# Improvement of liver fibrosis in efruxifermin-treated patients with MASH: correlation between conventional histopathology, AI-based digital histopathology, and non-invasive biomarkers of fibrosis

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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]. The anti-fibrotic effects of EFX were sustained and expanded over a total of 96 weeks, with up to 75% of participants experiencing fibrosis improvement without MASH worsening in the phase 2b HARMONY study (NCT04767529).

To corroborate these results, changes in liver fibrosis as scored by consensus of MASH-clinical research network (CRN)-trained pathologists were compared to changes in non-invasive measures of liver fibrosis. Additionally, liver biopsy tissue was scored using second-harmonic generation/two-photon excitation fluorescence microscopy (SHG-TPEF) and Histoindex's proprietary AI-based digital pathology algorithm, qFibrosis®. Fibrosis analysis using qFibrosis® incorporated a steatosis-area correction, in which fat area was subtracted from the total liver tissue to remove confounding effects on fibrosis area parameters.

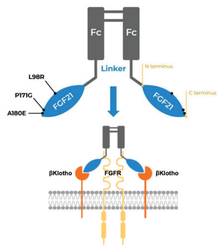



**Figure 1**. Efruxifermin (EFX) is a bivalent Fc-FGF21 fusion protein with three amino acid substitutions to enhance formulation stability, receptor binding affinity, and resistance to proteolytic degradation

## STUDY DESIGN AND PARTICIPANT DEMOGRAPHICS

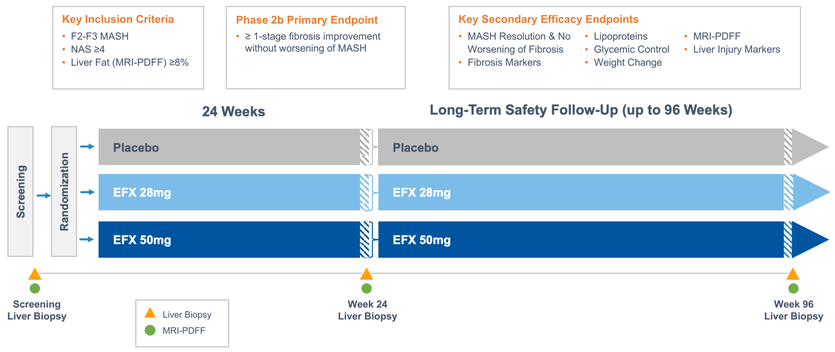



**Figure 2**. Study design for the Phase 2b HARMONY study of EFX in pre-cirrhotic (F2-F3) MASH

| Parameter (Units), mean unless 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 |
| Type 2 Diabetes (%) | 65 | 76 | 70 |
| MASH-CRN Fibrosis Stage (%F3) | 70 | 64 | 63 |
| Mean MASH-CRN Fibrosis Stage | 2.70 | 2.64 | 2.63 |
| qFibrosis® Stage, steatosis-corrected | 2.73 | 2.90 | 3.13 |
| qFibrosis® Continuous Score, steatosis-corrected | 4.21 | 4.31 | 4.68 |
| Enhanced Liver Fibrosis (ELF) Score | 9.8 | 9.7 | 9.8 |
| Pro-C3 (µg/L) | 125 | 113 | 145 |
| Liver Stiffness by VCTE (FibroScan) (kPa) | 15 | 14 | 16 |
| Hepatic Fat Fraction by MRI-PDFF (%) | 17.1 | 18.5 | 17.5 |
| Alanine Aminotransferase (ALT) (U/L) | 62 | 50 | 63 |

**Table 1**. Baseline demographics and characteristics of all enrolled participants in HARMONY. All participants were fibrosis stage 2 or 3 by MASH-CRN staging at baseline. VCTE, vibration-controlled transient elastography. PDFF, proton-density fat fraction.

