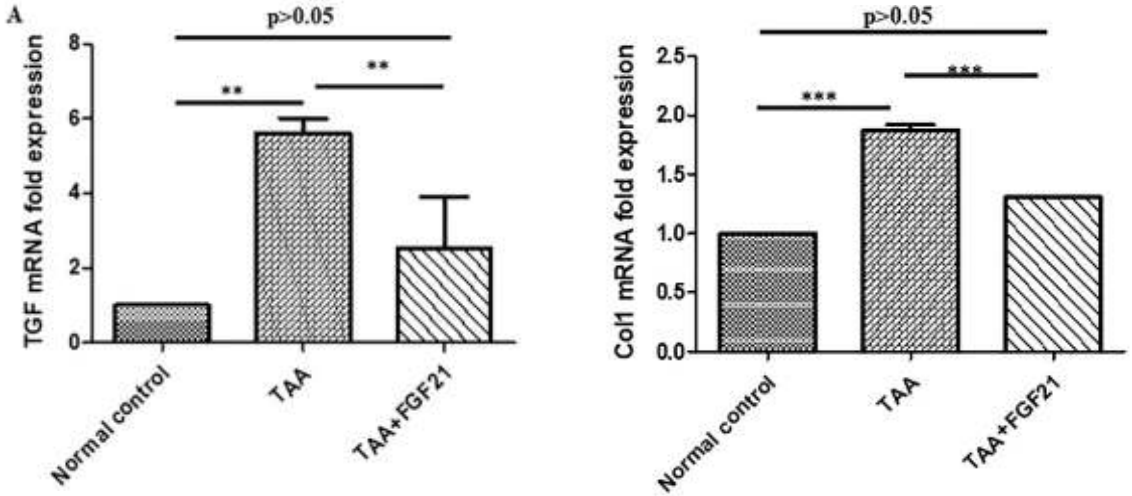
3) Suppresses fibrosis: exerts hepatic anti-fibrotic effects *in vivo* after chemical injury, not driven by metabolic insult

FGF21 suppresses fibrogenic gene expression in mouse liver following dimethyl nitrosamine-induced liver injury and fibrosis[1]

FL: low-dose FGF21
FH: high-dose FGF21



FGF21 suppresses fibrogenic gene expression in mouse liver following thioacetamide-induced liver injury and fibrosis[2]

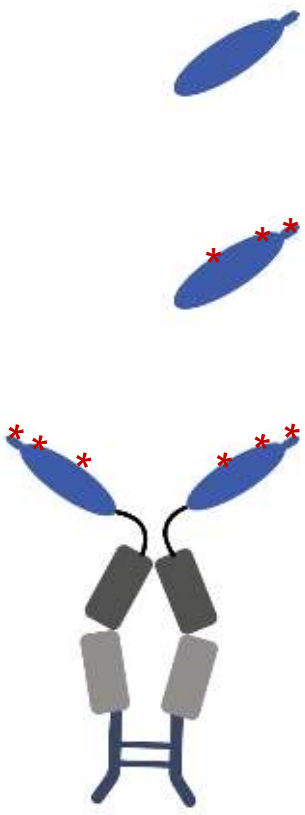


3. …while accelerating fibrosis regression

1. Xu, P. *et al.* (2016). *Toxicol Appl Pharm* **290**, 43–53;

2. Opoku, Y. K. *et al.* (2020) *EXCLI J* **19**, 567–581.

Efruxifermin (EFX): an Fc-FGF21 fusion protein engineered to deliver sustained agonism of FGF21's receptors *in vivo*



FGF21

FGF21:p.L98R, P171G, A180E

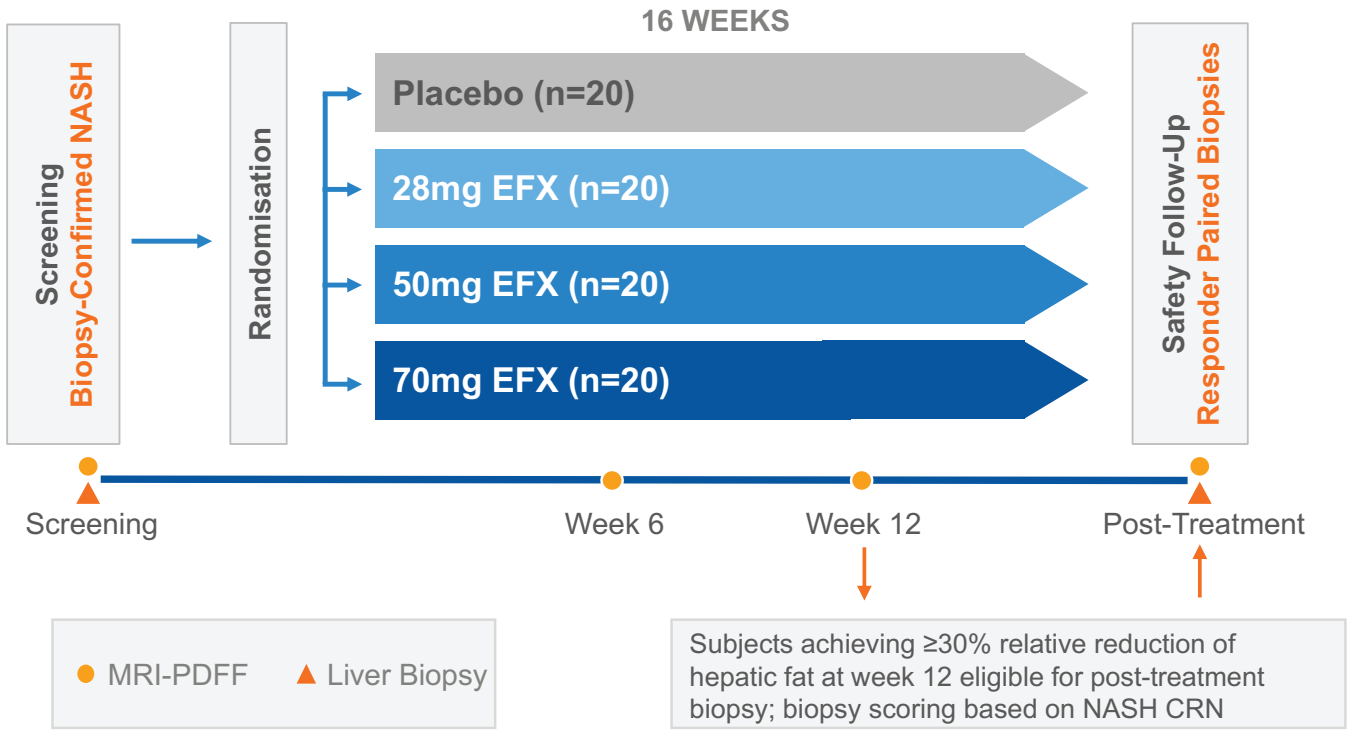
EFX (IgG1 Fc – linker – FGF21(RGE)

Half-life	N-terminus	C-terminus	β-Klotho affinity	FGFR agonism
Minutes/ hours	Susceptible to degradation	Susceptible to degradation	nM	**Balanced at 1c/2c/3c, no activity at 4**
Hours	Susceptible to degradation	Stabilized via P171G, A180E mutations	**sub-nM** due to A180E mutation	**Balanced at 1c/2c/3c, no activity at 4**
Days	**Stabilized** via linker/Fc	**Stabilized** via P171G, A180E mutations	**sub-nM** due to A180E mutation	**Balanced at 1c/2c/3c, no activity at 4**

