Efruxifermin significantly improved collagen biomarkers, consistent with beneficial ECM remodeling in patients with F2-F3 fibrosis due to MASH

P-2031

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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).

Across multiple phase 2 studies in patients with moderate-to-severe fibrosis or compensated cirrhosis due to MASH, EFX led to significant rates of histological improvement, including fibrosis improvement and/or MASH resolution[1,2,3,4]. Across all studies, EFX significantly improved markers of liver injury, fibrosis, and fibrogenesis.

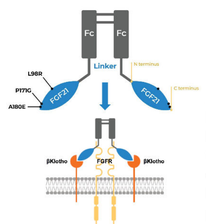


Figure 1. Efruxifermin (EFX) is a bivalent Fc-FGF21 fusion protein with three amino acid substitutions to enhance formulation stability, receptor binding affinity, and resistance to proteolytic degradation

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)

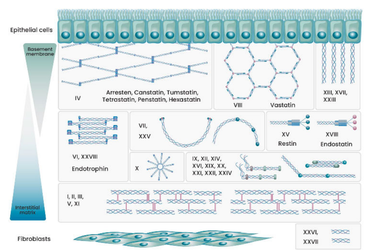


Figure 2. Localization of different collagens within various compartments of the ECM. *Courtesy of Nordic Bioscience*

STUDY DESIGN

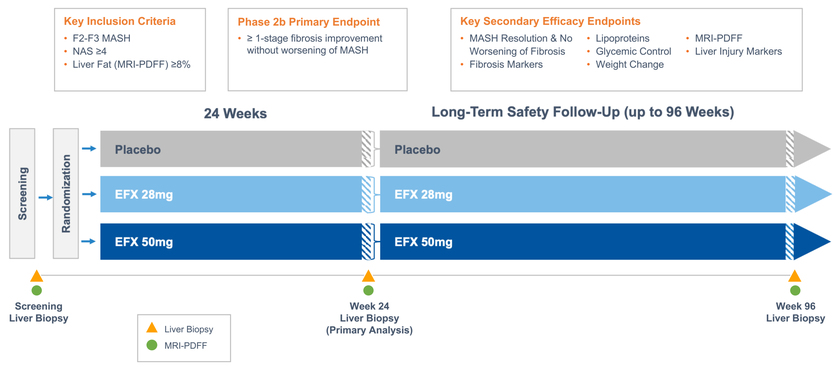
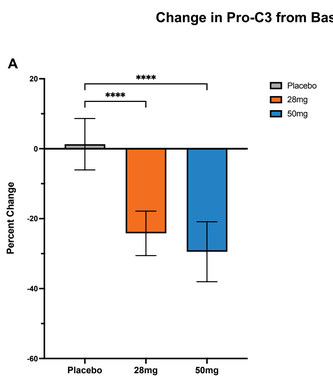


Figure 3. Study design for the Phase 2b HARMONY Trial of EFX in pre-cirrhotic (F2-F3) MASH

RESULTS



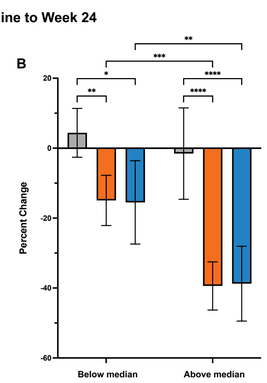
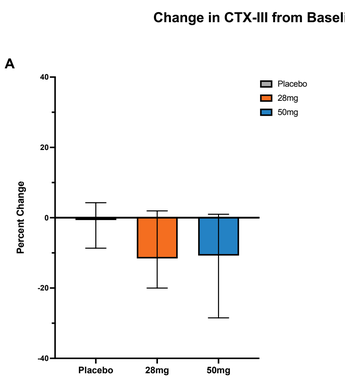


Figure 4. EFX significantly reduced Pro-C3, a biomarker of type-III collagen synthesis and liver fibrosis. Data are presented as mean ± 95% confidence interval. A, Pro-C3 percent change from baseline to week 24 by dose group. ****p<0.0001, one-way ANOVA and Dunnett's multiple comparison test. B, Pro-C3 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.