## RESULTS

**Figure 3. EFX significantly improved liver fibrosis over 24– 96 weeks.** Data are from the liver biopsy analysis set, comprising all participants with a biopsy at baseline and the specified timepoint. †p<0.05 vs placebo at W24; *** p<0.001 vs placebo at W96 (Cochran-Mantel-Haenszel Test)

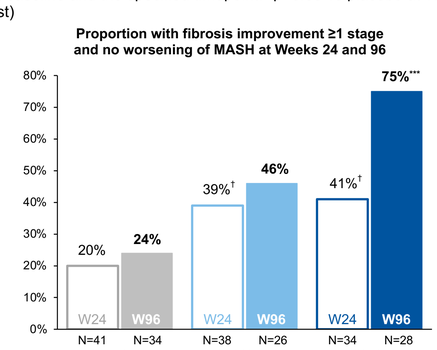



**Figure 4. EFX significantly reduced biomarkers of liver fibrosis and fibrogenesis over 96 weeks.** Sustained improvements in (A) Pro-C3, (B) ELF Score, and (C) Liver Stiffness (FibroScan VCTE). Data are presented as LS mean change ±95% CI, comprising all participants with data at given timepoint for a given biomarker. *p<0.05, **p<0.01, ***p<0.001 vs placebo (MMRM).

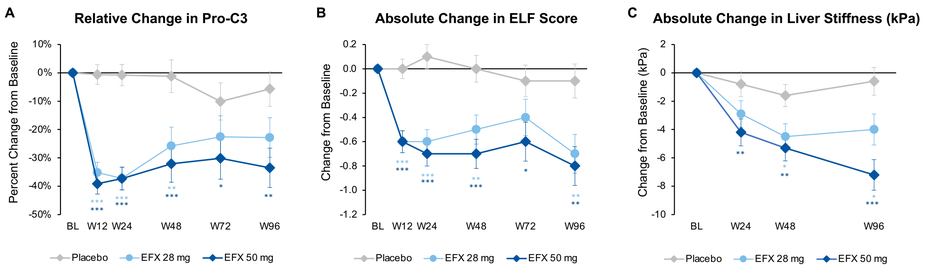
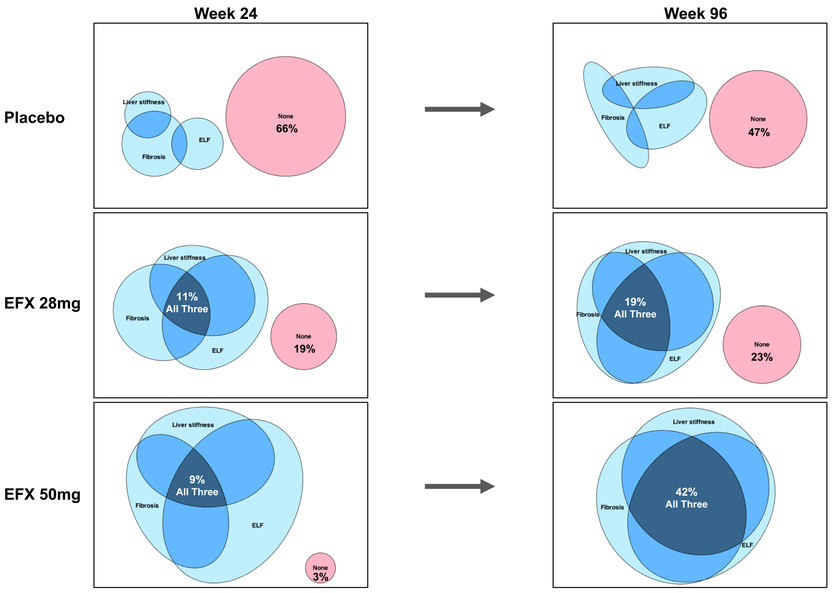