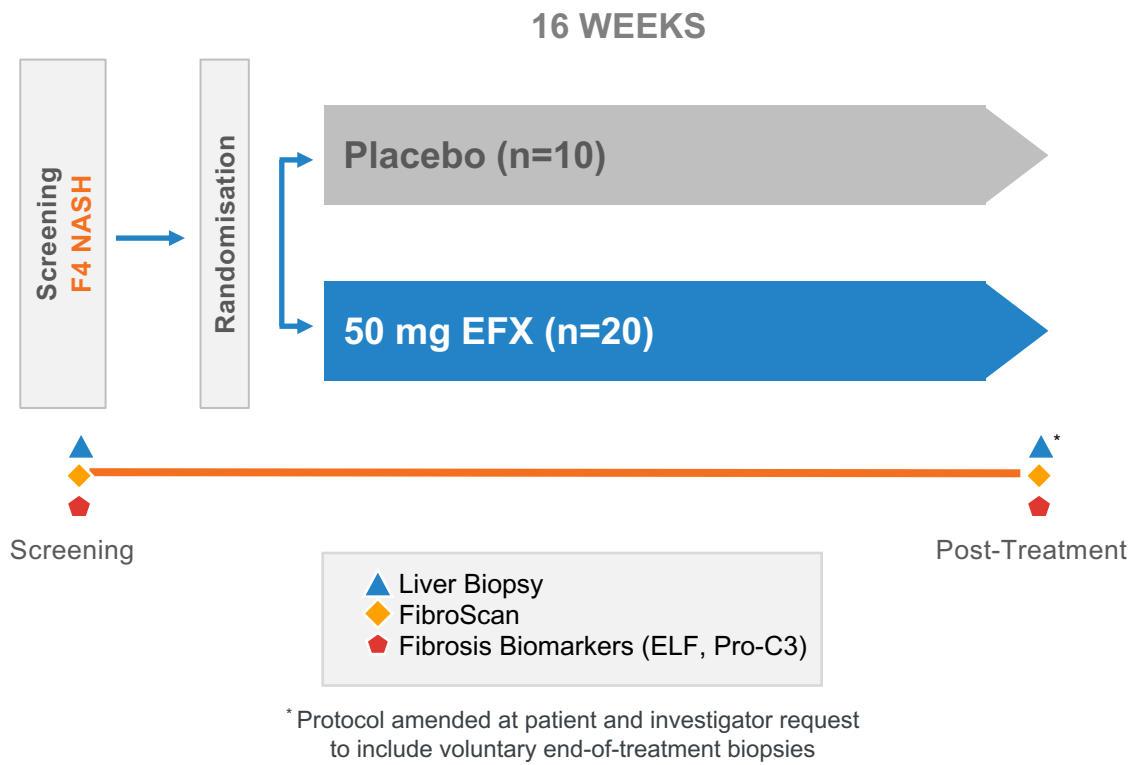
L98R reduces propensity for aggregation, enhancing biopharmaceutical properties

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

Main Study



Cohort C



* Protocol amended at patient and investigator request to include voluntary end-of-treatment biopsies

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

EFX was safe and well-tolerated in patients with F1-F4 NASH

Most Frequent (≥15%) Drug-Related AEs*	Main Study (F1-F3)				Cohort C (F4)	
	Placebo (N=21)	EFX 28mg (N=19)	EFX 50mg (N=19)	EFX 70mg (N=20)	Placebo (N=10)	EFX 50mg (N=17)
Diarrhea	2 (10%)	5 (26%)	10 (53%)	6 (30%)	1 (10%)	7 (41%)
Nausea	0 (0%)	6 (32%)	4 (21%)	9 (45%)	1 (10%)	5 (29%)
Increased appetite	1 (5%)	4 (21%)	4 (21%)	5 (25%)	0	2 (12%)
Vomiting	0 (0%)	5 (26%)	2 (11%)	2 (10%)	0	1 (6%)
Injection site erythema	0 (0%)	2 (11%)	0 (0%)	5 (25%)	0	4 (24%)
Injection site reaction	0 (0%)	2 (11%)	1 (5%)	3 (15%)	0	5 (29%)
Headache	1 (5%)	0	0	2 (10%)	0	3 (18%)
TEAE/SAE Disposition	**Placebo**	**28mg**	**50mg**	**70mg**	**Placebo**	**EFX 50mg**
Deaths	0	0	0	0	0	0
TEAE Leading to Discontinuation	1[a]	2[b]	0	4[c]	0	1[e]
Serious Adverse Event (SAE)	0	1[d]	0	1	1[f]	0

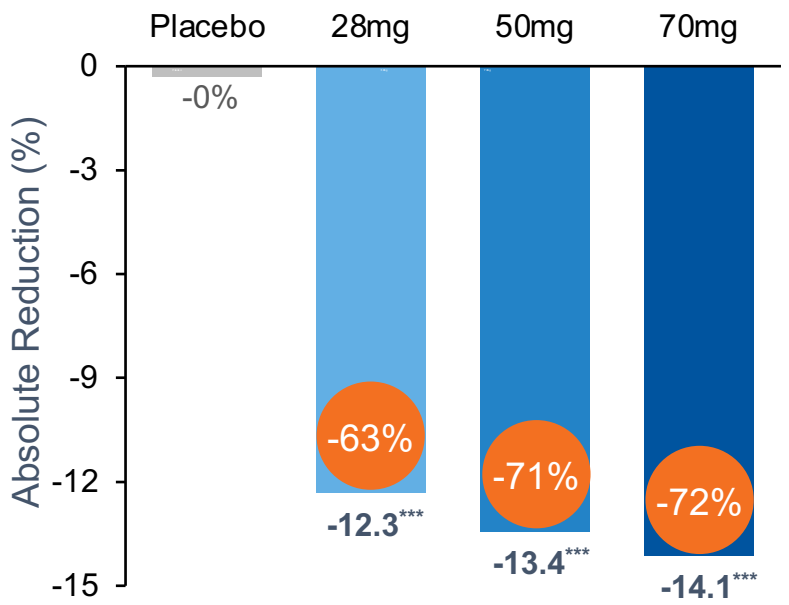
* Across EFX dose groups in either Main Study or Cohort C

[a] Muscular Weakness & Myalgia; [b] Nausea, Vomiting & Dysgeusia; Panic Attack and Anxiety-Linked Tremor; [c] Dysphagia (Not Drug Related); Acute Pancreatitis (also an SAE); Vomiting; Fatigue & Nausea; [d] Related to pre-dosing liver biopsy; [e] abdominal distension, constipation, diarrhea, pruritus; [f] pulmonary embolism

Source Data: Safety Set, F1-F3 (all BALANCED main study subjects who received at least one dose of study drug); F4 (all Cohort C subjects confirmed by central reader as F4 at baseline who received at least one dose of study drug)

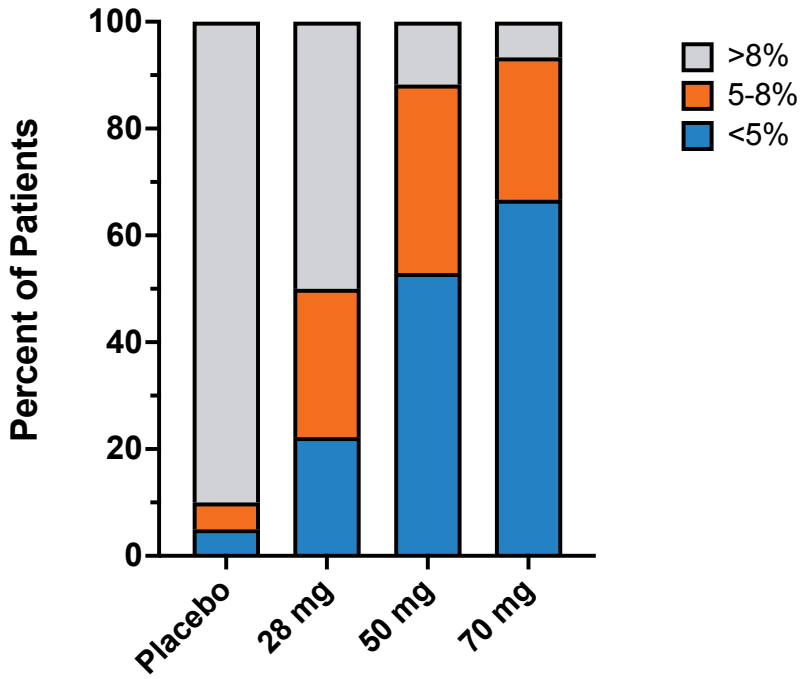
EFX reduced lipotoxic liver fat sufficiently to normalize LFC (≤5%) in almost half of treated patients within 12 weeks

LS Mean Reduction in Liver Fat



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

Proportion of patients achieving specified liver fat content at week 12

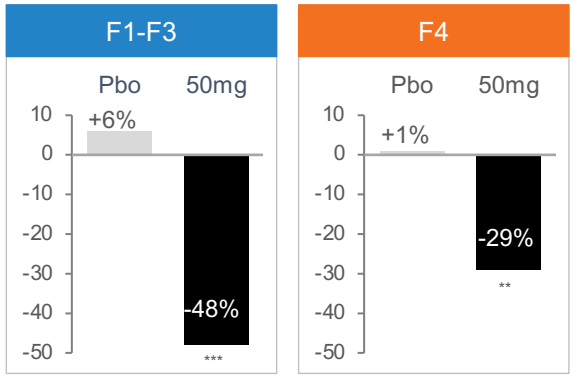


Harrison, SA et al (2021) *Nat Med* **27**, 1262–1271.

