Noninvasive tests of liver injury, inflammation and fibrosis are improved by efruxifermin and correlate with histological improvements in patients with F2-F3 NASH: secondary analysis of Ph2b HARMONY study (Abstract 1669)

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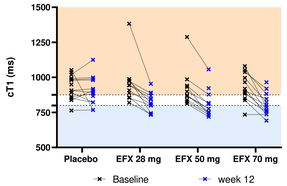
BACKGROUND

Non-invasive tests (NITs) are needed to monitor histological improvement in patients with nonalcoholic steatohepatitis (NASH) in clinical trials. In a phase 2a study (BALANCED) of participants with NASH and F1–F3 fibrosis or compensated cirrhosis, including those with type 2 diabetes (T2D) at baseline, efruxifermin (EFX; a long-acting Fc-FGF21 fusion protein) decreased liver fat content and markers of liver injury, inflammation, and fibrosis, while improving metabolic health.[1,2] These observations have been confirmed in a phase 2b study (HARMONY).[3]

Post hoc analysis of the 16-week BALANCED study evaluated liver fibro-inflammation at week 12 using the imaging biomarker cT1 (iron-corrected T1) to assess likelihood of at-risk NASH, defined as a diagnosis of NAS>4 and F≥2.[4]

	Placebo (N=14)	EFX 28mg (N=12)	EFX 50mg (N=11)	EFX 70mg (N=12)
Mean baseline cT1 (ms)	930.8	956.3	921.0	929.1
cT1 ≤ 800 ms at week 12	1 /11 (9%)	4 / 11 (36%)	6 / 11 (55%)	6 / 10 (60%)
≥ 88 ms cT1 reduction from baseline at week 12	1 / 12 (8%)	6 / 11 (55%)	10 /11 (91%)	9 / 11 (82%)

cT1 ≤ 800: associated with low likelihood of at-risk NASH
cT1 > 875: associated with high likelihood of at-risk NASH
CFB in cT1 ≥ 88 ms: associated with 2-point reduction in NAS



Ongoing clinical evaluation of EFX will further explore imaging and circulating markers of NASH histopathology.

AIMS

The aims of this study were to assess:

1) NIT results from participants who received EFX for up to 24 weeks, and
2) Their association with histologic features of NASH.

METHODS

This study analyzed treatment-related changes in NITs from 115 participants after 24 weeks in the ongoing, randomized, placebo-controlled phase 2b HARMONY study, which is evaluating EFX 28 and 50 mg, dosed subcutaneously (SC), once weekly (QW).[3] Changes in NIT results were analyzed for correlations with the following histologic improvements based on NASH-CRN scores: fibrosis improvement without NASH worsening; NASH resolution without fibrosis worsening; and both fibrosis improvement and NASH resolution.

Participants with biopsy-confirmed F2–F3 NASH (n=128) were randomized (1:1:1) to groups that received 28 mg or 50 mg EFX or placebo, SC QW; 126 received at least 1 dose of study drug; 113 participants underwent liver biopsy at week 24. Biopsies were scored independently by two NASH-CRN-trained pathologists, blinded to groups and biopsy sequence.

RESULTS

Figure 1. HARMONY study design

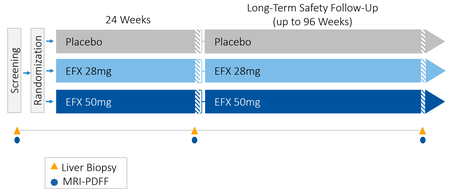


Table 1. Change from Baseline (CFB) for NITs at Week 24

Parameter (Unit) Category LS mean (SE) unless otherwise noted	Placebo	EFX 28 mg	EFX 50 mg
LFC (%), MRI-PDFF	N=42	N=38	N=35
Relative (%) CFB	–6.0 (4.01)	–51.6 (4.31)	–63.7 (4.42)
P vs placebo	NA	<0.001	<0.001
Pro-C3 (measured by ELISA)	N=40	N=37	N=35
Absolute CFB (ng/ml)	0.1 (0.70)	–5.1 (0.74)	–5.2 (0.74)
P vs placebo	NA	<0.001	<0.001
ELF score	N=41	N=37	N=32
Absolute CFB	0.1 (0.10)	–0.6 (0.10)	–0.7 (0.11)
P vs placebo	NA	<0.001	<0.001
NIS-4 Score	N=39	N=35	N=31
Absolute CFB	0.0 (0.03)	–0.3 (0.04)	–0.3 (0.04)
P vs placebo	NA	<0.001	<0.001
Liver stiffness, FibroScan (VCTE)	N=42	N=38	N=36
Relative (%) CFB	–0.4 (5.82)	–15.4 (6.19)	–24.7 (6.37)
P vs placebo	NA	0.064	0.004
FAST score	N=39	N=37	N=34
Mean (SD) CFB	–0.05 (0.19)	–0.31 (0.22)	–0.46 (0.14)
P vs placebo	NA	<0.0001	<0.0001

