Efruxifermin, a long-acting, bivalent FGF21 analog, normalized noninvasive measures of liver injury, fibrosis, and metabolic health in patients with NASH and F2/F3 fibrosis over 24 weeks

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BACKGROUND

Efruxifermin (EFX) is a long-acting Fc-FGF21 analog being developed as a potential therapy for subjects with fibrosis due to non-alcoholic steatohepatitis (NASH). In the phase 2a BALANCED study of 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].

In the ongoing phase 2B HARMONY study of subjects with biopsy-confirmed NASH (F2-3), 24-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.

We analyzed normalization of non-invasive markers of liver injury and fibrosis in the context of improvement in liver histology associated with EFX treatment. Normalization of these markers, including Liver Fat Content (LFC), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Pro-C3, Enhanced Liver Fibrosis (ELF), FibroScan-AST (FAST), HbA1c, and Triglycerides, is useful for stratifying subjects at risk of progressive disease.

STUDY DESIGN AND BASELINE DEMOGRAPHICS

Figure 1. HARMONY Study Design

128 subjects with biopsy-confirmed F2-F3 NASH were randomized 1:1:1 to 28-, 50-mg EFX, or placebo, administered SC QW (**Fig. 1**), of whom 126 received at least one dose of study drug. 113 subjects received a primary endpoint week 24 liver biopsy. Biopsies were scored independently by two NASH-CRN trained pathologists, who were blinded to treatment and sequence with a third pathologist available to adjudicate if necessary.

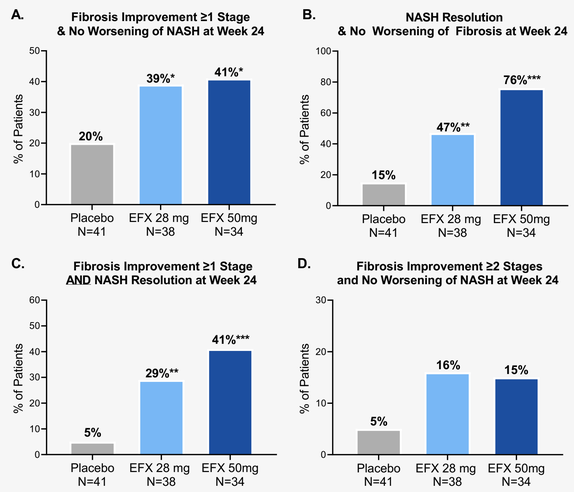
Reference values of normalization were based on Central Laboratory reference values (ALT: 48 U/L for males or 42 U/L for females; AST: 40 U/L) or published thresholds as indicated.

Table 1. Baseline demographics

Baseline characteristics (Mean unless otherwise noted)	Placebo (N=43)	EFX 28mg (N=42)	EFX 50mg (N=43)
Age (Years)	55	57	52
Sex (% Female)	63	69	53
Weight (kg)	108	104	103
Fibrosis Stage (%F2/%F3)	30/70	36/64	37/63
Liver Fat Content (%, MRI-PDFF)	17.1	18.5	17.5
ALT (U/L)	62	50	63
AST (U/L)	57	42	52
HbA1c (%)	6.8	6.8	6.8
% Type 2 Diabetes	65	76	70
Triglycerides (mg/dL)	170	158	154
ELF Score	9.8	9.7	9.8
FAST Score	0.68	0.61	0.67
Pro-C3 (µg/L)	16.5	15.3	18.4
Liver Stiffness by VCTE (Fibroscan) (kPa)	15	14	18

