Efruxifermin treatment improved collagen biomarkers consistent with remodelling of the extracellular matrix in patients with F2-F3 fibrosis due to MASH

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BACKGROUND AND AIMS

Efruxifermin (EFX) is a long-acting, bivalent Fc-FGF21 fusion protein (Figure 1) currently in Phase 2b and Phase 3 clinical trials for treatment of advanced (F2/F3) liver fibrosis and compensated cirrhosis (F4) due to metabolic dysfunction-associated steatohepatitis (MASH).

EFX led to significant rates of histological improvement across multiple Phase 2 studies in patients with advanced fibrosis or compensated cirrhosis due to MASH, including fibrosis improvement and/or MASH resolution[1,2,3,4]. In addition, EFX significantly improved markers of insulin resistance, dyslipidemia, liver injury, fibrosis, and fibrogenesis.

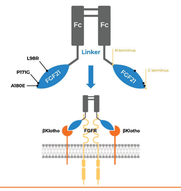

Figure 1. Efruxifermin (EFX) is a bivalent Fc-FGF21 fusion protein with three amino acid substitutions to enhance formulation stability, receptor binding affinity, and resistance to proteolytic degradation

In the Phase 2b HARMONY study of patients with F2-F3 MASH, we further investigated biomarkers of synthesis and/or degradation of collagens associated with pathological fibrosis (types III, VI, and VIII), components of the basement membrane (type IV), and regulators of extracellular matrix (ECM) metalloproteinase activity (TIMP-1) to understand how EFX modulates distinct components of the ECM (Figure 2)

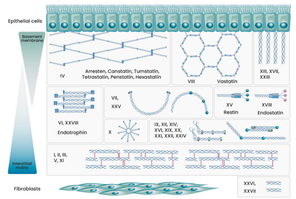

Figure 2. Localization of different collagens within various compartments of the ECM.

STUDY DESIGN

Key Inclusion Criteria
- F2-F3 MASH
- NAS ≥4
- Liver Fat (MRI-PDFF) ≥8%

Phase 2b Primary Endpoint
- ≥ 1-stage fibrosis improvement without worsening of MASH at 24 weeks

Key Secondary Efficacy Endpoints
- MASH Resolution & No Worsening of Fibrosis
- Fibrosis Biomarkers
- Lipoproteins
- Glycemic Control
- Weight Change
- MRI-PDFF
- FibroScan
- Liver Injury Biomarkers

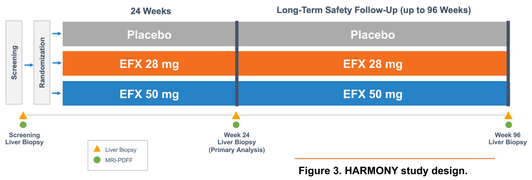

Figure 3. HARMONY study design.

Table 1. Baseline characteristics of subjects enrolled in the HARMONY study

Mean (SD) or n (%)	Placebo N=43	EFX 28 mg N=42	EFX 50 mg N=43
Age, years	55.0 (10.1)	56.5 (9.3)	52.4 (11.4)
Female, n (%)	27 (63%)	29 (69%)	23 (53%)
F2 / F3 (%)	30% / 70%	36% / 64%	34% / 66%
NAFLD Activity Score	5.4 (1.2)	5.1 (1.0)	5.6 (1.1)
T2D, n (%)	28 (65%)	32 (76%)	30 (70%)
HbA1c, %	6.8 (1.1)	6.8 (1.0)	6.7 (1.2)
ALT, U/L	62.2 (41.7)	49.7 (23.3)	63.3 (34.3)
AST, U/L	57.0 (45.0)	41.8 (18.2)	52.4 (30.0)
ELF Score	9.8 (0.7)	9.7 (0.8)	9.8 (0.8)
P3NP	11.9 (4.1)	10.5 (4.3)	12.6 (5.9)
TIMP-1	292.1 (57.5)	287.0 (70.2)	288.6 (80.8)
HA	78.3 (72.8)	72.4 (51.5)	78.0 (78.7)
Median (IQR)			
Pro-C3 (Gen1), µg/L	15.8 (12.8, 17.3)	14.7 (10.9, 17.5)	17.6 (12.9, 20.8)
CTX-III, µg/L	19.8 (13.3, 36.1)	17.2 (9.4, 31.8)	27.2 (11.5, 43.7)
Pro-C3:CTX-III ratio	0.84 (0.34, 1.35)	0.65 (0.38, 1.90)	0.64 (0.30, 1.28)
Pro-C4, µg/L	6692.6 (6231.2, 7306.6)	6779.1 (6170.4, 7375.9)	6864.0 (6176.0, 7400.1)
C4M, µg/L	247.4 (214.2, 295.6)	258.9 (210.8, 296.4)	253.2 (217.5, 299.6)
Pro-C4/C4M ratio	25.5 (23.5, 32.3)	26.1 (24.0, 30.9)	26.5 (22.9, 32.2)
Pro-C6, µg/L	11.6 (10.1, 14.3)	12.5 (9.7, 16.2)	12.6 (10.2, 16.1)

