AI-powered histology analysis of HARMONY reveals efruxifermin-driven changes in the liver microarchitecture in F2/F3 MASH

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BACKGROUND

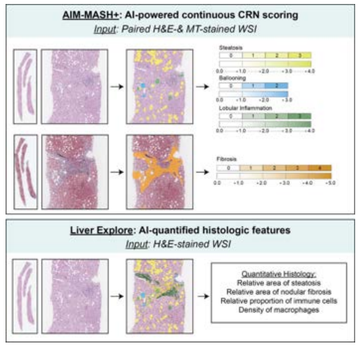
In Phase 2b trials for metabolic dysfunction-associated steatohepatitis (MASH), efruxifermin improved fibrosis without worsening MASH in participants with F2-F3 disease (HARMONY)[1] and reversed cirrhosis in participants with compensated F4 MASH (SYMMETRY).[2]

STUDY AIM

Here, to investigate changes in fibrosis and other cardinal MASH features resulting from efruxifermin treatment, we conducted a retrospective analysis of HARMONY (NCT04767529) using two AI-powered pathology algorithms (Fig. 1):

- **AIM-MASH+**,[3*] which provides NAS CRN scores as a continuous output from paired H&E- and Masson Trichrome-stained whole slide images (WSIs).
- **Liver Explore**,[4*] which provides granular and quantitative characterization of the liver microarchitecture (tissue regions, cell types, and fibrosis subtypes) from a H&E-stained WSI.

Figure 1. AI pathology models used for this study.



METHODS

HARMONY

- In HARMONY, participants (N=128) were randomized to placebo, 28 mg efruxifermin, or 50 mg efruxifermin, and biopsies were taken at baseline, week 24, and week 96.
- Analyses were performed in the liver biopsy analysis set, n=113 for baseline and week 24; n=88 for week 96.
- Biopsies were scanned to yield whole slide images (WSIs).

AIM-MASH+ continuous CRN scoring

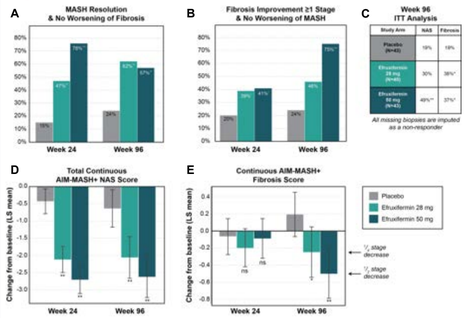
- Paired H&E- and Trichrome-stained WSIs were analyzed using AIM-MASH+ to generate continuous CRN scores.
- For each study arm, changes from baseline in AI-derived continuous CRN scores were compared to placebo using ANCOVA.

Liver Explore-powered liver microarchitecture analysis

- H&E-stained WSIs of biopsies from all study arms and timepoints were analyzed using Liver Explore to classify and quantify liver tissue regions, cells, and fibrosis subtypes.
- For each study arm, changes in Liver Explore metrics from baseline to weeks 24 and 96 were calculated and compared to placebo using ANCOVA.

RESULTS

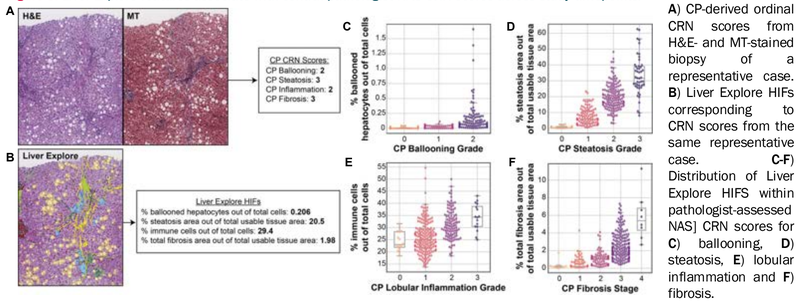
Figure 2. AIM-MASH+ continuous scores confirm MASH resolution and fibrosis reversal with longer efruxifermin treatment.