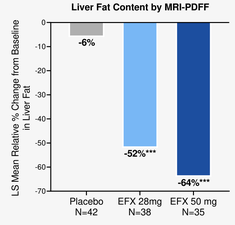
ELF, enhanced liver fibrosis; FAST, FibroScan-AST; LFC, liver fat content; NA, not applicable, PDFF, proton density fat fraction; Pro-C3, N-terminal type III collagen propeptide; VCTE, vibration-controlled transient elastography

Notes: Two EFX-treated participants analyzed for LFC normalization did not have week-24 biopsies available. One EFX-treated participants analyzed for LFC normalization did not have week 24-biopsies available.

LS Means, SEs, and p-values from a mixed-model repeated-measures (MMRM) with baseline as a covariate and controlling for stratification factors for comparisons between the EFX and placebo groups for Pro-C3 and ELF score. FAST p-values are from 1-way ANOVA, Dunnett's multiple comparisons test. Baseline is the last non-missing measurement prior to the first dose of study drug.

Figure 2. EFX Robustly Reduced Liver Fat, Normalizing LFC in a Significant Proportion of Participants

Participants achieving endpoint, n (%)	Placebo (N=42)	EFX 28 mg (N=38)	EFX 50 mg (N=35)
Liver Fat Normalization (>5% at Baseline, ≤5% at Week 24)	0	13 (34%)***	18 (51%)***
≥50% Relative Reduction in Liver Fat Content at Week 24	1 (2.4%)	24 (63%)***	27 (77%) ***



LS Mean Relative (%) CFB: ***p<0.001, vs placebo (ANCOVA)

Figure 3. EFX Significantly Improved NASH Histopathology

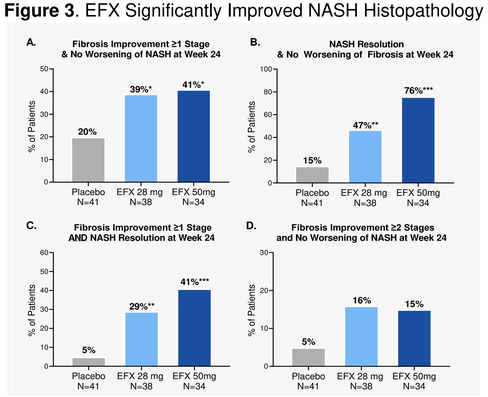
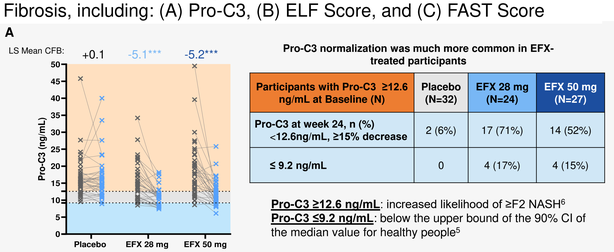


Figure 4. EFX Significantly Improved NITs Associated with NASH and Fibrosis, including: (A) Pro-C3, (B) ELF Score, and (C) FAST Score



LS Mean Absolute CFB, ***p<0.001, versus placebo (MMRM)

Pro-C3 normalization was much more common in EFX-treated participants

Participants with Pro-C3 ≥12.6 ng/mL at Baseline (N)	Placebo (N=32)	EFX 28 mg (N=24)	EFX 50 mg (N=27)
Pro-C3 at week 24, n (%) <12.6ng/mL, ≥15% decrease	2 (6%)	17 (71%)	14 (52%)
≤ 9.2 ng/mL	0	4 (17%)	4 (15%)

Pro-C3 ≥12.6 ng/mL: increased likelihood of ≥F2 NASH[6]
Pro-C3 ≤9.2 ng/mL: below the upper bound of the 90% CI of the median value for healthy people[5]

ELF score normalized in EFX-treated participants, consistent with reduced likelihood of advanced fibrosis (F≥3)

Participants with ELF Score ≥9.8 at Baseline (N)	Placebo (N=19)	EFX 28mg (N=14)	EFX 50mg (N=12)
ELF Score <9.8 at week 24, n (%)	4 (21%)	6 (43%)	9 (75%)

ELF Score <9.8: lower risk of disease progression (development of cirrhosis or liver-related events)

A greater proportion of EFX-treated participants improved FAST score, consistent with reduced likelihood of NASH with fibrosis (NAS ≥4 and F≥2)