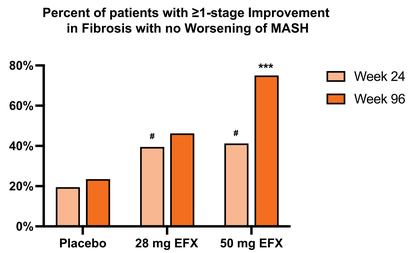

Figure 4. EFX significantly improved liver fibrosis after 24 and 96 weeks (liver biopsy analysis set, i.e., those with evaluable paired biopsies for the timepoint). After 24 weeks, 39% of subjects receiving 28 mg EFX (N=38) and 41% of subjects receiving 50 mg EFX (N=34) experienced at least a 1-stage improvement in fibrosis without MASH worsening, compared to 20% of placebo (N=41); #p<0.05 vs placebo, Cochran-Mantel-Haenszel (CMH) test. After 96 weeks, 46% of subjects receiving 28 mg EFX (N=26) and 75% of subjects receiving 50 mg EFX (N=28) experienced at least a 1-stage improvement in fibrosis without MASH worsening, compared to 24% of placebo (N=34); ***p<0.001 vs placebo, CMH test. Statistical tests were run independently on the liver biopsy analysis sets at Week 24 and Week 96.

RESULTS

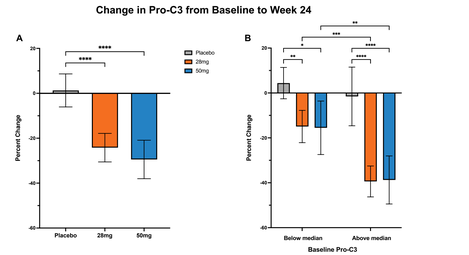

Figure 5. EFX significantly reduced Pro-C3, a biomarker of type-III collagen synthesis and liver fibrosis. Data are presented as mean ± 95% confidence interval. A, Pro-C3 percent change from baseline to week 24 by dose group. ***p<0.0001, one-way ANOVA and Dunnett's multiple comparison test. B, Pro-C3 percent change from baseline to week 24 by dose group and baseline Pro-C3 levels (above or below study-wide baseline median). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, 2-way ANOVA and Dunnett's multiple comparisons test.

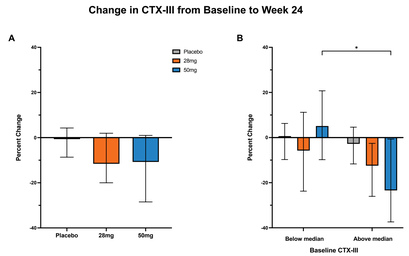

Figure 6. EFX tended to reduce CTX-III, a biomarker of type-III collagen degradation, with larger effects in those with high levels at baseline. Data are presented as median ± 95% confidence interval. A, CTX-III percent change from baseline to week 24 by dose group. B, CTX-III percent change from baseline to week 24 by dose group and baseline CTX-III levels (above or below study-wide baseline median). *p<0.05, 2-way ANOVA and Dunnett's multiple comparisons test.

