Correlation between changes in liver fat content and improvements in serum markers of liver injury, fibrosis, and metabolism, and in histologic parameters following treatment with efruxifermin

S. HARRISON [1], E. TILLMAN [2], R. SHRINGARPURE [2], C. BEHLING [3], C. HU [4], E. FONG [2], B. de TEMPLE [2], T. ROLPH [2], A. CHENG [2], and K. YALE [2]

[1] Pinnacle Clinical Research, San Antonio, TX, USA; [2] Akero Therapeutics, South San Francisco, CA, USA; [3] UCSD, San Diego, CA, USA; [4] Medpace, Cincinnati, OH, USA

EASL The Home of Hepatology

PO-1762

akero

INTRODUCTION

Efruxifermin (EFX) is a long-acting Fc-FGF21 analogue being developed as a potential therapy for patients with non-alcoholic steatohepatitis (NASH) fibrosis. In the phase 2a BALANCED study (ClinicalTrials.gov NCT03976401) patients with biopsy-confirmed NASH (F1-3), 16-week treatment with EFX significantly reduced liver fat content and improved markers of liver injury, fibrosis, and lipid and glucose metabolism while demonstrating an acceptable safety and tolerability profile[1].

As a regulator of whole-body metabolism, FGF21 coordinates whole body metabolism between liver, adipose tissue, and other organs that store and utilise energy. The post-hoc analyses presented herein sought to investigate the extent to which EFX drives metabolic improvements in a similarly coordinated manner.

AIMS

This additional analysis of the BALANCED study evaluates the association between changes in liver fat content (LFC) and biomarkers of liver injury and fibrosis, glucose and lipid metabolism, and histologic features of NASH following treatment with EFX. The analyses are based on all patients and a subset of patients diagnosed with type 2 diabetes at baseline.

METHODS

Figure 1. BALANCED Study Design

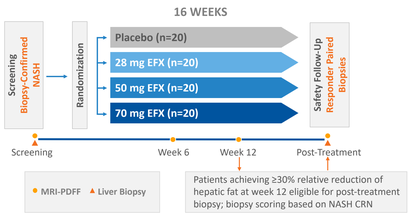
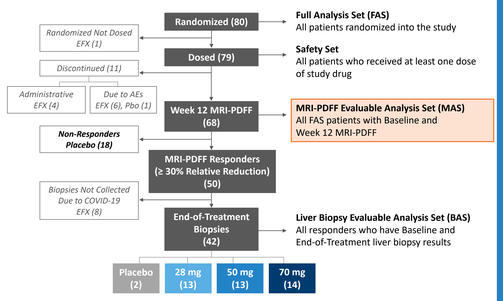


Figure 2. Patient Disposition



BALANCED Main Study randomized 80 patients (Full Analysis Set). Week 12 MRI-PDFF data were available for 68 patients comprising the MRI-PDFF Evaluable Analysis Set (MAS). Patients with ≥30% relative reduction in liver fat content at week 12 were eligible to receive end-of-treatment liver biopsy. Baseline and end-of-treatment liver biopsies were available for 42 patients comprising the Biopsy Analysis set (BAS). All histology data in this analyses are based on the BAS.

RESULTS

Table 1. Baseline Demographics and Characteristics

Parameter		Placebo (N=21)	EFX 28mg (N=19)	EFX 50mg (N=20)	EFX 70mg (N=20)
Age (Years)		52	50	53	53
Sex (Male/Female)		6/15	9/10	10/10	9/11
BMI (kg/m^2)		37.6	38.8	36.7	37.2
Body weight (kg)		99.6	108.2	103.6	103.1
Liver Fat Content (LFC, % by MRI-PDFF)		19.3	21.4	18.3	19.4
NAFLD Activity Score (NAS)		5.1	5.6	5.1	5.6
Alanine Aminotransferase (ALT) (U/L)		50.7	62.5	53.4	56.8
Aspartate Aminotransferase (AST) (U/L)		38.6	41.1	35.4	44.6
Fasting Plasma Glucose (mg/dL)		128.1	121.3	124.4	134.8
Triglycerides (mg/dL)		208.3	176.3	176.5	180.0
Fibrosis Stage F2/F3, n (%)		13 (62)	12 (63)	13 (65)	13 (65)
Type 2 Diabetes, n (%)		14 (67)	7 (37)	10 (50)	10 (50)
Pro-C3 (µg/mL)		16.1	19.2	16.2	17.2
ELF Score		9.5	9.5	9.5	9.5
HbA1c (%)	Full Analysis Set	6.49	6.20	6.43	6.23
	T2D Subset	6.96	6.89	7.01	6.95
Adiponectin (mg/L)	Full Analysis Set	4.4	4.7	3.5	5.4
	T2D Subset	4.7	5.9	3.7	5.4