50mg EFX improved markers of lipid and glucose metabolism consistently across patients with F1-F4 NASH

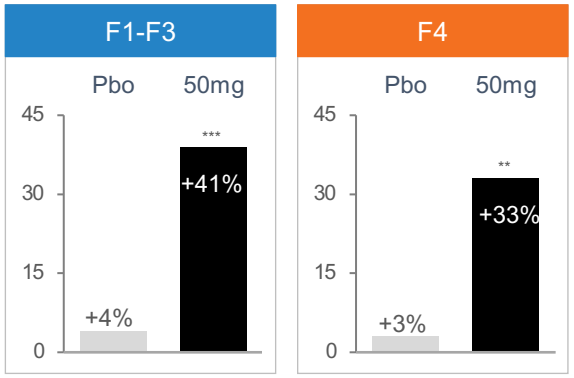
Triglycerides (%)

LS Mean Change From Baseline at Week 16 (%)



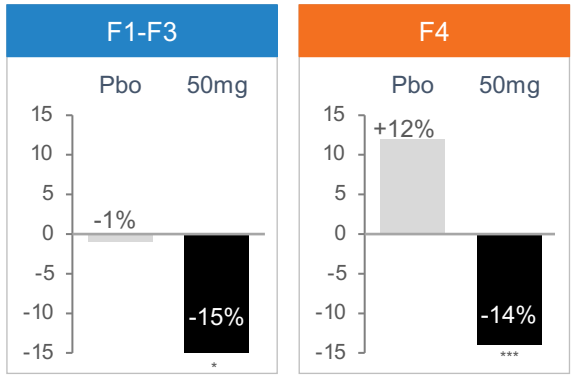
HDL Cholesterol (%)

LS Mean Change From Baseline at Week 16 (%)



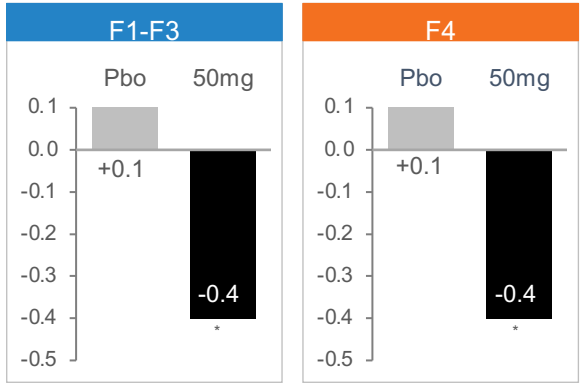
Non-HDL Cholesterol (%)

LS Mean Change From Baseline at Week 16 (%)



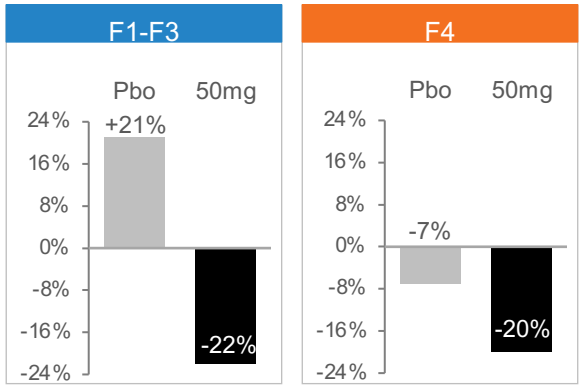
HbA1c, %

LS Mean Abs. Change From Baseline at Week 16 (%)



C-peptide (%)

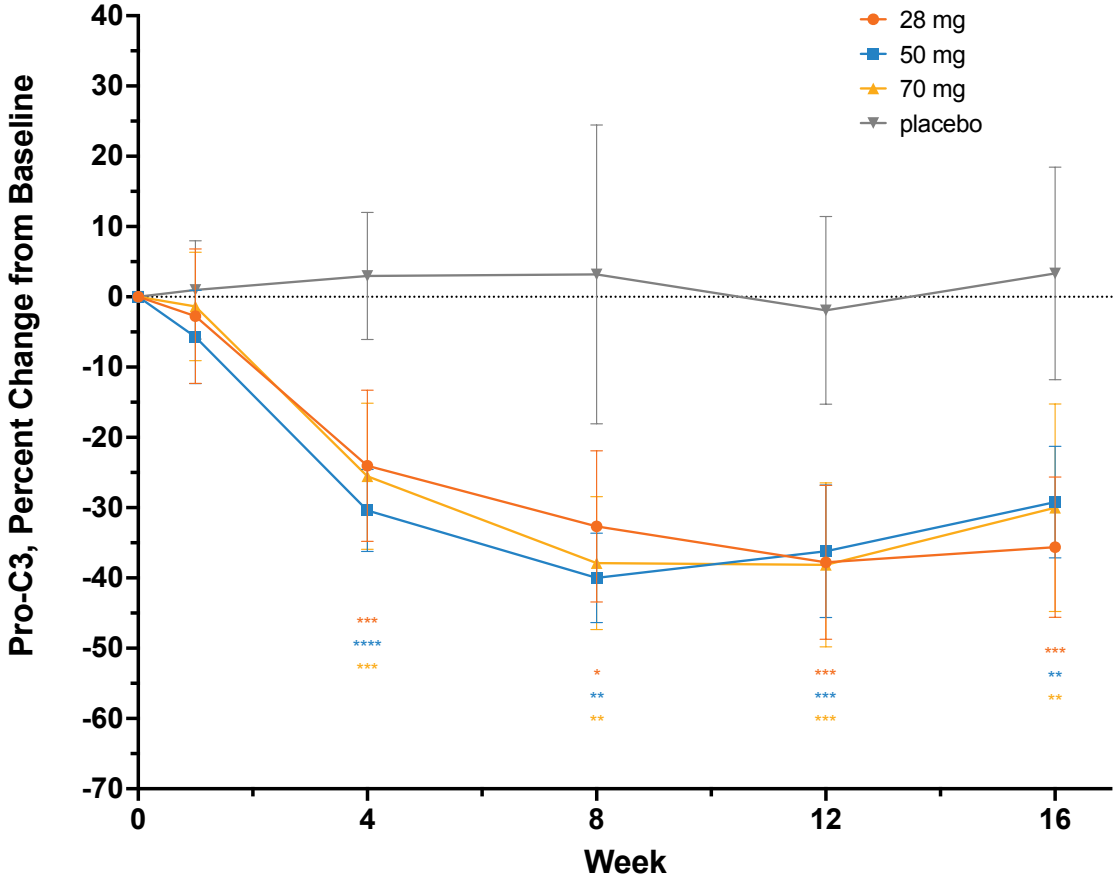
LS Mean Change From Baseline at Week 16 (%)

