Efruxifermin in MASH with F2/F3 fibrosis: post hoc analysis indicated early histologic features of regression were associated with week 96 fibrosis improvement

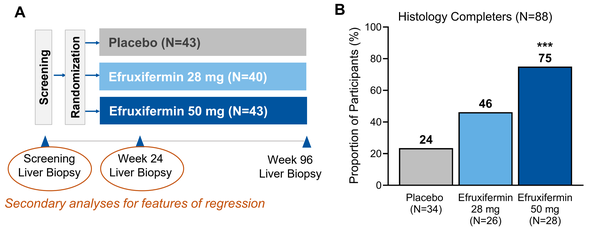
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Background

- Efruxifermin is a bivalent FGF-21 analog in development for treatment of MASH.
- In the phase 2b HARMONY trial (NCT04767529) (Figure 1A), efruxifermin improved histology-defined fibrosis at Week 96 in participants with MASH and F2/F3 fibrosis (Figure 1B) and also improved noninvasive fibrosis measures, markers of liver injury, lipid profile, and insulin sensitivity.[1,2]
- Efruxifermin was generally well tolerated.[1,2] Mild to moderate gastrointestinal adverse events were more common with efruxifermin than placebo.

Figure 1. (A) Study design and (B) Fibrosis improvement at week 96



***p<0.001 vs placebo. Histology Completers included all participants with baseline and W96 liver biopsies. Fibrosis improvement was defined as participants with ≥1-stage fibrosis improvement and no worsening of MASH.

Aims

- **Characterize early improvement in features of fibrosis regression at week 24 in week 96 histology responders.**
- **Assess week 96 histology and noninvasive measures of fibrosis in participants with early improvement in more features compared to those with early improvement in less features.**

Methods

- The analysis set included participants with liver biopsies at baseline and week 24.
- Two pathologists independently analyzed liver biopsy images and scored each biopsy for 6 predetermined features of regression at baseline and week 24. Biopsies were not paired, and pathologists were blinded to subject treatment and visit sequence.
- Improvement in a feature was defined by an increase in the Combined Score from baseline to week 24. The number of features with improvement at week 24 was determined for each participant. Increased presence of a feature, or increased number of features, is suggestive of histological improvement.

For each biopsy image:
Independent scoring of 6 features by two pathologists

Absence of feature = **Y**, Prescence of feature = **N**

↓

Derive Combined Score for each feature

- Both pathologists scored **N** → **Combined Score = 0** (Feature is absent)
- One pathologist scored **N**, one pathologist scored Y → **Combined Score = 1** (Feature may be present)
- Both pathologists scored Y → **Combined Score = 2** (Feature is present)

↓

For each participant, calculate change in Combined Score from baseline to week 24 for each of the 6 features to determine which features improved

↓

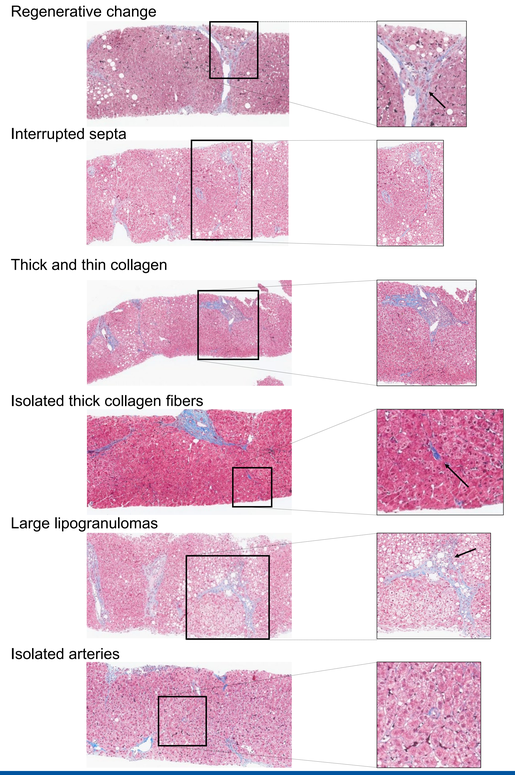
Sum the number of features with improvement from baseline to week 24
Range: 0-6

Features of Regression

Table 1. Definitions of features of regression

Feature of Regression [3,4]	Definition
Regenerative change	Hepatocytes of normal appearance separating thin strands of collagen, often occurring as a row of hepatocytes between two strands of collagen
Interrupted septa	Linear strands of collagen with an obvious break in the strand, can be as small as the width of a single hepatocyte
Isolated thick collagen fibers	Thick but short, often square or rectangular, collagen fibers in the hepatic parenchyma, not associated with a vascular or portal structure
Thick and thin collagen	Broad bands of collagen with either an abrupt termination or abrupt transition into a much thinner collagen strand
Large lipogranulomas	Large collections of intraportal or pericentral macrophages containing >3 fat droplets
Isolated arteries	Small arteries located in the hepatic parenchyma and not associated with other vascular structures or portal areas

Figure 2. Example histology images of features

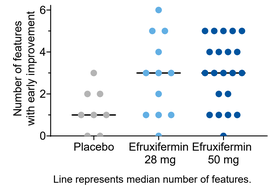


Results

Early Feature Improvement in Week 96 Histology Responders

Figure 3. Number of features with early improvement at week 24

Subgroup: Week 96 Histology Responders



Line represents median number of features.