Demographics and characteristics are presented as mean unless otherwise noted

Table 2. Extent of Reduction in Liver Fat Content (LFC) at Week 12

Endpoint	Placebo [a] (N=20)	28 mg (N=16)	50 mg (N=17)	70 mg (N=15)
Relative Reduction in LFC				
≥50%	5%	69%**	100%***	93%***
≥70%	5%	50%*	53%**	80%***
Normalization of LFC				
≤5% at Week 12	5%	25%*	53%**	67%***

* p<0.05, ** p<0.01, *** p<0.001 versus placebo (ANCOVA)
[a] A single placebo responder lost 25 pounds over 16 weeks (11% weight reduction)

Table 3. Correlation Between Relative Change in LFC from Baseline to Week 12 and Percent Change in Serum Biomarkers from Baseline to Week 16

	All Patients with Week 12 MRI-PDFF (N=68)		Patients with Type 2 Diabetes (N=35)	
Biomarker	Spearman R	p value	Spearman R	p value
ALT	0.5885	<0.0001	0.6911	<0.0001
AST	0.6144	<0.0001	0.6361	<0.0001
GGT	0.7539	<0.0001	0.7855	<0.0001
Adiponectin	-0.6886	<0.0001	-0.6357	<0.0001
Triglycerides	0.6542	<0.0001	0.6428	<0.0001
HbA1c (%) [1]	0.5768	<0.0001	0.6956	<0.0001
HOMA-IR	0.4489	0.0002	0.4827	0.0038
C-peptide	0.4961	<0.0001	0.5218	0.0016
Urate	0.4966	<0.0001	0.4834	0.0038
Pro-C3	0.5281	<0.0001	0.6765	<0.0001
Pro-C3/C3M Ratio	0.4289	0.0004	0.5385	0.0015
ELF Score [1,2]	0.4678	<0.0001	0.6845	<0.0001

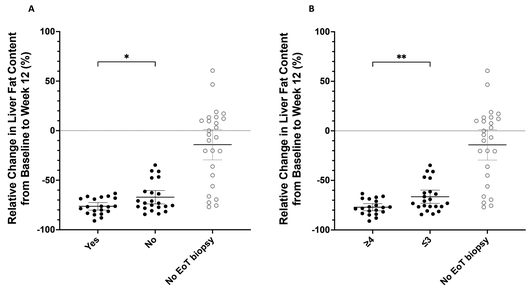
[1] Absolute Change; [2] Week 12; Spearman R = Spearman Correlation Coefficient

- **The majority of EFX-treated patients achieved ≥70% relative reduction in liver fat**
- **Over 50% of NASH patients treated with the two highest doses of EFX achieved liver fat normalization (≤5% LFC)**
- **Decreases in LFC correlated with improvements in markers of liver injury and fibrosis, as well as markers of whole-body metabolism**
- **Correlations between liver fat reduction and improved biomarkers of liver and whole-body metabolic health generally were equivalent or stronger in patients with T2D**

Histology Assessment

- 2/20 (10%) patients receiving placebo and 48/48 (100%) EFX-treated patients with biopsy-confirmed NASH achieved ≥30% relative reduction in liver fat content at week 12, and were eligible for end-of-treatment biopsy
- 1/20 (5%) patients receiving placebo and 23/48 (48%) EFX-treated patients achieved liver fat normalization at week 12, all of whom achieved ≥30% relative reduction in liver fat
- 42 patients obtained end-of-treatment biopsies in the BALANCED main study, comprising 40 EFX-treated and 2 placebo patients

Figure 3. Greater reductions in liver fat content (LFC) were associated with both NASH resolution[1] without worsening of fibrosis (A) and ≥4-point NAS improvement[2] (B), key histological endpoints, in patients with ≥30% relative reduction in LFC and end-of-treatment biopsy



* p<0.05 (two-tailed t test with Welch's correction)

[1] 0- or 1-point for lobular inflammation and 0 points for ballooning components of NAFLD Activity Score

** p<0.01 (two-tailed t test with Welch's correction)

[2] At least 2 points from lobular inflammation and/or ballooning components of NAFLD Activity Score