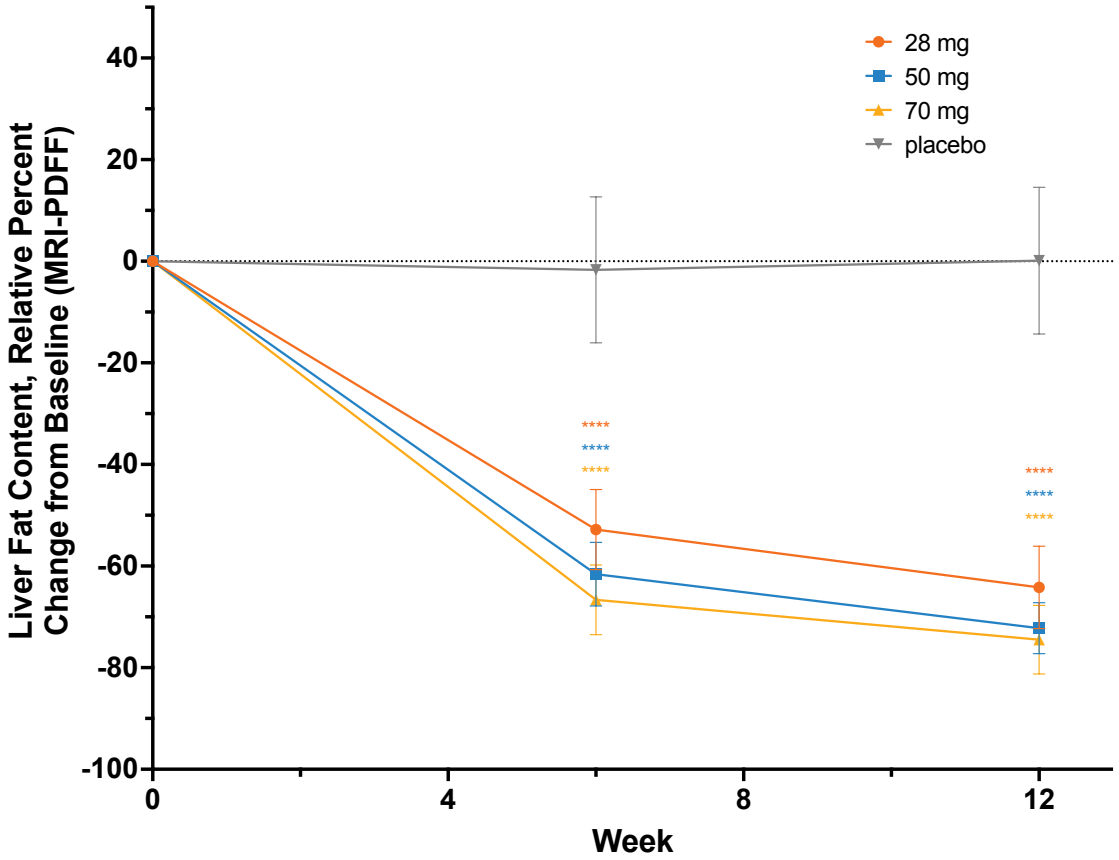


* p<0.05, ** p<0.01, *** p<0.001, versus placebo (ANCOVA)

Source Data: Full Analysis Set, F1-F3; Full Analysis Set, F4

EFX rapidly reduced Pro-C3, appearing to precede maximal reduction in liver fat

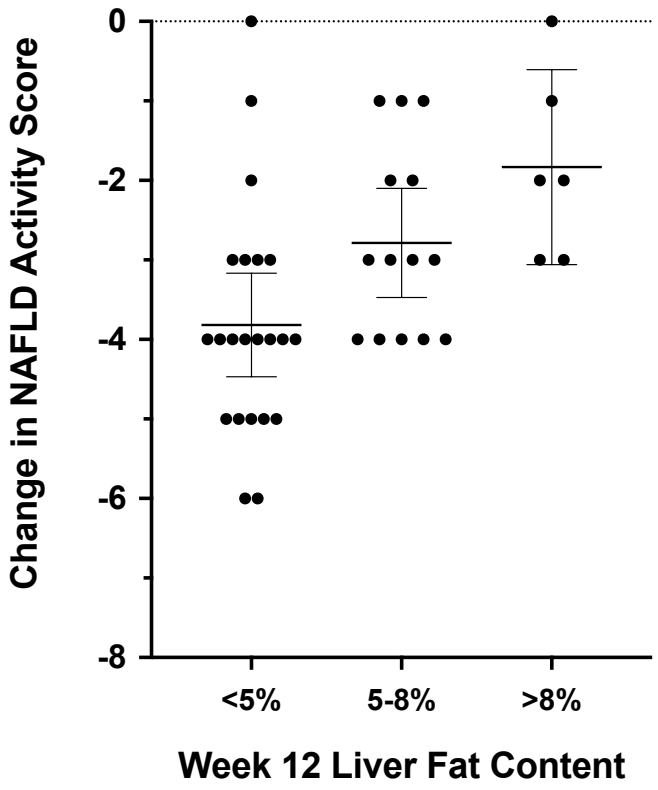




* p<0.05; ** p<0.01; *** p<0.001; *** p<0.0001.

Data shown are mean ± 95% confidence interval, with p values from mixed-effects model with repeated measures

LFC normalization significantly associated with NASH resolution and reduction in NAS by ≥4 points in F1-F3 NASH



Normalization of LFC (≤5%) increases probability of NASH resolution or ≥4-point improvement in NAS, compared to not normalizing LFC (>5%)

Week 12 Liver Fat	Histologic Endpoint	Odds Ratio (95% CI) [a]	P value [b]
LFC normalization [c]	NASH Resolution [1]	4.08 (1.18, 13.21)	0.0365
	NAS Reduction by ≥4 [2]	6.43 (1.78, 15.56)	0.0068

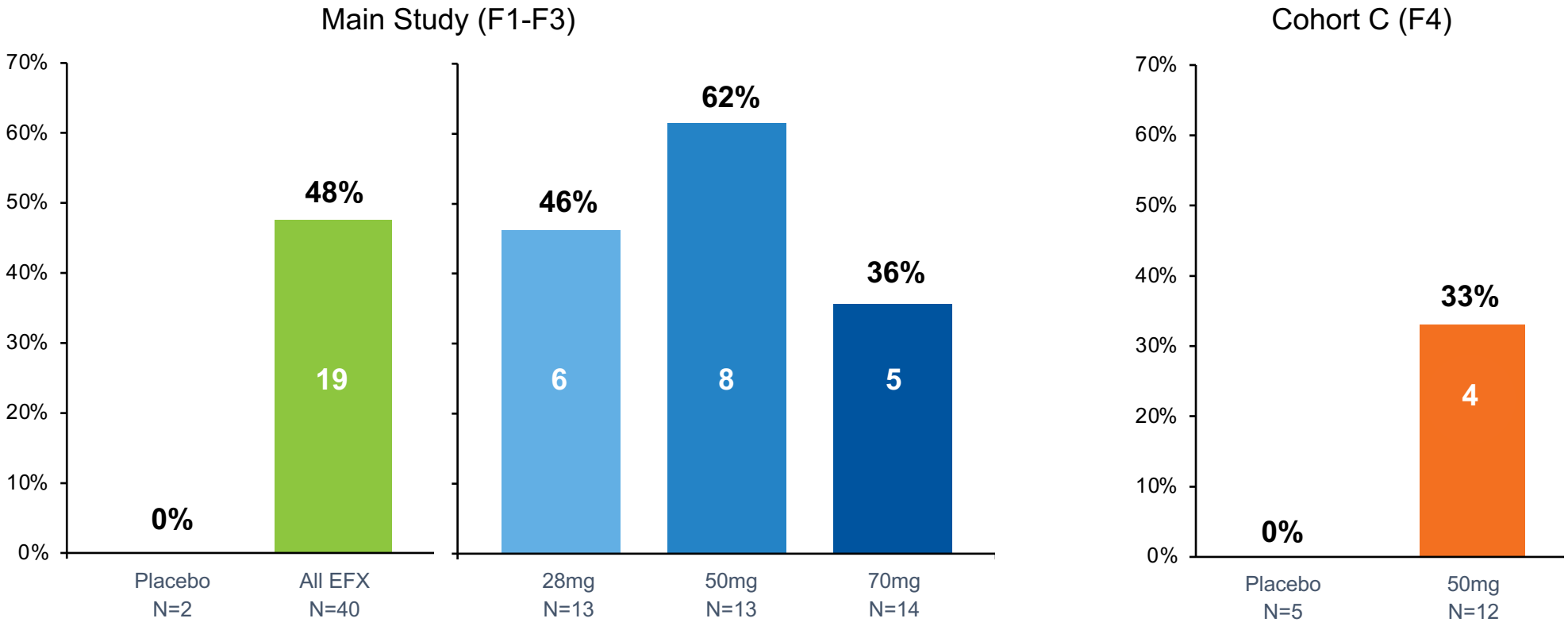
[a] Wald 95% Confidence Interval; [b] Fisher's exact test; [c] ≤5% Liver Fat Content at Week 12