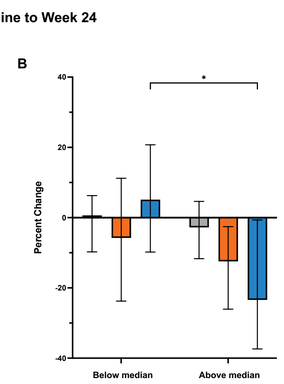
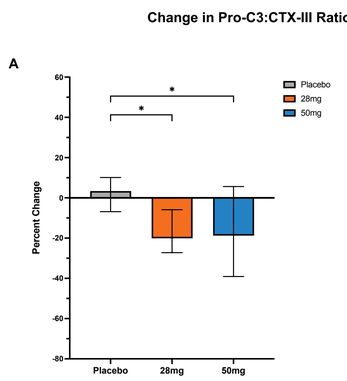
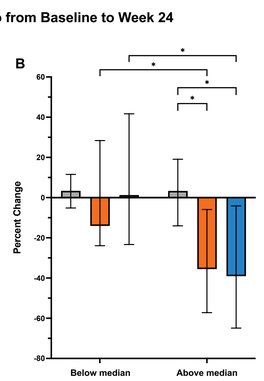
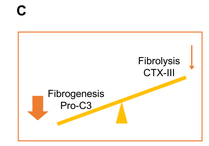


Figure 5. EFX tended to reduce CTX-III, a biomarker of type-III collagen degradation, with larger effects in those with high levels at baseline. Data are presented as median ± 95% confidence interval. A, CTX-III percent change from baseline to week 24 by dose group. B, CTX-III percent change from baseline 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.

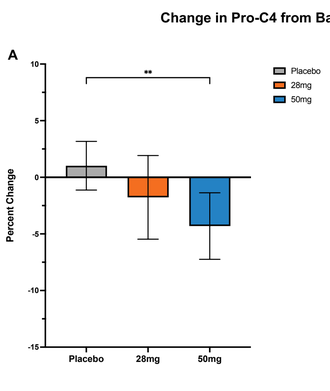






Reduced interstitial matrix fibril burden,
through greater reduction of Pro-C3 relative to CTX-III

Figure 6. 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.



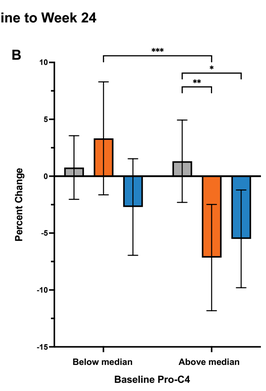
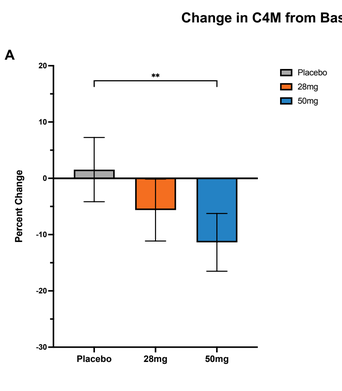


Figure 7. EFX modestly reduced Pro-C4, a biomarker of type-IV collagen synthesis, particularly in those with high levels at baseline. Data are presented as mean ± 95% confidence interval. A, Pro-C4 percent change from baseline to week 24 by dose group. **p<0.01, one-way ANOVA and Dunnett's T3 multiple 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.



