qFibrosis enables earlier detection of fibrosis response in Efruxifermin-treated patients with F2-F3 MASH in 96-week HARMONY study

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Introduction

Efruxifermin (EFX) has been observed to improve fibrosis without worsening MASH, by conventional histopathology, with a doubling of response rates between week 24 and week 96 for the 50mg EFX group, with a slight increase observed for the 28mg EFX group in the Liver Biopsy Analysis Set (LBAS). The placebo-adjusted effect sizes for fibrosis improvement without worsening of MASH grew from 21% to 52% between week 24 and week 96 for the 50mg group and from 20% to 22% for the 28mg group.

Aim

This post-hoc analysis investigates changes in fibrosis using AI-based qFibrosis® that can detect subtle intra-stage changes by using collagen morphometry for precise quantification on a continuous scale.

Method

Subjects with unstained biopsies at baseline (BL), week 24 (W24), and week 96 (W96) (n=82) were available for qFibrosis® analysis using Second Harmonic Generation/Two-Photon Excitation Fluorescence (SHG/TPEF) imaging. The qFibrosis® score incorporated a correction to account for a significant reduction in hepatic fat observed with EFX treatment, as well as offering a detailed assessment of fibrosis dynamics across the following defined hepatic zones: portal, peri-portal (zone 1), peri-sinusoidal (zone 2), central, and peri-central (zone 3).

Results

In this analysis, for the 28mg EFX group, conventional histopathology identified most responders at W24 (n=9), with 2 new responders identified at W96. In contrast, qFibrosis® captures more responders at W24, with 70-75% of subjects showing a statistically significant improvement of ≥1 fibrosis stage. qFibrosis® also captures most responders at W24 (n=18) for the 50mg group, a response rate which ultimately converges with that for ≥1-stage fibrosis improvement by conventional histopathology at W96 (70-80%) (Figure 1). These analyses demonstrate the capability of qFibrosis® to capture the W24 regression of fibrosis associated with EFX treatment earlier than conventional histopathology.

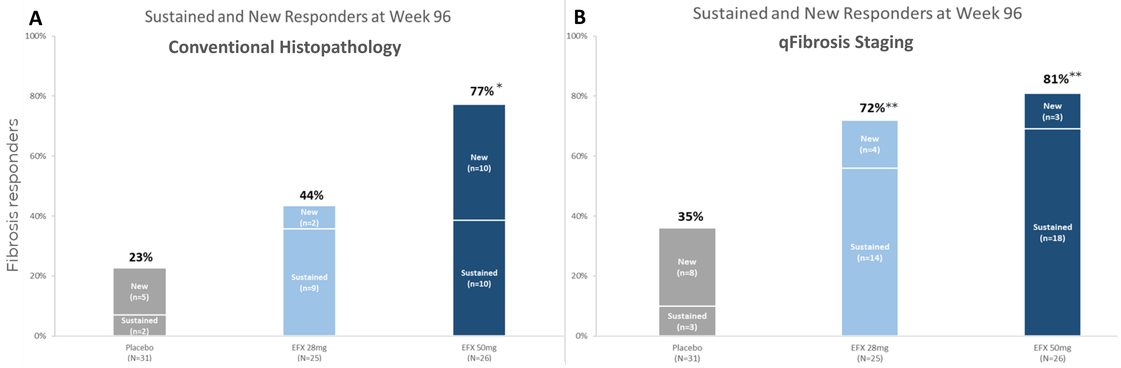

***Figure 1**: Proportion of subjects with EITHER ≥1 stage fibrosis improvement from baseline to W24 with **sustained** fibrosis response at W96, OR with ≥1 stage fibrosis improvement from baseline to W96 who had not improved by W24 (**new** fibrosis responders), based on (A) conventional histopathology and (B) qFibrosis® staging.*

The earlier capture of W24 responders by qFibrosis® is evident in the statistically significant regression of fibrosis in Zones 1 and 2 in EFX arms compared to placebo, which was sustained in EFX arms at W96 (Figure 2). The quantitative regression in Zones 1 and 2 was observed in subjects whether or not improvements in fibrosis had been seen by conventional histopathology staging, highlighting the consistency and sensitivity of qFibrosis® in capturing subtle but significant fibrosis reductions for EFX-treated subjects.