(*Top*) Central pathologist (CP)-assessed results from the HARMONY biopsy analyses set (all participants with baseline and specified timepoint) for **A**) MASH resolution and no worsening of fibrosis,[1] **B**) fibrosis improvement ≥ 1 stage with no worsening of MASH,[1] and **C**) Intent to treat (ITT) analyses from week 96.[1] Significance was assessed via Cochran-Mantel-Haenszel test: * p<0.05, ** p<0.001, ns: not significant.

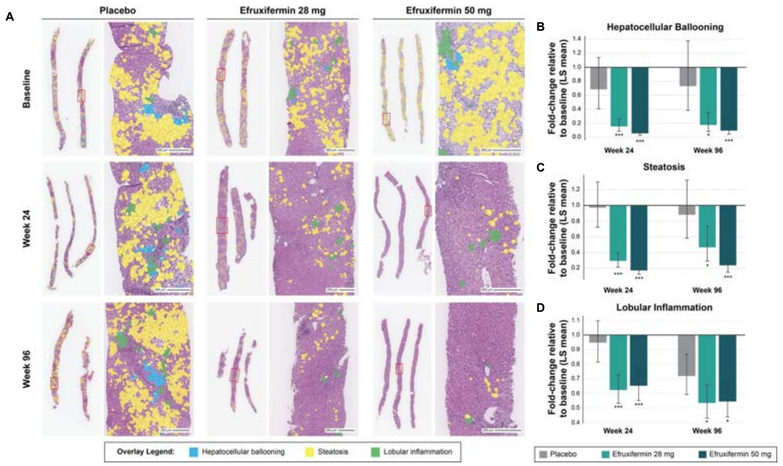
(*Bottom*) AIM-MASH+ analysis of continuous NAS scores from HARMONY biopsy analysis set. LS mean change from baseline in **D**) AI-derived continuous NAS score (steatosis, hepatocellular ballooning, lobular inflammation) and **E**) AI-derived continuous fibrosis stage. Significance was assessed using ANCOVA. Error bars represent 95% confidence intervals. * p<0.05, ** p<0.001, ns: not significant.

Figure 3. Liver Explore features associate with central pathologist NAS CRN scores across study timepoints.



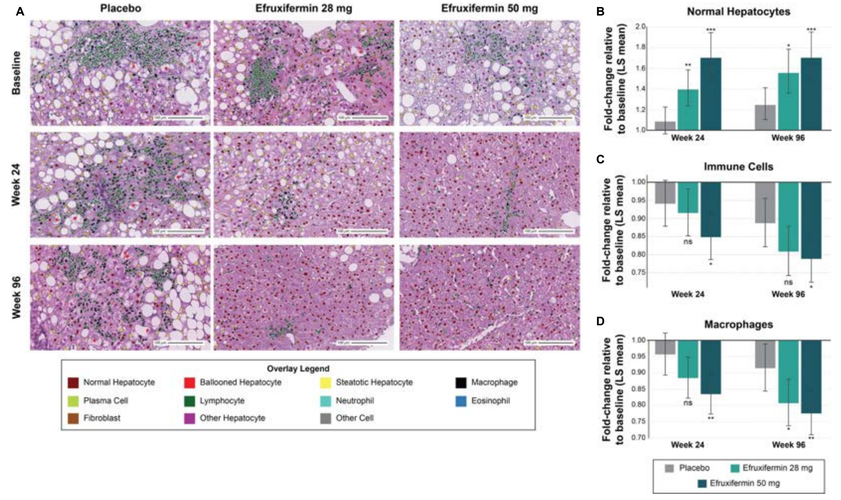
A) CP-derived ordinal CRN scores from H&E- and MT-stained biopsy of a representative case. **B**) Liver Explore HIFs corresponding to CRN scores from the same representative case. **C-F**) Distribution of Liver Explore HIFS within pathologist-assessed NAS] CRN scores for **C**) ballooning, **D**) steatosis, **E**) lobular inflammation and **F**) fibrosis.

Figure 4. Improvements in Liver Explore-quantified MASH features with efruxifermin.