[1] 0- or 1-point for lobular inflammation and 0 points for ballooning components of NAFLD Activity Score;
[2] At least 2 points in lobular inflammation and/or ballooning components of NAFLD Activity Score

Not solely driven by reduction in steatosis. Reductions in ballooning and inflammation in 16 weeks may reflect the induction of protective pathways in liver

Rapid regression of fibrosis in patients with F1-F4 NASH, following only 16 weeks treatment

Frequency of responders with fibrosis improvement ≥1 Stage and no worsening of NASH[1,2]

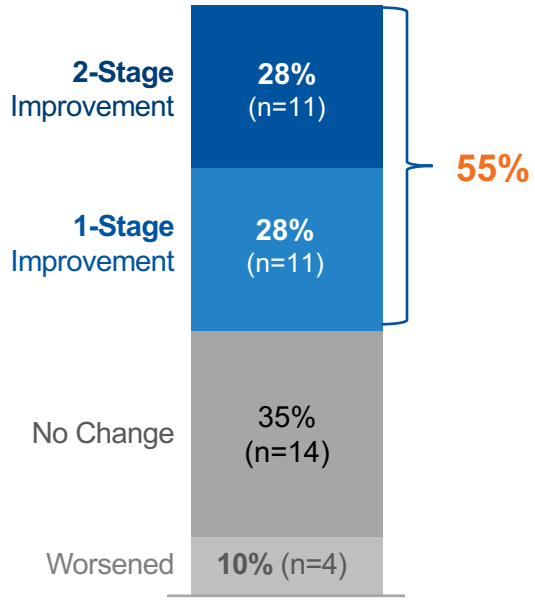


[1] Improvement in liver fibrosis greater than or equal to one stage and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)
[2] Secondary and exploratory histological endpoints were not powered for statistical significance

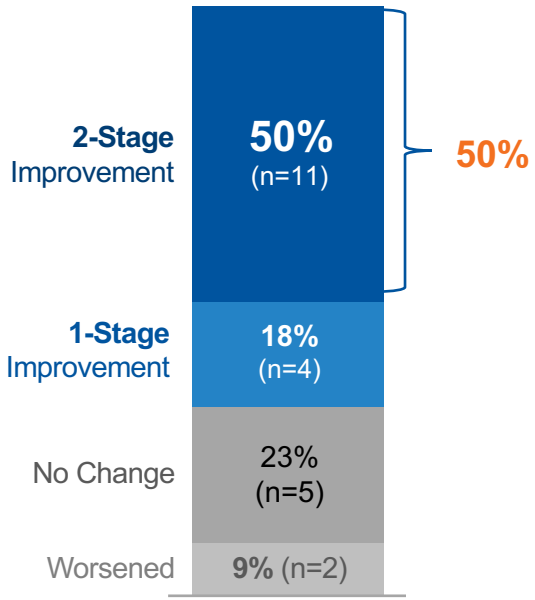
Source Data: Liver Biopsy Evaluable Analysis Set, F1-F3 (all BALANCED Main Study PDFF responders who had baseline and end-of-treatment liver biopsy results; Liver Biopsy Analysis Set, F4

Rapid fibrosis regression in advanced fibrosis: Half F2/F3 patients regressed by 2 stages after just 16 weeks of treatment

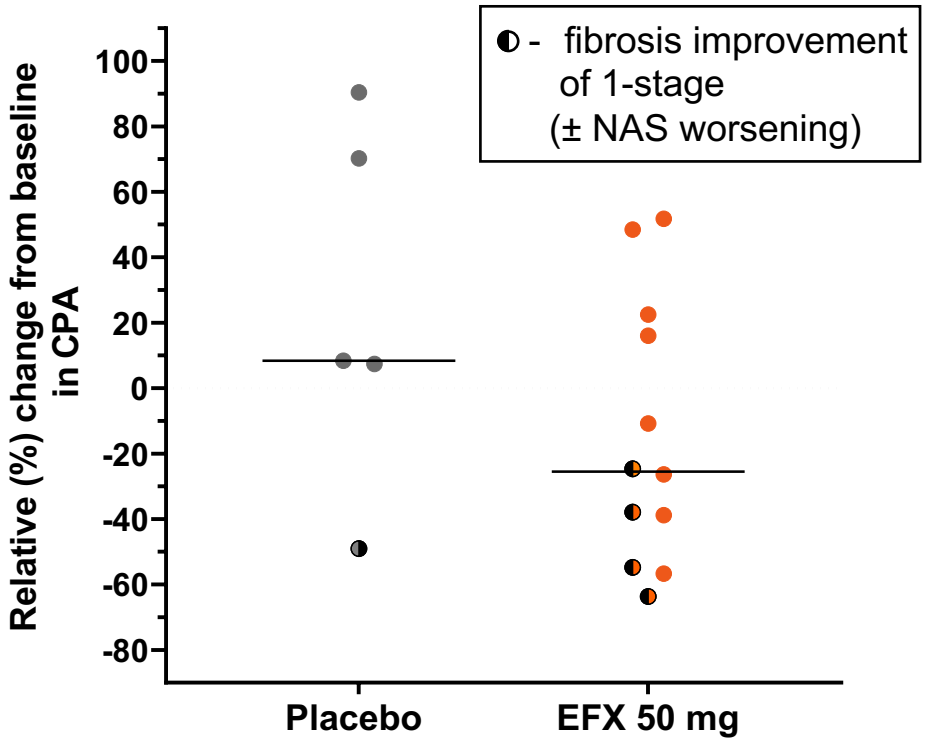
Fibrosis Change in EFX-Treated Patients with Baseline F1-F3 Fibrosis (n=40)



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

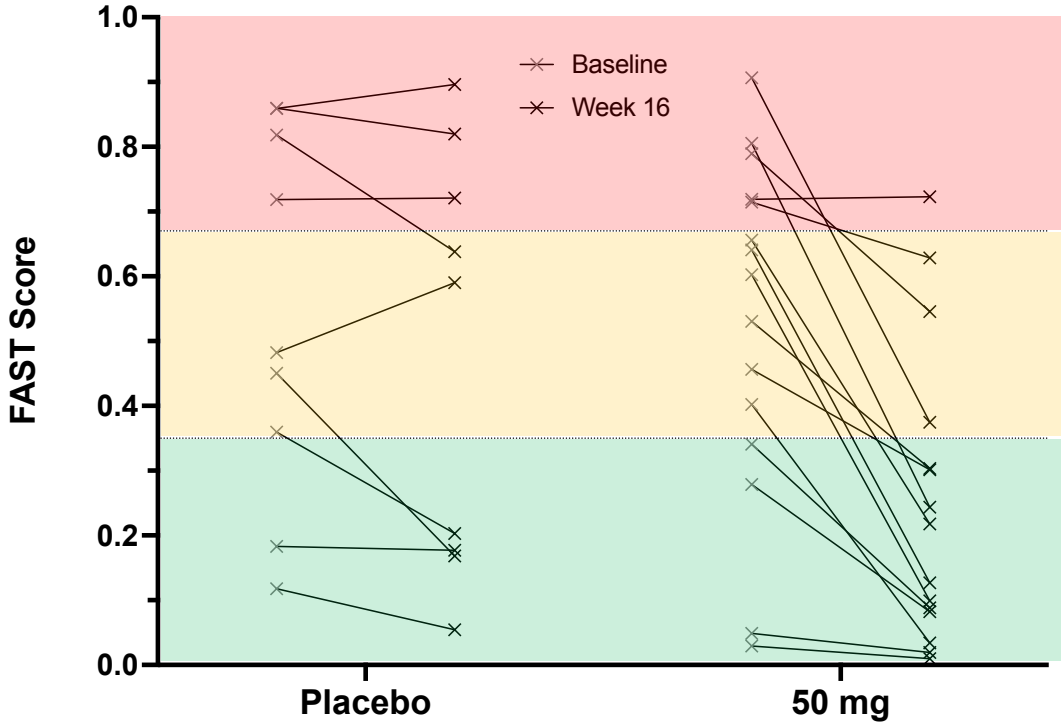


Clear trend to histologic and noninvasive improvements in Cohort C:
1) Greater reduction in collagen proportionate area (PathAI)
2) Larger reduction in FAST score