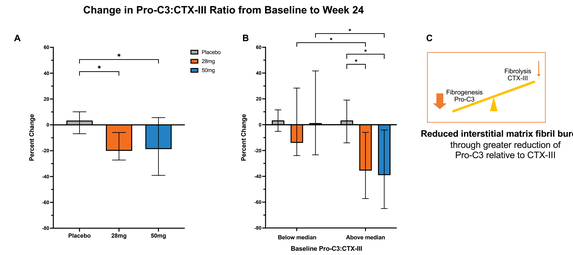

Figure 7. EFX significantly decreased relative fibrogenesis-to-fibrolysis of type-III collagen, particularly in those with a fibrogenic interstitial matrix phenotype at baseline. Data are presented as median ± 95% confidence interval. A, Pro-C3:CTX-III percent change from baseline to week 24 by dose group. *p<0.05, Kruskal-Wallis and Dunn's multiple comparisons test. B, Pro-C3:CTX-III percent change from baseline to week 24 by dose group and baseline Pro-C3:CTX-III ratio (above or below study-wide baseline median). *p<0.05, 2-way ANOVA and Dunnett's multiple comparisons test. C, Illustration of overall shift towards type-III collagen fibrolysis.

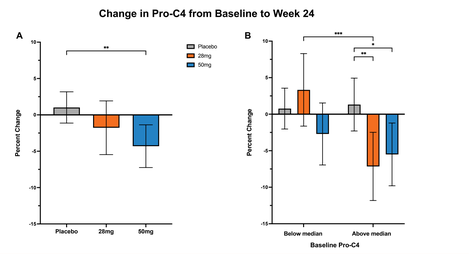

Figure 8. EFX modestly reduced Pro-C4, a biomarker of type-IV collagen synthesis, particularly in those with high levels at baseline. Data are presented as mean ± 95% confidence interval. A, Pro-C4 percent change from baseline to week 24 by dose group. **p<0.01, one-way ANOVA and Dunnett's T3 multiple comparison test. B, Pro-C4 percent change from baseline to week 24 by dose group and baseline Pro-C4 levels (above or below study-wide baseline median). *p<0.05, **p<0.01, ***p<0.001, 2-way ANOVA and Dunnett's multiple comparisons test.

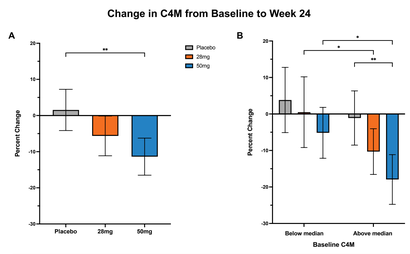

Figure 9. EFX reduced C4M, a biomarker of type-IV collagen degradation, particularly in those with high levels at baseline. Data are presented as mean ± 95% confidence interval. A, C4M percent change from baseline to week 24 by dose group. **p<0.01, one-way ANOVA and Dunnett's multiple comparison test. B, C4M percent change from baseline to week 24 by dose group and baseline C4M levels (above or below study-wide baseline median). *p<0.05, *p<0.01, 2-way ANOVA and Dunnett's multiple comparisons test.

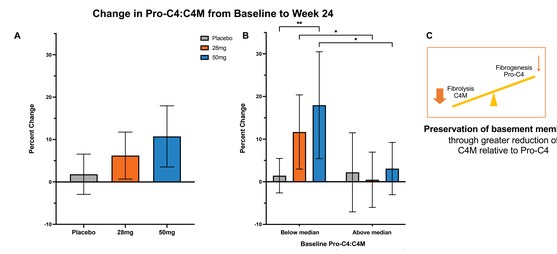

Figure 10. EFX significantly increased relative fibrogenesis-to-fibrolysis of type-IV collagen, particularly in those with a fibrolytic basement membrane phenotype at baseline. Data are presented as mean ± 95% confidence interval. A, Pro-C4:C4M percent change from baseline to week 24 by dose group. *p<0.05, Kruskal-Wallis and Dunn's multiple comparisons test. B, Pro-C4:C4M percent change from baseline to week 24 by dose group and baseline Pro-C4:C4M ratio (above or below study-wide baseline median). *p<0.05, **p<0.01, 2-way ANOVA and Dunnett's multiple comparisons test. C, Illustration of overall shift towards type-IV collagen regeneration.