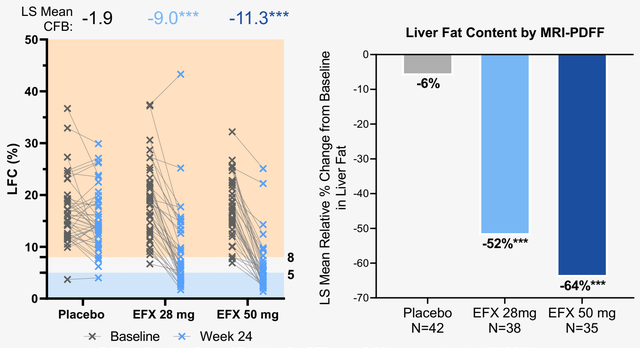
RESULTS

Figure 2. EFX significantly improved NASH histopathology



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

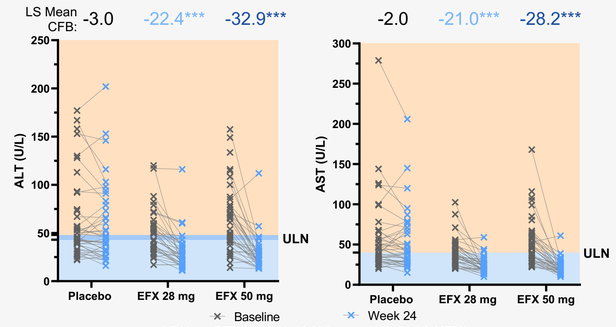
Figure 3. EFX normalized LFC in many subjects within 24 weeks



LS Mean Absolute (%) and Relative (%) CFB: ***p<0.001, versus placebo (ANCOVA)

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

Figure 4. EFX normalized ALT and AST within 24 weeks

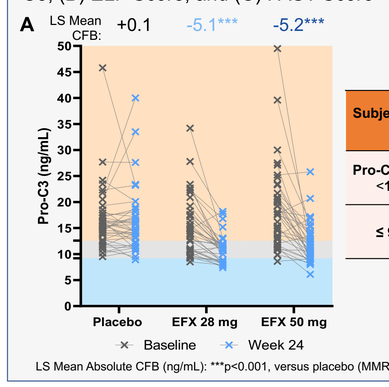


LS Mean CFB (U/L): ***p<0.001, versus placebo (MMRM)

Subjects >ULN at Baseline Achieving Endpoint, n/N (%)	Placebo	EFX 28mg	EFX 50mg
ALT Normalization at Week 24 (≤ULN with ≥15% decrease)	3/22 (14%)	13/18 (72%)	17/20 (85%)
AST Normalization at Week 24 (≤ULN with ≥15% decrease)	4/15 (27%)	13/14 (93%)	18/19 (95%)

EFX restored liver health as observed with normalization of liver fat, ALT and AST, leading to resolution of NASH in a majority of patients treated with EFX 50 mg.

Figure 5. EFX significantly improved non-invasive tests for NASH fibrosis, including (A) Pro-C3, (B) ELF Score, and (C) FAST Score

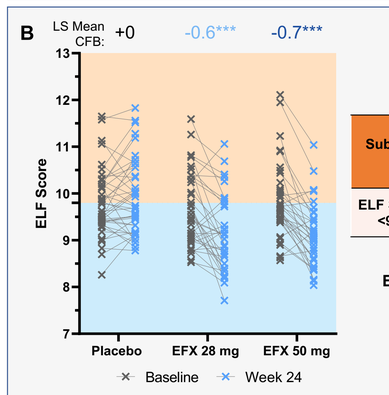


LS Mean Absolute CFB (ng/mL): ***p<0.001, versus placebo (MMRM)

Pro-C3 ≥12.6 ng/mL: increased likelihood of ≥F2 NASH, **Pro-C3 ≤9.2 ng/mL**: below the upper bound of the 90% confidence interval of the median value in healthy people

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

Pro-C3, a biomarker of collagen synthesis, was normalized in EFX-treated subjects.

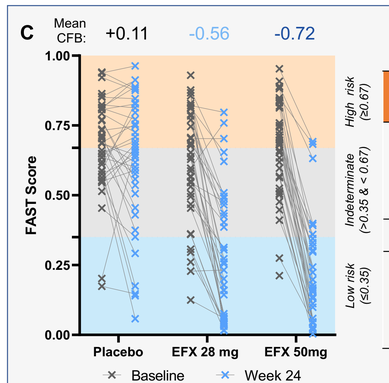


LS Mean Absolute CFB, ***p<0.001, versus placebo (MMRM)

ELF Score ≥9.8: increased likelihood of advanced fibrosis

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

ELF score normalized in a greater proportion of EFX-treated subjects, consistent with reduced likelihood of advanced fibrosis.



