AASLD The Liver Meeting®

AI AND DIGITAL-BASED PATHOLOGY CORROBORATE REDUCTION IN FIBROSIS OBSERVED BY CONVENTIONAL PATHOLOGY WITH EFRUXIFERMIN TREATMENT OF PATIENTS WITH F2-F3 MASH IN THE HARMONY STUDY

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INTRODUCTION

- Efruxifermin (EFX), a bivalent Fc-FGF21 fusion protein has demonstrated significant improvement in fibrosis by conventional pathology in the HARMONY trial (NCT04767529).
- This was associated with significantly reduced hepatic fat content and significant improvement in secondary endpoints including resolution of MASH and the composite of fibrosis improvement and MASH resolution.

AIM

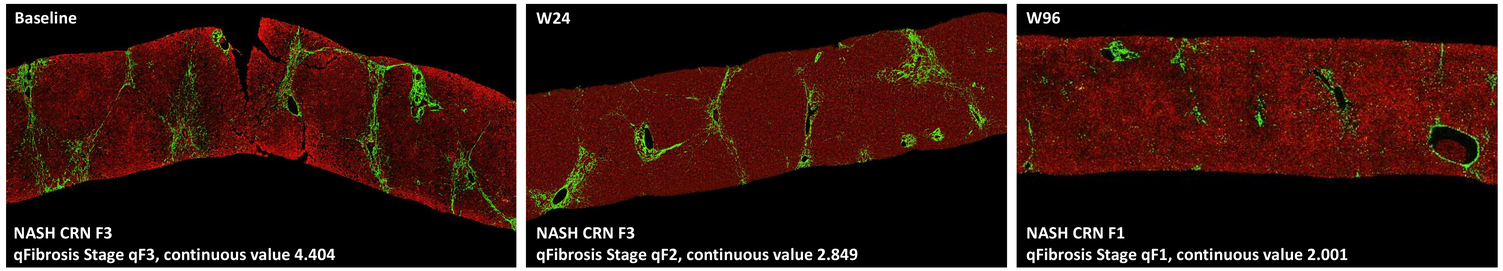
This post-hoc analysis investigates the fibrosis changes across liver zones, utilizing Second Harmonic Generation/Two-Photon Excitation Fluorescence (SHG/TPEF) microscopy and HistoIndex's proprietary qFibrosis® scoring, and concurrence with conventional pathologist consensus scoring.

METHOD

- 82 subjects with unstained biopsies available at baseline (BL), week 24 (W24) and week 96 (W96) were analysed by SHG/TPEF imaging coupled with qFibrosis®.
- The analysis of fibrosis using qFibrosis® incorporated a steatosis-area correction. Briefly, the steatosis area (by SHG/TPEF) was subtracted from the total liver tissue area on each of the baseline and post-treatment (W24, W96) images to circumvent the confounding effect of large reductions in steatosis associated with EFX treatment
- A detailed zonal analysis across the following defined hepatic zones: portal tract, peri-portal (zone 1), peri-sinusoidal (zone 2), peri-central (zone 3) and central vein, was also performed to evaluate changes in fibrosis between baseline, W24 and W96 for placebo, 28mg and 50mg groups. Collagen area was normalized across all dose groups, timepoints, and fibrosis stages to allow for cross-group comparisons.

RESULTS

Figure 1: *Case example of a subject (50mg EFX) demonstrates the increased sensitivity of SHG/TPEF and AI ability to detect changes in fibrosis and to quantify changes in fibrosis within a NASH CRN stage. Steatosis-corrected qFibrosis® is reported.*



- NASH CRN staging demonstrated bridging fibrosis by conventional pathology in both baseline and W24 biopsies. (NASH CRN stage F3 → NASH CRN stage F3).
- At W24, qFibrosis® demonstrates a decrease in the total amount of collagen. (qFibrosis® stage qF3 → qFibrosis® stage qF2).
- At W96, **both** conventional pathology and qFibrosis® indicate a response. (NASH CRN stage F3 → NASH CRN stage F1, and qFibrosis® stage qF3 → qFibrosis® stage qF1)

Figure 2: *Steatosis-corrected qFibrosis® improvement is presented for all available subjects after 24- and 96-weeks treatment. **(A)** ≥1-stage improvement according to NASH CRN staging, **(B)** ≥1-stage improvement according to qFibrosis® ; and after stratification into proportion of qFibrosis® responders in subjects with **(C)** NASH CRN F2 at baseline or **(D)** NASH CRN F3 at baseline. Statistical Analysis using Cochran–Mantel–Haenszel test (CMH) stratified by T2DM status and baseline fibrosis stage; p-value denotes the significance between the respective EFX arms (28mg, 50mg) versus placebo arm.*