FAST Risk Category		Placebo (N=39)	EFX 28mg (N=37)	EFX 50mg (N=34)
Improvement	High to Indeterminate	7 (18%)	9 (24%)	4 (12%)
	Indeterminate to Low	4 (10%)	12 (32%)	13 (38%)
	High to Low	0	6 (16%)	14 (41%)
No Change		21 (54%)	9 (24%)	3 (9%)
Worsening	Low to Indeterminate	1 (3%)	0	0
	Indeterminate to High	6 (15%)	1 (3%)	0
	Low to High	0	0	0

FAST Risk Categories for likelihood of NAS ≥4 and F≥2: low (≤0.35), indeterminate (>0.35 & < 0.67) and high (≥ 0.67)

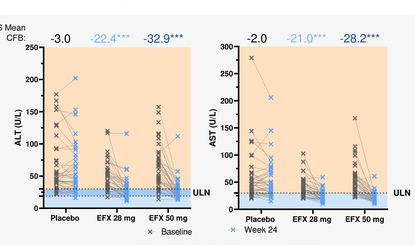
Statistics not calculated for arithmetic mean CFB in FAST score

Table 2. Normalization of Liver Fat, AST, and ALT by EFX was Significantly Associated With Increased Odds of Histologic Improvement

Odds of Achieving Histologic Endpoint with Biomarker Normalization (Among EFX-treated Participants)	Odds Ratio [95% CI]
Normalization of Liver Fat Content	
NASH resolution and no worsening of fibrosis	4.6 [1.5, 14.2] **
Fibrosis improvement with no worsening of NASH	1.4 [0.5, 3.6]
NASH resolution AND fibrosis improvement	3.4 [1.4, 8.3] *
AST Normalization	
NASH resolution and no worsening of fibrosis	6.7 [1.7, 24.7] **
Fibrosis improvement with no worsening of NASH	3.2 [0.9, 11.8]
NASH resolution AND fibrosis improvement	2.3 [0.6, 8.7]
ALT Normalization	
NASH resolution and no worsening of fibrosis	4.2 [1.4,11.9] *
Fibrosis improvement with no worsening of NASH	1.76 [0.7, 4.8]
NASH resolution AND fibrosis improvement	2.1 [0.7, 6.5]

* P < 0.05, ** P < 0.01 by Fisher's exact test

Figure 5. EFX Significantly Reduced ALT and AST Levels



LS Mean CFB (U/L): ***p<0.001, vs placebo (MMRM)

EFX Normalized ALT and AST Levels Within 24 Weeks

Proportion of Participants Achieving Normalization	Placebo	EFX 28 mg	EFX 50 mg
ALT (Males: ≥30 U/L at baseline, <30 U/L at week 24; Females: ≥19 U/L at baseline, <19 U/L at week 24)	2/40 (5.0%)	9/32 (28.1%)	17/34 (50.0%)
AST (>30 U/L at baseline, ≤ 30 U/L at week 24)	5/33 (15.2%)	18/27 (66.7%)	22/26 (84.6%)

Table 3. EFX Improved NIS-4 (NASH Risk) Scores

NIS-4 Risk Category		Placebo (N=36)	EFX 28 mg (N=26)	EFX 50 mg (N=24)
Improvement	High to Indeterminate	2 (5.6%)	7 (26.9%)	6 (25.0%)
	Indeterminate to Low	2 (5.6%)	1 (3.8%)	2 (8.3%)
	High to Low	3 (8.3%)	7 (26.9%)	9 (37.5%)
No Change		27 (75.0%)	10 (38.5%)	7 (29.2%)
Worsening	Low to Indeterminate	0	0	0
	Indeterminate to High	0	1 (3.8%)	0
	Low to High	2 (5.6%)	0	0

NIS-4 < 0.36: low risk for at-risk NASH (NAS ≥4 and F≥2)
0.37 ≤ NIS-4 ≤ 0.63: moderate risk for at-risk NASH
NIS-4 > 0.63: at-risk for NASH

CONCLUSIONS

- In the phase 2b HARMONY study in patients with NASH and F2 or F3 fibrosis, 24 weeks treatment with EFX led to significant improvements in histopathology of NASH and fibrosis
- EFX-associated changes in NIT results were associated with changes in NASH histopathology
- EFX significantly reduced liver fat, and improved circulating and imaging-based biomarkers of liver injury, inflammation, and fibrosis compared with placebo
- Normalization of liver fat content, AST, or ALT in EFX-treated participants was associated with a higher probability of resolving histopathologic features of NASH.
- Although most participants began the study in high-risk NIT categories based on Pro-C3 (fibrogenesis), ELF(fibrosis burden), and FAST (liver fat, fibrosis, and injury) scores, treatment with EFX was associated with significant shifts to lower risk categories.
- Results of NITs may be useful in predicting responses to EFX among treated patients with moderate-to-severe (F2/F3) fibrosis and NASH.

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ACKNOWLEDGMENTS

The authors wish to thank the study participants, their families, and study investigators.

This study and all analyses were funded by Akero Therapeutics.

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