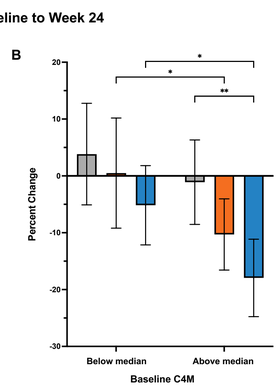
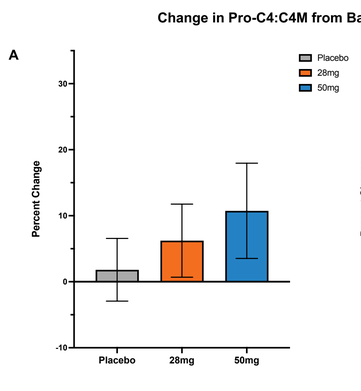
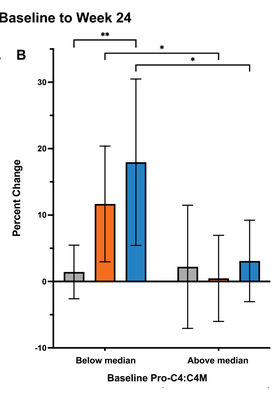
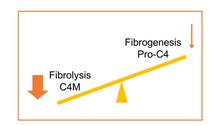


Figure 8. EFX reduced C4M, a biomarker of type-IV collagen degradation, particularly in those with high levels at baseline. Data are presented as mean ± 95% confidence interval. A, C4M percent change from baseline to week 24 by dose group. **p<0.01, one-way ANOVA and Dunnett's multiple comparison test. 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.

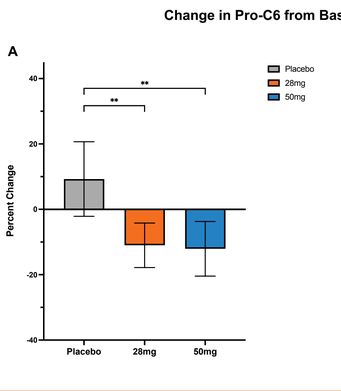






Preservation of basement membrane,
through greater reduction of C4M relative to Pro-C4

Figure 9. 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.



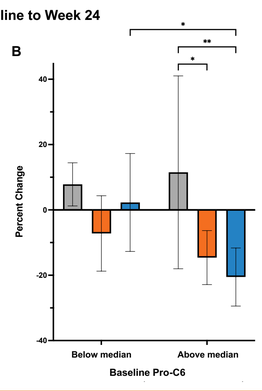


Figure 10. EFX reduced Pro-C6, a biomarker of type-VI collagen synthesis and pro-fibrogenic hormone associated with cardiovascular outcomes[5], especially in those with high levels at baseline. Data are presented as mean ± 95% confidence interval. A, Pro-C6 percent change from baseline to week 24 by 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.

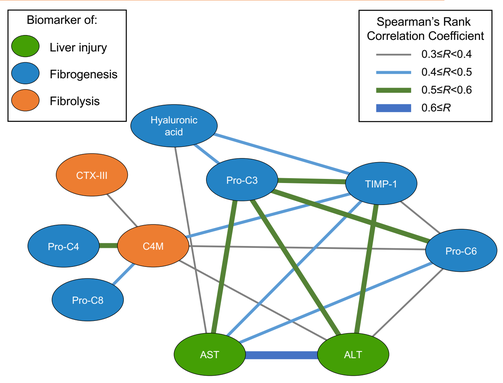


Figure 11. Associations between changes from baseline to week 24 in markers of ECM turnover, and with markers of liver injury. Pairwise Spearman's rank correlation coefficients were calculated using all non-missing data across subjects in all three dose groups (i.e., placebo, 28mg EFX, and 50mg EFX).

CONCLUSIONS

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)

Concerted changes in biomarkers of EM remodeling were associated with **improvements in markers of liver injury**

Longer treatment with EFX may reveal potential associations between ECM remodeling through 24 weeks, and fibrosis improvement after 96 weeks

REFERENCES

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ACKNOWLEDGMENTS

This study and all analyses were funded by Akero Therapeutics. We are grateful to the patients and their families, as well as investigators and their teams, for participation in the HARMONY trial.