- In the subgroup of week 96 histology responders, participants treated with efruxifermin showed numerically more early features of regression than placebo (Figure 3).

Table 2. Proportion of participants with early improvement in each feature

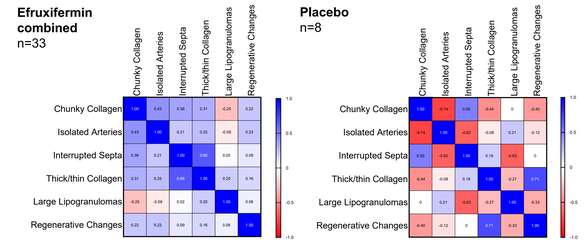
Subgroup: Week 96 Histology Responders

Feature of Regression	Placebo n=8	Efruxifermin 28 mg n=12	Efruxifermin 50 mg n=21
Regenerative Changes	2 (25%)	7 (58%)	14 (67%)
Interrupted Septa	4 (50%)	7 (58%)	13 (62%)
Chunky Collagen	1 (13%)	7 (58%)	11 (52%)
Thick/thin Collagen	1 (13%)	6 (50%)	9 (43%)
Large Lipogranulomas	2 (25%)	3 (25%)	9 (43%)
Isolated Arteries	2 (25%)	4 (33%)	8 (38%)

- In the subgroup of week 96 histology responders, changes in features related to collagen morphology were more commonly observed at week 24 (Table 2).

Figure 4. Association of change between features

Subgroup: Week 96 Histology Responders

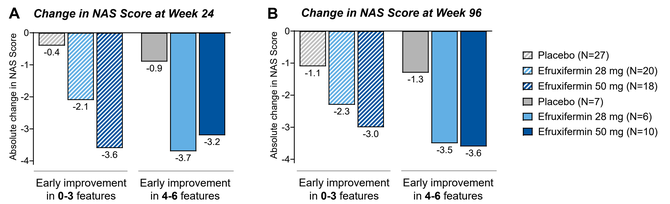


Strong positive correlations (**blue**) indicated that improvement in one feature was associated with improvement in another feature (both features improved at week 24). Strong negative correlations (**red**) indicated that improvement in one feature was not associated with improvement in another feature (one feature improved but the other did not).

- In the subgroup of week 96 efruxifermin histology responders, there was an association between improvement in interrupted septa and improvement in thick/thin collagen at week 24 (Figure 4). Improvement in large lipogranulomas was not associated with improvements in other evaluated features.

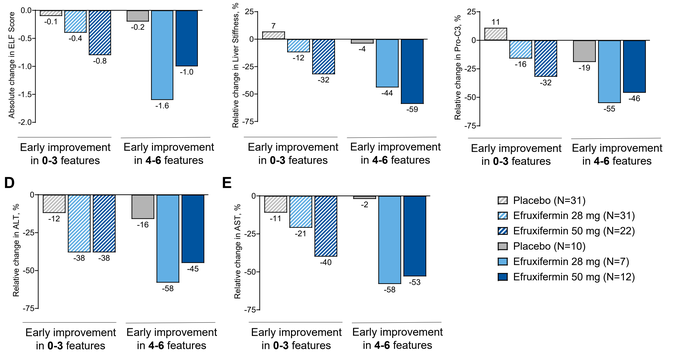
Association Between Number of Early Feature Improvement and Week 96 Response in All Participants

Figure 5. Change in NAS Score at (A) week 24 and (B) week 96 in participants with early improvement of less (0-3) versus more (4-6) features



Analysis set included those with available biopsies at baseline, week 24, and week 96.
Data are ad hoc analyses. Statistical tests were not performed.

Figure 6. Change in markers of fibrosis (A) ELF, (B) Liver Stiffness, (C) Pro-C3 and markers of liver injury (D) ALT (E) AST at week 96 in participants with early improvement of less (0-3) versus more (4-6) features



Analysis set included those with available biopsies at baseline and week 24, and available noninvasive test data at baseline and week 96.
Data are ad hoc analyses. Statistical tests were not performed.

- Greater improvements at week 96 were observed in efruxifermin-treated participants who showed early improvement in more features (Figures 5 and 6).

Summary and Conclusions

- In histology responders at week 96, more improved features were identified at week 24 in efruxifermin than placebo, and improvements in features of collagen morphology were most commonly observed. This suggests these features may capture subtle changes that are linked to greater improvements at later timepoints.
- An association between improvement in interrupted septa and improvement in thick/thin collagen at week 24 was observed, indicating that these features may improve together.
- In efruxifermin-treated participants with more early features of regression, larger improvements in NAS score, noninvasive fibrosis tests, and markers of liver injury were observed at week 96, compared to those with less early features.
- Phase 3 trials of efruxifermin are enrolling patients with MASH and F2/F3 fibrosis (SYNCHRONY Histology) or compensated cirrhosis (SYNCHRONY Outcomes).

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