Use of multi-parametric measures to differentiate and better assess fibrosis patterns between baseline and end-of-treatment (EOT) patients in NASH clinical trials: results from the Falcon-1 and 2 clinical trials

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INTRODUCTION

- Recent NASH clinical trials target specific pathological pathways in development of fibrosis, steatosis and inflammation.
- Quantitative fibrosis assessment as single measure by biomarkers like ProC3 or histology-based measures like collagen proportionate area (CPA) show limited association with biopsy-determined fibrosis dynamics between Baseline (BL) and End-Of-Treatment (EOT).
- We describe the possibility of overcoming these limitations using multi-parametric measurements such as qFibrosis (AI based SHG/TPE microscopy, evaluates more than 180 fibrosis parameters) assessments.
- **Multi-parametric measurements** refer to assessments that incorporate multiple distinct parameters or factors to provide a more comprehensive and accurate understanding of a complex phenomenon or condition, whereas **Single parameter measures** analyse a solitary individual factor or characteristic to assess a specific aspect or feature of the same phenomenon or condition.
- **qFibrosis (qF):** A composite measure of fibrosis using SHG/TPE microscopy integrating more than 180 collagen morphological parameters through AI, enabling a holistic evaluation of fibrosis patterns (Figure 2).

MATERIALS AND METHODS

- Biopsies taken from FALCON-1, a phase 2 trial in NASH (NCT03486899) and FALCON-2, a phase 2 trial in NASH-cirrhosis (NCT03486912).
- SHG/TPE (Single Harmonic Generation/Two-Photon Excitation) microscopy and AI (Artificial-Intelligence) analysis were employed to quantify fibrosis parameters on 301 biopsy slide pairs (n=602).
- Biopsy data from FALCON-1 was obtained at 24-weeks, while data from FALCON-2 was at 48-weeks.
- Biomarkers of these patients, such as serum AST and ALT, ProC3, PC3X, ELF, Somascan were correlated with SHG/TPE microscopy parameters like qFibrosis continuous values, qFibrosis stages, and %SHG-CPA (% area of SHG) using Spearman correlation (r-value).
- Outcomes were compared with pathologist-based NASH-CRN staging, the currently accepted standard for NASH clinical trial primary endpoints.

RESULTS

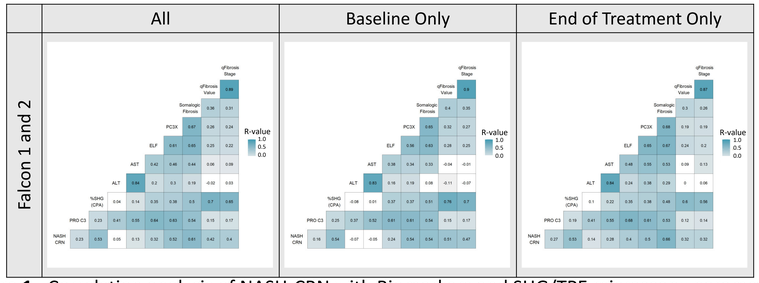

Figure 1. Correlation analysis of NASH-CRN with Biomarkers and SHG/TPE microscopy parameters. The statistically significant (p≤0.001) correlations are marked in blue-grey cells, white cells indicate statistically insignificant correlations.

- Correlation analysis against NASH-CRN staging scores are depicted in Figure 1.
- Strongest correlation with NASH-CRN found in Somalogic (r=0.61), followed by PC3X (r=0.52) among biomarkers.
- NASH-CRN staging exhibited highest correlations with %SHG-CPA (r=0.53) and qF (r=0.42).
- Comparing baseline and EOT NASH-CRN data, minimal differences in r-values seen in single-parameter measures like PC3X (r=0.54 to r=0.5) and %SHG-CPA (r=0.54 to r=0.53).
- More pronounced differences between BL and EOT NASH-CRN data observed in multi-parameter measures like Somalogic (r=0.54 to r=0.66) and qF (r=0.51 to r=0.32).
- Correlations (r-value) between qF and NASH-CRN decreases to 0.32 in EOT data, suggesting a reduced alignment with NASH-CRN staging. This indicates that central reader assessment of changes in fibrosis at EOT might be different from qF based assessments.
- Multi-parameter measures show marked variations in correlations (r-values) between baseline and EOT data (Table 1).

Table 1. Correlations (r-values) of Multi-parameter vs Single parameter measures

		NASH-CRN (BL)	NASH-CRN (EOT)
PC3X	Single parameter measures	0.54	0.50
%SHG-CPA		0.54	0.53
Somalogic	Multi-parametric measures	0.54	0.66
qFibrosis values		0.51	0.32

CONCLUSIONS

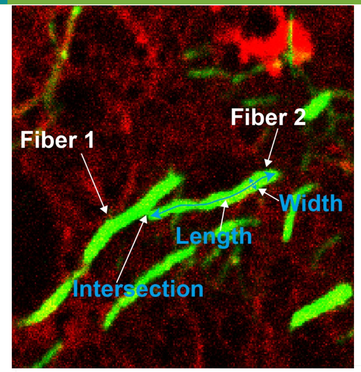

Figure 2: Collagen morphological features such as fiber length, width, intersection, etc. that are evaluated in calculating qF score

- As promising NASH drugs approach approval, identifying optimal measures of fibrosis dynamics is crucial for assessing post-treatment fibrosis changes effectively.
- Drug impacts on SHG/TPE parameters reveal distinctive fibrosis regression and progression patterns, warranting revaluation of correlations with blood biomarkers.
- This study shows importance of devising fibrosis measures that encompass changes between BL and EOT patients, incorporating multi-parametric aspects to better capture dynamic trends and enhance comprehensive assessment of dynamic fibrosis progression and regression in post-drug approval era.
- Future analysis could explore correlations between SHG/TPE imaging and multi-parametric biomarkers, enhancing our understanding of fibrosis regressions.

CONTACT INFORMATION

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