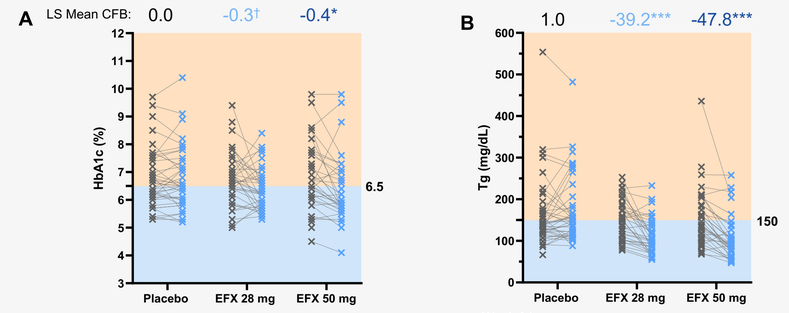
Statistics not calculated for arithmetic mean CFB in FAST Score

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

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

Greater proportion of EFX-treated subjects improved FAST Score by one-to-two risk categories, consistent with reduced likelihood of active NASH with fibrosis.

Figure 6. Normalization of Metabolic Markers: (A) Glycemic Marker HbA1c, (B) Triglycerides



LS Mean Absolute CFB (HbA1c (%), Tg (mg/dL)); †p< 0.05, versus baseline; *p<0.05, ***p<0.001, versus placebo (MMRM)

Subjects with HbA1c > 6.5% at Baseline (N)	Placebo (N=22)	EFX 28 mg (N=24)	EFX 50 mg (N=20)
Normalization of HbA1c (≤ 6.5%), n (%)	3 (14%)	9 (38%)	8 (40%)

Subjects with Triglycerides > 150 mg/dL at Baseline (N)	Placebo (N=17)	EFX 28 mg (N=19)	EFX 50 mg (N=16)
Normalization of Triglycerides (≤ 150 mg/dL with ≥ 15% decrease), n (%)	2 (12%)	11 (58%)	10 (63%)

EFX treatment was associated with normalization of HbA1c and triglycerides, important markers of glucose and lipid metabolism, consistent with restoration of a healthy whole-body metabolic phenotype.

Figure 7. Normalization of markers of liver health is associated with increased odds of achieving histologic improvements in EFX-treated subjects

Odds Ratios (OR) of Histologic Improvement among EFX-treated subjects	
Normalization of liver fat content (LFC), N=71	**OR [95% CI]**
Odds of NASH resolution and no worsening of fibrosis	4.6 [1.5, 14.2] **
Odds of fibrosis improvement with no worsening of NASH	1.4 [0.5, 3.6]
Odds of NASH resolution AND fibrosis improvement	3.4 [1.4, 8.3] *
Normalization of ALT, N=37	**OR [95% CI]**
Odds of NASH resolution and no worsening of fibrosis	+inf [2.9, +inf] **
Odds of fibrosis improvement with no worsening of NASH	+inf [1.0, +inf] *
Odds of NASH resolution AND fibrosis improvement	+inf [0.9, +inf]
Normalization of AST, N=32	**OR [95% CI]**
Odds of NASH resolution and no worsening of fibrosis	+inf [0.6, +inf]
Odds of fibrosis improvement with no worsening of NASH	+inf [0.2, +inf]
Odds of NASH resolution AND fibrosis improvement	+inf [0.2, +inf]

*p<0.05, **p<0.01 by Fisher's exact test;
inf = infinity (all subjects that achieved the histologic outcome also normalized ALT or AST)

Normalization of LFC and ALT were associated with greater odds of achieving NASH resolution and fibrosis improvement.

CONCLUSIONS

- In addition to meeting histological endpoints[5], EFX treatment for 24 weeks normalized diverse noninvasive biomarkers of NASH severity
- Before treatment, most subjects were in high-risk categories of noninvasive tests including Pro-C3 level, ELF and FAST composite scores. EFX markedly improved these, with high rates of normalization
- Almost all EFX-treated subjects with elevated ALT or AST at baseline achieved normalization of these markers of liver injury
- Normalization of LFC or ALT was associated with higher odds of NASH resolution and fibrosis regression with EFX-treatment
- Although fibrosis histopathology regressed in 40% of patients treated with EFX, non-invasive markers of fibrosis normalized in most patients, suggesting longer treatment could lead to more regression of fibrosis
- Markers of glycemic control (HbA1c) and lipid metabolism (triglycerides) were normalized in substantially more EFX-treated subjects than placebo, reflecting significantly improved whole-body metabolism

REFERENCES

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