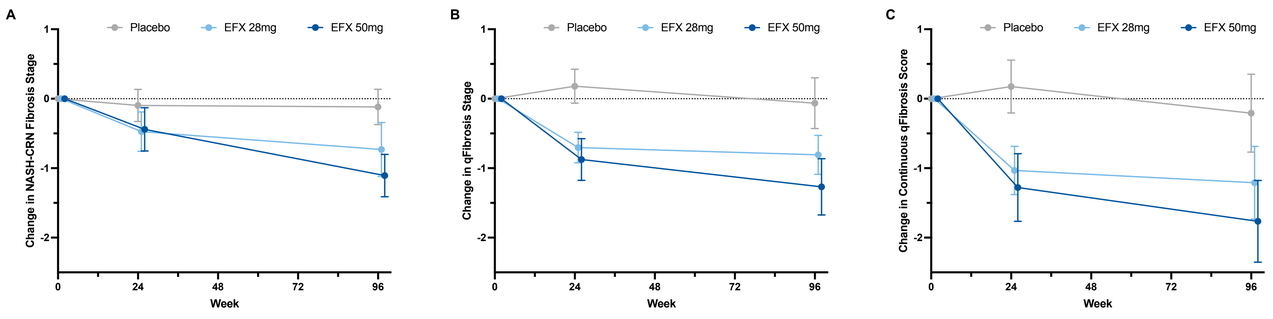

**Figure 5. EFX treatment was associated with greater proportions of participants experiencing clinically-meaningful responses**. ELF response is defined as ≥0.5 reduction in ELF score from baseline. Liver stiffness response is defined as ≥30% reduction in FibroScan VCTE from baseline. Fibrosis response is defined as ≥1-stage reversal of fibrosis without MASH worsening (conventional histopathology). Response proportions are shown out of all participants with ELF Score, liver stiffness, and liver biopsy at baseline and each timepoint.




| Proportion with response at Week 24 | Placebo (N=41) | EFX 28mg (N=37) | EFX 50mg (N=34) |
|---|---|---|---|
| ELF Score | 12% | 51% | 71% |
| Liver Stiffness (FibroScan) | 10% | 41% | 44% |
| Fibrosis (pathologist consensus) | 20% | 41% | 41% |
| ELF + Liver Stiffness | 0% | 30% | 26% |
| ELF + Liver Stiffness + Fibrosis | 0% | 11% | 9% |

| Proportion with response at Week 96 | Placebo (N=32) | EFX 28mg (N=26) | EFX 50mg (N=24) |
|---|---|---|---|
| ELF Score | 25% | 58% | 71% |
| Liver Stiffness (FibroScan) | 19% | 50% | 71% |
| Fibrosis (pathologist consensus) | 22% | 46% | 75% |
| ELF + Liver Stiffness | 6% | 38% | 54% |
| ELF + Liver Stiffness + Fibrosis | 0% | 19% | 42% |

**Figure 6. Change in liver fibrosis over 96 weeks scored by (A) MASH-CRN pathologist consensus reads, (B) qFibrosis stage (steatosis-corrected), or (C) qFibrosis continuous score (steatosis-corrected).** Data on graphs are presented as mean ± 95% CI. Tables below each panel present the least-squares (LS) mean change from baseline at weeks 24 and 96. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs placebo (MMRM).