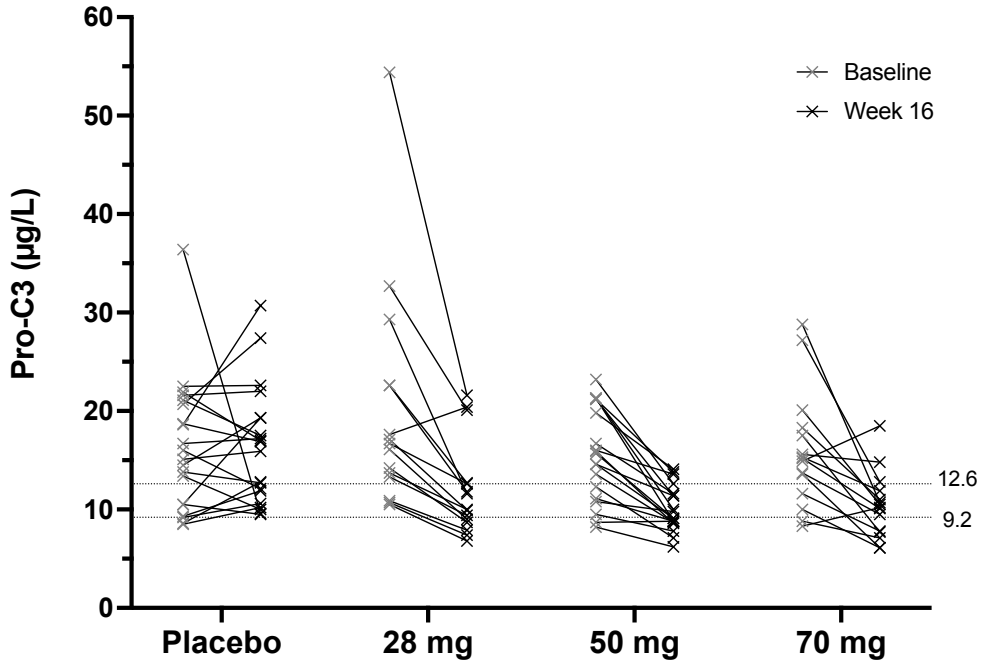


Median (IQR) Relative (%) Change in Collagen Proportionate Area from Baseline	
Placebo	EFX 50 mg
+8.4% (-20.8%, 80.3%)	**-25.5%** (-50.8%, 20.8%)

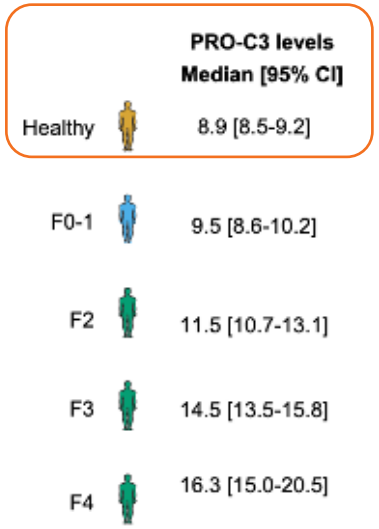
10/11 EFX-treated patients in indeterminate or high-risk group improved by ≥1 FAST risk-stage

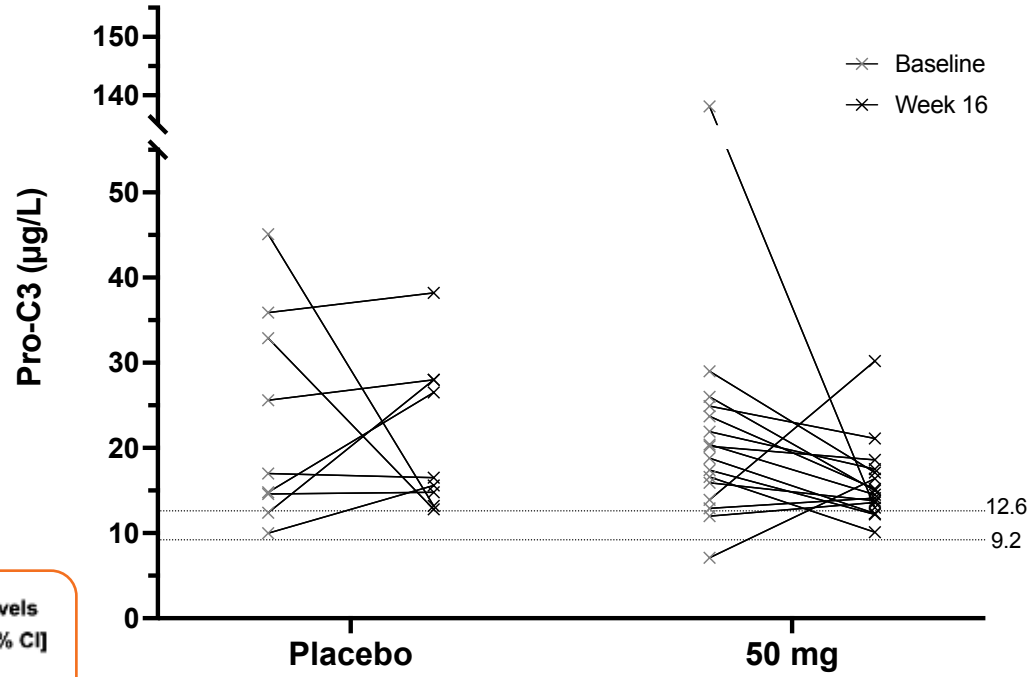


EFX consistently reduced soft tissue collagen synthesis; 1) Normalized Pro-C3 in patients with F1-F3 NASH 2) Significantly reduced Pro-C3 in patients with cirrhosis



Main study	Baseline ≤9.2ng/mL	Week 16 ≤9.2ng/mL	Decreased across threshold
Placebo	3/21 (14%)	0/19 (0%)	0/18 (0%)
28mg	0/19 (0%)	5/15 (33%)	5/15 (33%)
50mg	2/19 (11%)	8/16 (50%)	6/14 (43%)
70mg	2/20 (10%)	5/15 (33%)	4/13 (31%)



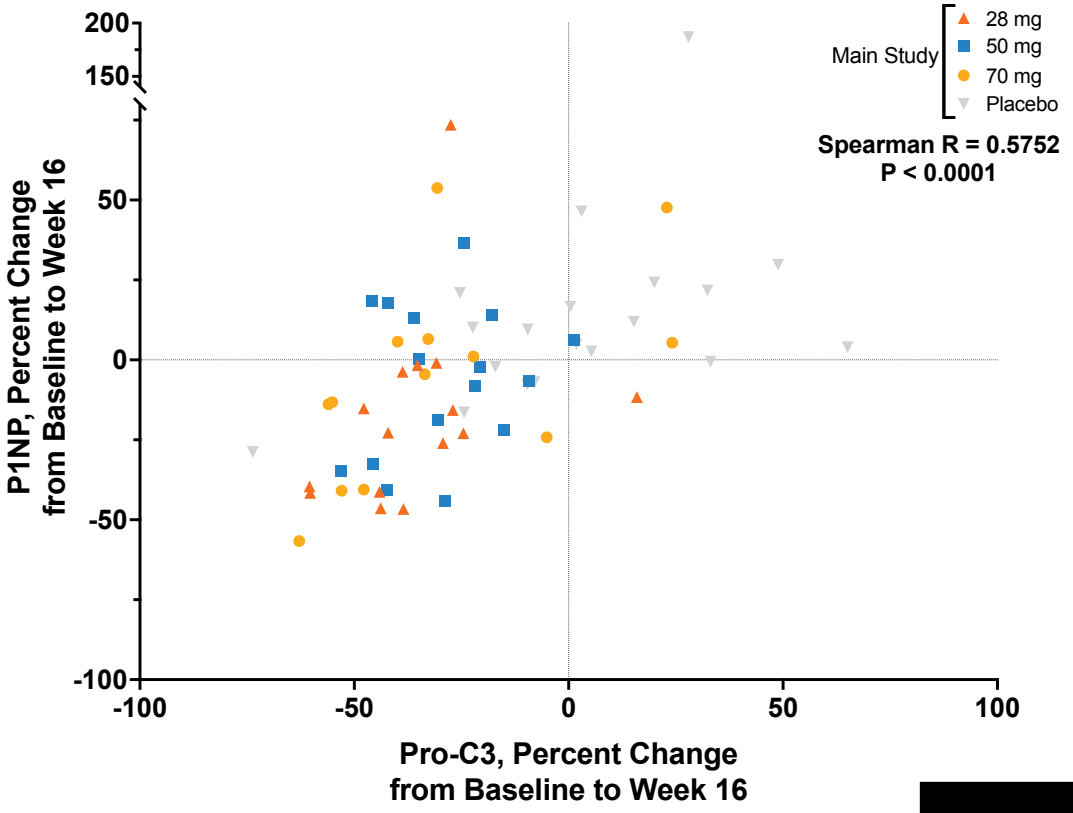


12.6 ng/mL: threshold for increased likelihood of ≥F2 NASH
9.2 ng/mL: upper 95% confidence interval of healthy values[1]