Table 4. Normalization of LFC (≤5% at Week 12) was associated with significantly greater odds of achieving NASH resolution without worsening of fibrosis or ≥4-point improvement in NAS relative to patients with Week 12 absolute LFC >5%, in patients with ≥30% relative reduction in LFC and end-of-treatment biopsy

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

Figure 4. Larger decreases in LFC across all treatment groups (A), but not normalization of LFC in EFX-treated patients (B), correlate with significantly greater reductions in ALT

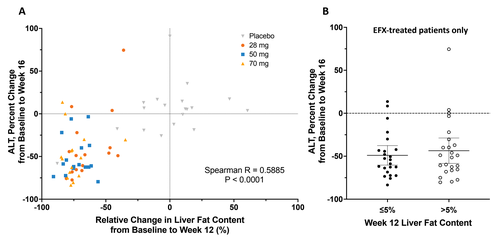


Figure 5. Larger decreases in LFC across all treatment groups (A), but not normalization of LFC among EFX-treated patients (B), correlate with significantly greater reductions in Pro-C3

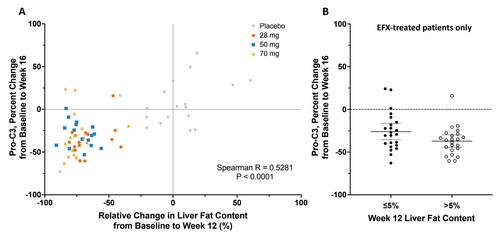
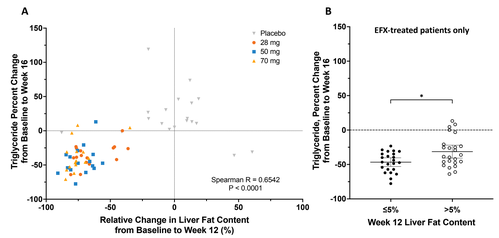
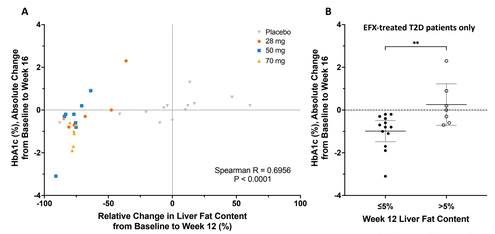


Figure 6. Both larger decreases in LFC across all treatment groups (A) and normalization of LFC in EFX-treated patients (B) correlate with significantly greater reductions in triglyceride



* p<0.01 (Mann-Whitney test)

Figure 7. In patients with T2D, both larger decreases in LFC across all treatment groups (A), and normalization of LFC in EFX-treated patients (B) correlate with significantly greater reductions in %HbA1c



** p<0.01 (Mann-Whitney test)

Liver fat normalization does not appear to provide additional reductions in ALT and Pro-C3 over EFX treatment

Liver fat normalization may correlate with greater whole-body metabolic improvements in EFX-treated patients, including those with T2D

In all figures, each dot represents an individual patient. Summary data are presented as mean ± 95% CI.

CONCLUSIONS

- EFX treatment significantly and dose-dependently reduced liver fat content (LFC) in patients with NASH and F1–F3 fibrosis (n=68), including those with type 2 diabetes (T2D) at baseline (n=35)
- Magnitude of LFC reduction correlated with improvements in non-invasive biomarkers of liver injury and fibrosis, as well as markers of lipid metabolism and glucose metabolism
  - Normalization of LFC was not associated with larger reductions in ALT and Pro-C3
  - On the other hand, normalization of LFC was associated with greater reductions in triglyceride, and in %HbA1c in the subset of patients with T2D, suggesting that normalization of LFC may have contributed to greater whole-body metabolic benefits
- Among 42 patients with paired biopsies (all of whom achieved ≥30% relative reduction in LFC over 12 weeks):
  - Greater reductions in LFC were associated with the FDA endpoint of NASH resolution without worsening of fibrosis, or an improvement of ≥4-points in NAS
  - Normalization of LFC (<5%) was associated with greatly increased probability of NASH resolution

ACKNOWLEDGMENTS

The authors wish to thank the patients, their families, and study investigators. This study and all analyses were funded by Akero Therapeutics.

REFERENCES

1. **Harrison SA et al**. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nature Medicine, in press*

CONTACT INFORMATION

Kitty Yale, Akero Therapeutics. kyale@akerotx.com