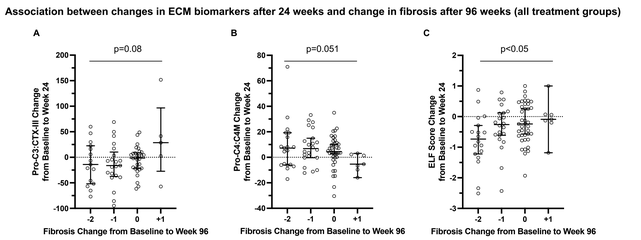

Figure 11. Changes in serum biomarkers of ECM turnover after 24 weeks trend towards association with improvements in liver fibrosis after 96 weeks (pooled placebo, 28 mg EFX, and 50 mg EFX). Data are presented as median ± IQR, all p values are from one-way ANOVA, test for linear trend. A, Pro-C3:CTX-III percent change from baseline to week 24 vs fibrosis change from baseline to week 96. B, Pro-C4:C4M percent change from baseline to week 24 vs fibrosis change from baseline to week 96. C, ELF Score absolute change from baseline to week 24 vs fibrosis change from baseline to week 96.

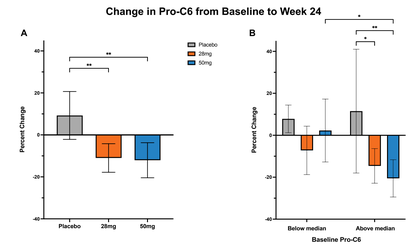

Figure 12. EFX reduced Pro-C6, a biomarker of type-VI collagen synthesis and fibrogenic hormone associated with cardiovascular outcomes[5], especially in those with high levels at baseline. Data are presented as mean ± 95% confidence interval. A, Pro-C6 percent change from baseline to week 24 by dose group. **p<0.01, one-way ANOVA and Dunnett's multiple comparison test. B, Pro-C6 percent change from baseline to week 24 by dose group and baseline Pro-C6 levels (above or below study-wide baseline median). *p<0.05, **p<0.01, 2-way ANOVA and Dunnett's multiple comparisons test.

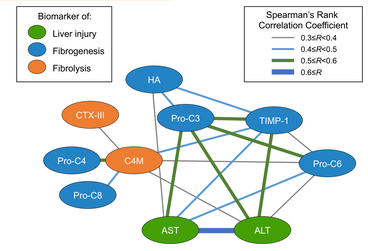

Figure 13. Associations between changes from baseline to week 24 in markers of ECM turnover, and with markers of liver injury. Pairwise Spearman's rank correlation coefficients were calculated using all non-missing data across subjects in all three dose groups (i.e., placebo, 28mg EFX, and 50mg EFX). HA, hyaluronic acid.

RESULTS

Over 24 weeks, EFX **significantly reduced biomarkers of fibrogenesis and collagen synthesis**, including Pro-C3, Pro-C6, and Pro-C8, in patients with F2-F3 fibrosis due to MASH.

EFX treatment was associated with a significant shift towards **fibrolysis relative to fibrogenesis** of the **fibrillar, interstitial type-III collagen** (decrease in Pro-C3:CTX-III ratio)

EFX treatment was associated with a significant shift towards **fibrogenesis relative to fibrolysis** of the **structural, basement membrane type-IV collagen** (increase in Pro-C4:C4M ratio)

Treatment-associated **improvements in biomarkers of ECM remodeling were greater in subjects with worse fibroblast dysfunction**, i.e., more active fibrogenesis of interstitial fibrillar collagen (type III) and more active fibrolysis of basement membrane collagen (type IV)

Improvements in biomarkers of ECM remodeling after 24 weeks correlated with **extent of fibrosis improvement** after 96 weeks

Concerted changes in biomarkers of EM remodeling were associated with **improvements in markers of liver injury** over the study's first 24 weeks

ACKNOWLEDGMENTS

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