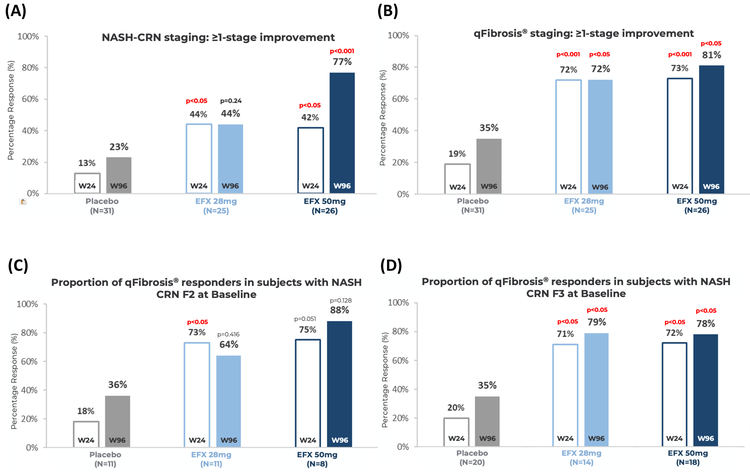
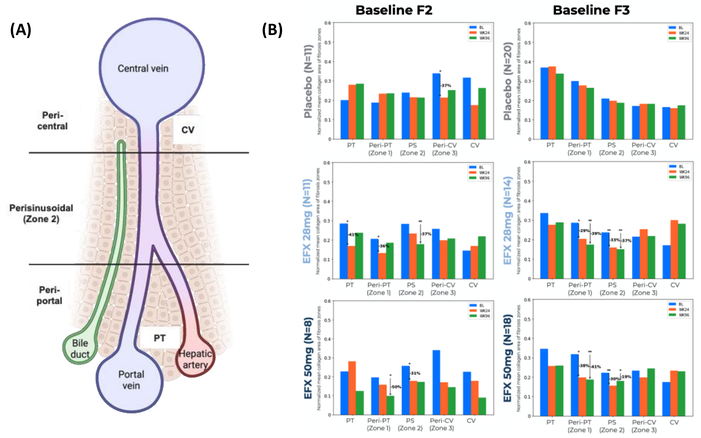


Figure 3: *(A) Schematic representation of the hepatic zones. **(B)** Zonal analysis stratified according to baseline fibrosis NASH CRN F2 or F3 across 5 pre-defined hepatic zones: portal tract (PT), peri-PT, perisinusoidal (PS), peri-central, and central vein (CV). Arrows with asterisk denotes a significant decrease (relative change) of collagen area in these zones at W24 or W96 from baseline. Paired t-test is used to determine significance between the Week 24 or Week 96 versus baseline.*



- **Figure 3B:** Among subjects with F2 or F3 fibrosis at BL, **significant reductions in fibrotic area were noted primarily in the peri-portal (zone 1) and peri-sinusoidal (zone 2) regions**. This was most evident in F3 subjects who had significantly less fibrosis in zones 1 and 2 after 24- and 96-weeks treatment with either 28mg or 50mg EFX, compared to placebo.

CONCLUSIONS

- In this post-hoc analysis, while placebo-treated subjects exhibited similar response across conventional and digital pathology assessments, a trend of higher fibrosis response was observed after 24- and 96-weeks of EFX treatment using digital pathology assessment. This trend was consistent across subjects with both F2 and F3 baseline fibrosis stage.
- The quantitative regression of fibrosis in zones 1 and 2 was evident in subjects regardless of fibrosis improvements observed by conventional pathologist staging, highlighting the sensitivity of AI-enhanced imaging in detecting significantly less fibrosis in two distinct liver zones and identifying reductions in collagen area even when F-stage remains unchanged by conventional pathology.
- Using AI digital pathology, the data corroborates conventional pathology results from the phase 2b HARMONY data, in which a significant proportion of EFX-treated subjects met the primary endpoint of ≥1 stage improvement in fibrosis with no worsening of MASH.

REFERENCES

1. Harrison SA, *et al.* Lancet Gastroenterol Hepatol. 2023 Dec;8(12):1080-1093.

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