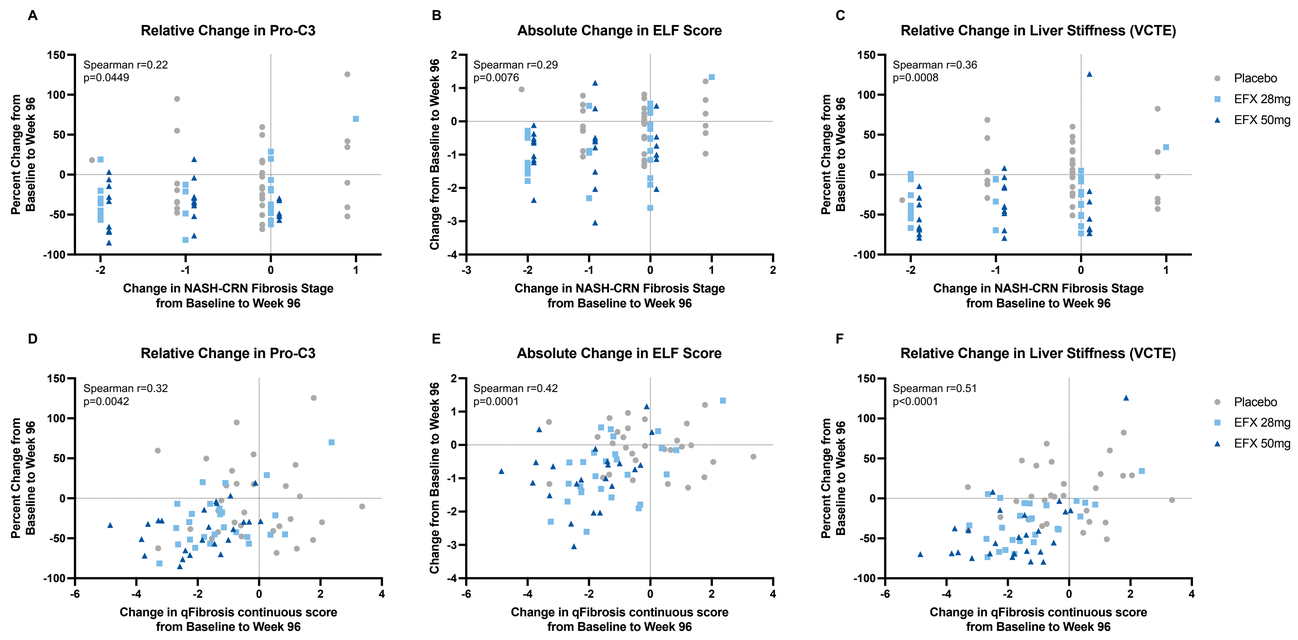



| LS Mean CFB, MASH-CRN Fibrosis Stage | Week 24 | Week 96 |
|---|---|---|
| Placebo | -0.10 | -0.12 |
| EFX 28mg | -0.47* | -0.73** |
| EFX 50mg | -0.44 | -1.11**** |

| LS Mean CFB, qFibrosis Stage | Week 24 | Week 96 |
|---|---|---|
| Placebo | +0.18 | -0.06 |
| EFX 28mg | -0.70**** | -0.81*** |
| EFX 50mg | -0.88**** | -1.27**** |

| LS Mean CFB, qFibrosis Continuous | Week 24 | Week 96 |
|---|---|---|
| Placebo | +0.17 | -0.21 |
| EFX 28mg | -1.03**** | -1.21** |
| EFX 50mg | -1.28**** | -1.77**** |

**Figure 7. Association between changes in noninvasive measures of liver fibrosis and fibrogenesis and biopsy-based changes in liver fibrosis**. Biopsy based changes in liver fibrosis were scored by (A-C) pathologist consensus reads, or (D-F) AI-based qFibrosis continuous score (steatosis-corrected). Data points represent individual participants with data for both plotted variables at both baseline and Week 96. Nonparametric Spearman correlation coefficients and two-tailed p values are calculated per-panel for all participants pooled across dose groups.




## CONCLUSIONS

EFX led to significant fibrosis reversal at 24 weeks, and this response was sustained, expanded (more participants with fibrosis reversal), and deepened (larger magnitude of fibrosis reversal) after 96 weeks of treatment

Non-invasive markers of liver fibrosis were significant reduced by week 24, and reductions were sustained and/or deepened through Week 96

For EFX-treated participants, longer treatment duration led to increasing concordance of response as measured by histopathology, imaging, and blood-based biomarkers, in contrast to minimal presence or expansion of concordant responses for placebo

Pathologist consensus and qFibrosis scoring of biopsy-based changes in liver fibrosis demonstrated progressive reversal of fibrosis with EFX treatment over 96 weeks, with a larger magnitude of reduction for EFX 50mg

Continuous measures of liver fibrosis such as qFibrosis may provide more precision than MASH-CRN pathologist consensus reads in evaluating the association between changes in biomarkers of liver fibrosis and fibrogenesis and changes in liver histopathology

Combinations of non-invasive markers of liver fibrosis appear to provide insight into the kinetics and magnitude of the antifibrotic activity of EFX, and concordant responses may offer effective means of monitoring treatment response without biopsy in clinical use

## REFERENCES

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## ACKNOWLEDGMENTS

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