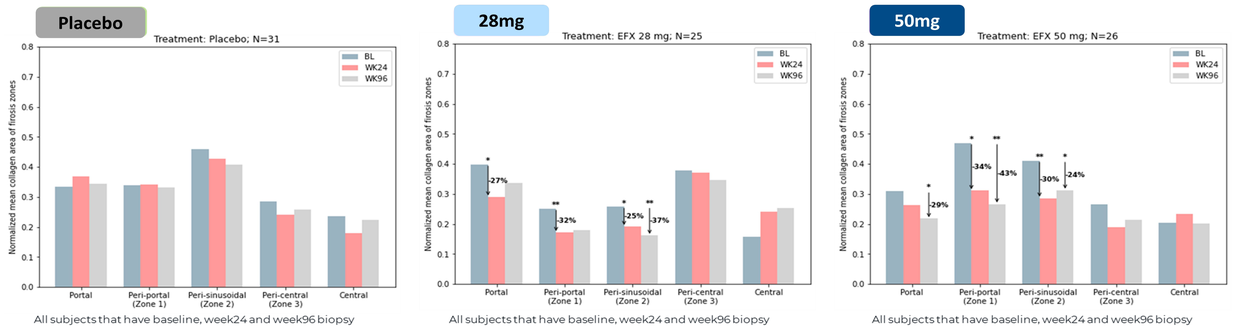

***Figure 2**: Analysis across 5 pre-defined hepatic zones: portal tract (PT), peri-PT, perisinusoidal (PS), peri-central, and central vein (CV). Arrows with asterisk denotes a significant decrease (relative change) of collagen area in these zones at W24 or W96 from baseline. Paired t-test is used to determine significance between the Week 24 or Week 96 versus baseline.*

At BL, both conventional histopathology and qFibrosis® demonstrated bridging fibrosis (NASH CRN stage F3; qFibrosis® stage qF3). At W24, qFibrosis® demonstrates a decrease in the total amount of collagen in Zones 1 and 2 (qFibrosis® stage qF3 to qFibrosis® stage qF2), unlike conventional histopathology which demonstrated no change from BL. At W96, both conventional histopathology and qFibrosis® indicate a response. (NASH CRN stage F3 to NASH CRN stage F1, and qFibrosis® stage qF3 to qFibrosis® stage qF1) (Figure 3).

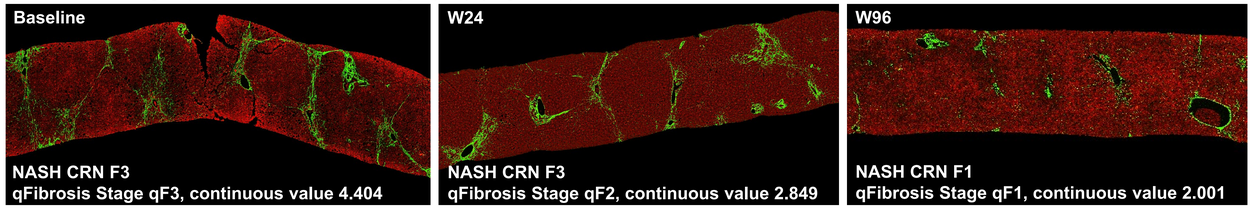

***Figure 3**: Case example of a subject (50mg EFX) demonstrates the increased sensitivity of SHG/TPEF combined with AI digital pathology to detect changes in fibrosis and to quantify changes in fibrosis based on a continuous scale spanning NASH CRN incremental staging.*

Conclusions

Analysis by qFibrosis® of W24 biopsies from subjects treated with 50mg EFX captures a higher proportion of responders than identified by conventional histopathology. These early responders became fibrosis responders at W96 by conventional histopathology.

This finding supports the potential utility of qFibrosis® zonal analysis based on digital pathology, to enable drug development by identifying improvements in patterns of zonal fibrosis earlier during interventional trials in subjects with F2 and F3 MASH.

Acknowledgements

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