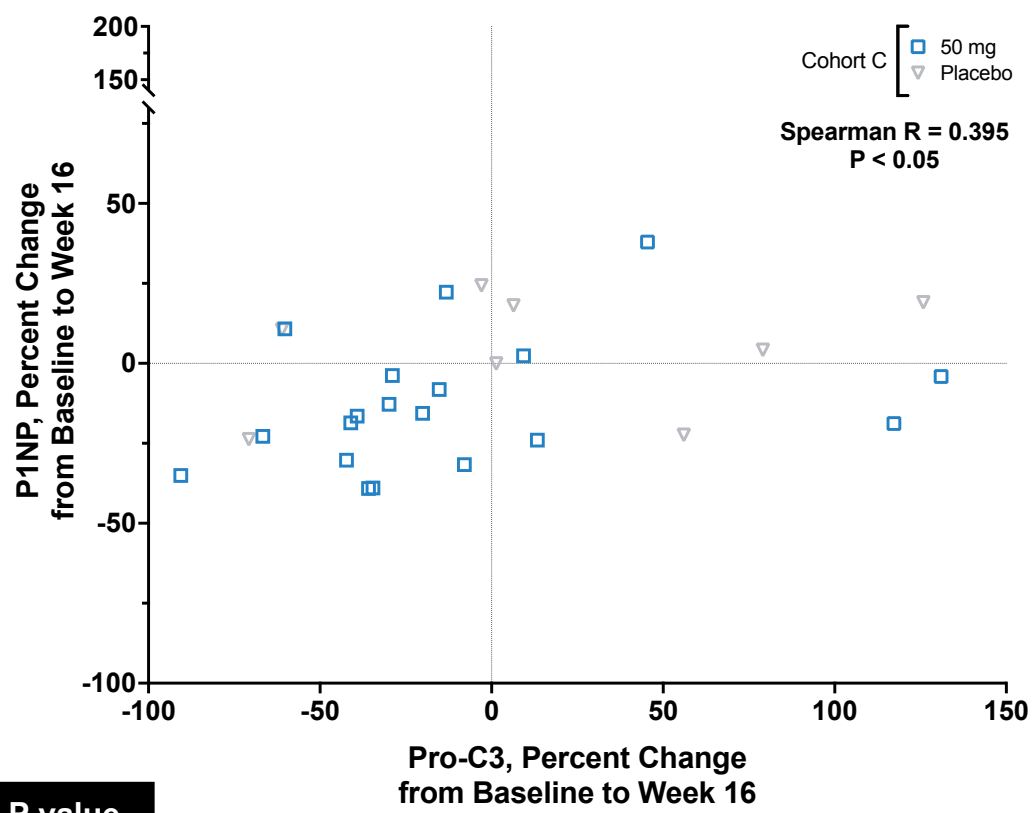
1. Erhardtsen *et al.* (2021) *JHEP Reports* 3(4):100317

EFX reduced synthesis of two major components of soft tissue ECM, collagen type-I and -III, in a concerted fashion

F1-F3 NASH (Main Study)

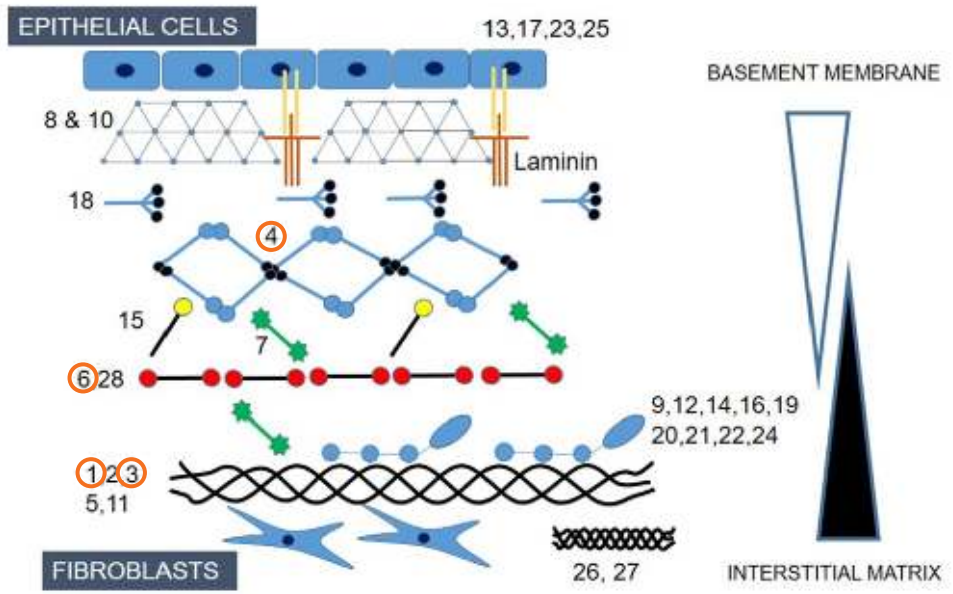


F4 NASH (Cohort C)



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

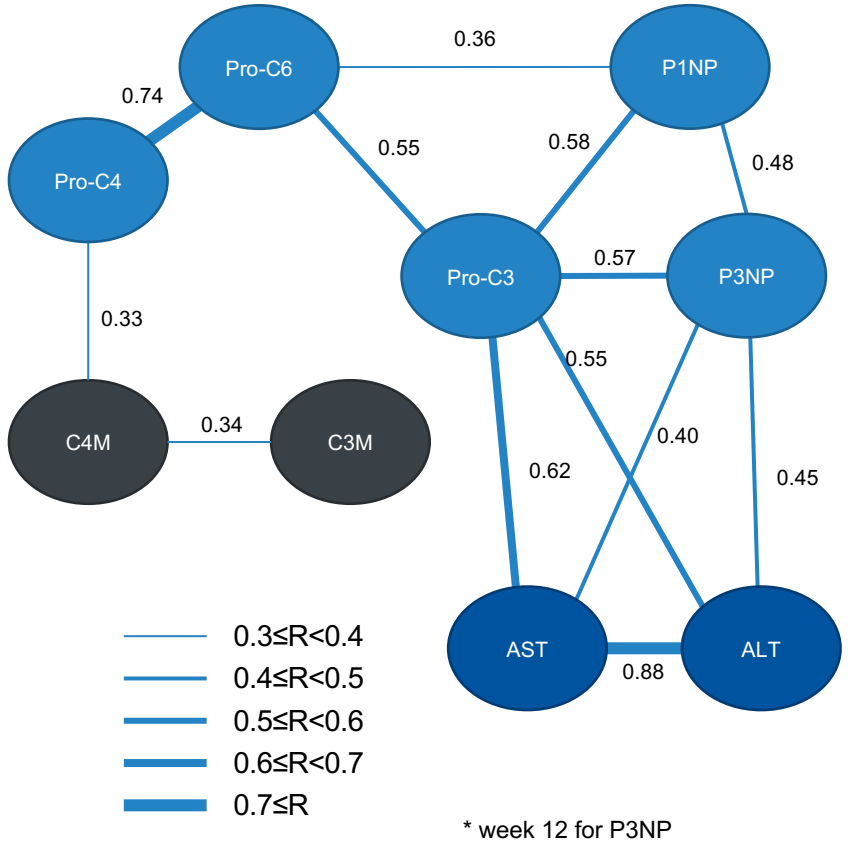
Reduction of liver injury in patients with F1-F3 NASH associated with concerted shift toward degradation of interstitial matrix and basement membrane components