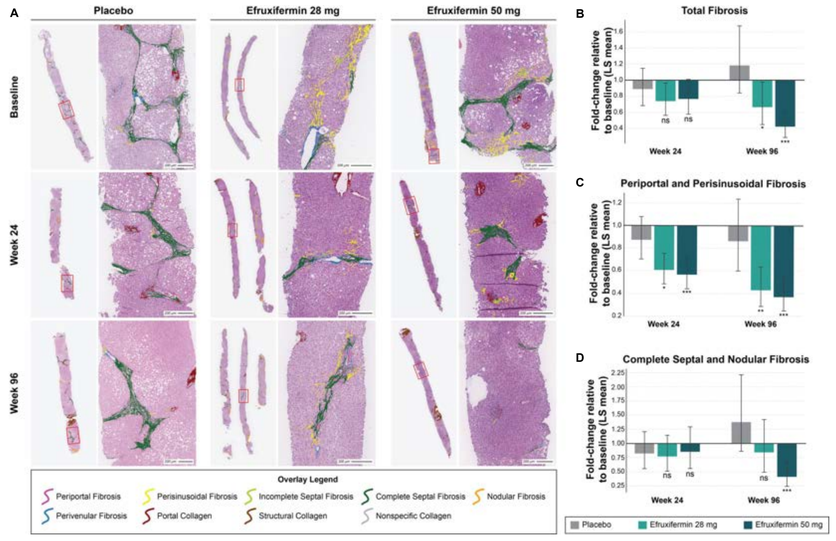
A) Liver Explore tissue overlays from representative biopsies across study arms and timepoints. **B-D**) Fold change from baseline of AI-quantified tissue features representative of MASH in placebo, efruxifermin 28 mg, and efruxifermin 50 mg specimens at weeks 24 and 96. Fraction of total tissue classified as **B**) hepatocellular ballooning, **C**) steatosis, and **D**) lobular inflammation. Error bars represent 95% confidence intervals. * p<0.05, ** p<0.001, *** p<0.0001, ns: not significant.

Figure 5. Increase in Liver Explore-quantified normal hepatocytes and reduction in immune cells with efruxifermin.



A) Liver Explore cell overlays from representative biopsies across study arms and timepoints. **B-D**) Fold change from baseline of AI-quantified cell features in placebo, efruxifermin 28 mg, and efruxifermin 50 mg specimens at weeks 24 and 96. Fold change from baseline in fraction of total cells classified as **B**) normal hepatocytes, **C**) immune cells, and **D**) macrophages. Error bars represent 95% confidence intervals. * p<0.05, ** p<0.001, *** p<0.0001, ns: not significant.

Figure 6. Improvements in Liver Explore-quantified fibrosis features with efruxifermin.



A) Liver Explore fibrosis overlays from representative biopsies across study arms and timepoints. **B-D**) Fold change from baseline of AI-quantified fibrosis features in placebo, efruxifermin 28 mg, and efruxifermin 50 mg specimens at weeks 24 and 96. Fraction of total tissue classified as **B**) total fibrosis, **C**) periportal and perisinusoidal (early-stage) fibrosis, and **D**) complete septal and nodular (advanced) fibrosis. Error bars represent 95% confidence intervals. * p<0.05, ** p<0.001, *** p<0.0001, ns: not significant.

CONCLUSIONS

- AI-powered continuous scoring (**AIM-MASH+**) aligns with conventional pathology.
- AI-powered digital histology (**Liver Explore**) expands the conventional findings with efruxifermin:
  - Hepatocellular ballooning, inflammation, and steatosis decrease starting at week 24.
  - An improvement in the proportion of normal hepatocytes and a reduction in the proportion of immune cells with efruxifermin 50 mg suggests overall improvements in liver health.
  - Early-stage fibrosis (perisinusoidal and periportal) decreased at the week 24 timepoint.
  - Significant reduction in advanced fibrosis (nodular and complete septal) occurred at 96 weeks in the efruxifermin 50 mg treated arm.
- The analysis underlines the utility of AI-powered pathology to assess disease stage and treatment effects.
- The potential efficacy of efruxifermin for decreasing patterns of advanced fibrosis is demonstrated.
- Efruxifermin is being evaluated in phase 3 clinical trials for treatment of MASH.

CONTACT

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* Liver Explore and AIM-MASH+ are For Research Use Only. Not for use in diagnostic procedures.

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DISCLOSURES

A full list of author disclosures can be found here:

The AASLD Liver Meeting, November 7-11, 2025, Washington, D.C.