1. Karsdal *et al.* (2017) *Drug Deliver Rev* 121:43–56

Main Study F1-F3

Network map of Spearman correlation coefficients for percent change from baseline to week 16* across markers of liver injury and collagen turnover



* week 12 for P3NP

Interpreting the Rapid Reversal of Fibrosis Observed in EFX-treated Patients with NASH

↓ Inflammation

↓ Collagen Synthesis

Directly anti-fibrotic

↓ Liver fat

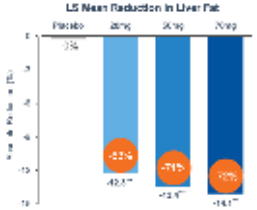
↓ Hepatocyte Stress

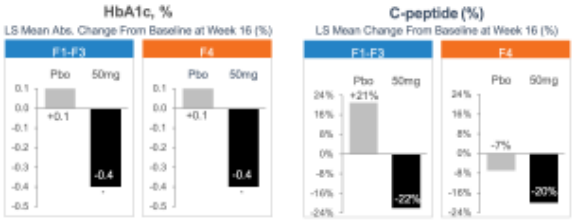
Indirectly anti-fibrotic

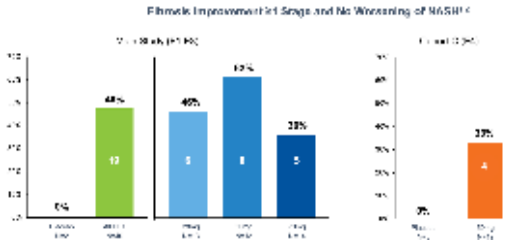
- Fibrosis reversal in patients with compensated cirrhosis (F4), two-stage improvement of fibrosis in patients with F2/F3 NASH, and corroborating non-invasive markers of fibrosis improvement in only 16 weeks likely reflects direct anti-fibrotic activity
- Fibrosis reversal is especially advantageous for patients with cirrhotic NASH who face high risk of mortality and severe morbidity
- Addressing underlying NASH disease drivers may indirectly contribute to fibrosis reversal for patients with F1-F3 NASH with adequate time for the liver to regenerate
- Addressing the underlying NASH disease drivers is necessary to sustain fibrosis reversal across all fibrosis stages
- Supports broader metabolic improvements

Early clinical data suggest EFX may achieve key goals of a foundational NASH therapy

NASH treatment should aim to:		In patients with F1-F4 NASH, EFX:
1. Reduce lipotoxic burden on liver,	✓	Significantly reduced, and even normalized, liver fat
2. By leveraging improvements in whole-body metabolism,	✓	Improved insulin sensitivity, glucose metabolism, and lipid metabolism
3. While accelerating fibrosis regression	✓	Achieved fibrosis regression within 16 weeks







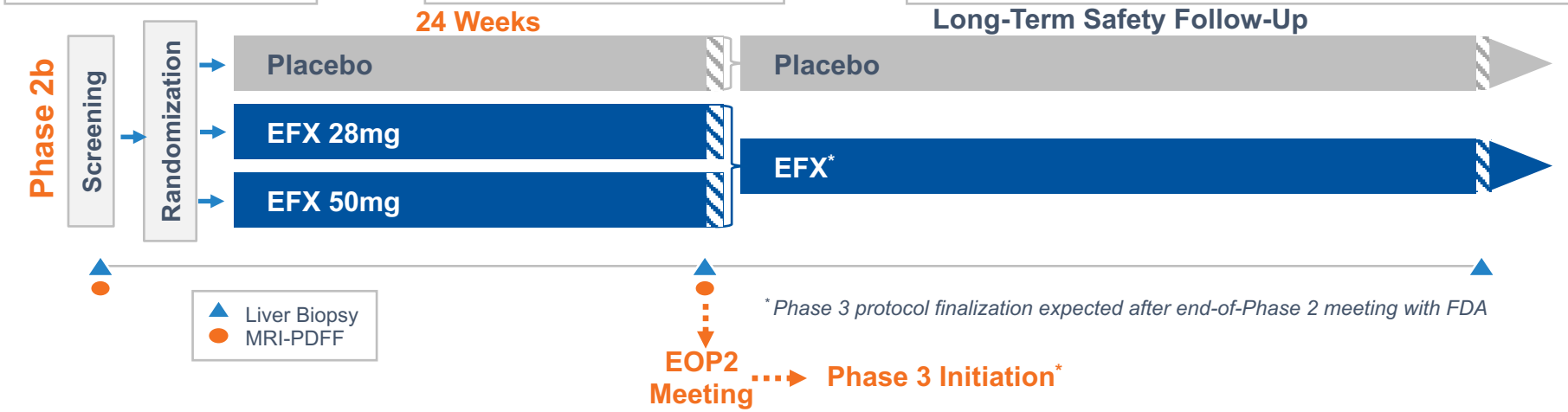
Ongoing clinical studies of EFX in patients with advanced fibrosis and cirrhosis due to NASH

F2/F3

Key Inclusion Criteria
- F2-3 NASH
- NAS ≥4
- Liver fat ≥8%

Phase 2b Primary Endpoint
- Fibrosis Improvement

Key Secondary Efficacy Endpoints
- NASH Resolution
- Fibrosis Markers
- MRI-PDFF
- Lipoproteins
- Glycemic Control
- Weight Change
- Liver Injury Markers



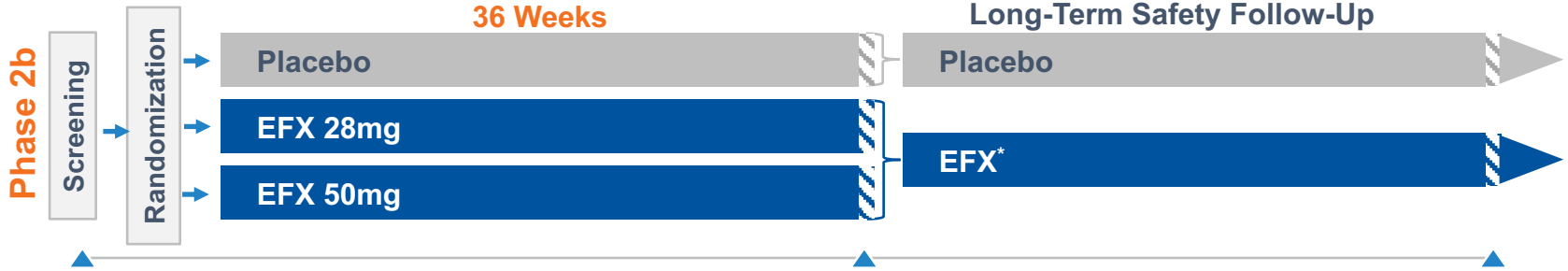
*Phase 3 protocol finalization expected after end-of-Phase 2 meeting with FDA

F4

Key Inclusion Criteria
- F4 NASH

Phase 2b Primary Endpoint
- Fibrosis Improvement (Cirrhosis reversal)

Key Secondary Efficacy Endpoints
- NASH Resolution
- Fibrosis Markers
- Lipoproteins
- Glycemic Control
- Weight Change
- Liver Injury Markers



*Pending finalization of Phase 3 protocol

We acknowledge and thank the patients, their families and caregivers, and the investigators involved in these studies.

Dr. Cindy Behling of Pacific Rim pathology performed centralized reading of liver biopsies for the BALANCED study.

PathAI performed AI-based scoring of digitized pathology slides.

Nordic Biosciences performed quantitation of biomarkers of collagen turnover.

Medpace and the Akero clinical development team designed and conducted the BALANCED study.

The BALANCED study and all analyses were funded by Akero Therapeutics, Inc.

erik@akerotx.com