Multimodality assessment of hepatic fibrosis: Ranked paired reading and artificial intelligence fibrosis improvement with Aramchol missed by conventional staging

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Background and Aims
Aramchol is a partial inhibitor of hepatic stearoyl-CoA desaturase (SCD1) with direct anti-fibrotic activity demonstrated in preclinical models1. A phase 2b, placebo-controlled study (NCT02279524), in patients with biopsy confirmed NASH demonstrated the potential of 52 weeks treatment with Aramchol 600mg once daily (QD) to improved liver histology and reduced liver fat, liver enzymes and HBa1c2. The ARMOR study is a Phase 3, multinational, randomized, double-blind, placebo-controlled trial assessing Aramchol 300mg twice daily (BID) in subjects with NASH (NCT04104321). An Open-Label Part was added to the study, designed to provide data on the new dosing regimen with the higher exposure as well as characterize the kinetics of histological outcomes (see Figure 1). Acknowledging the complexity, variability and moderate reproducibility in liver pathology reading, the Open Label part was also used to further assess different methodological approaches that may support and improve fibrosis scoring.

Methods
157 patients with NASH and fibrosis documented by biopsy were randomized 1:1:1 to receive Aramchol 300 mg BID and underwent a control biopsy at weeks 24, 48 or 72. Data is available from the first 51 patients with a post-baseline biopsy. All slides were assessed for fibrosis using 3 histopathological methodologies:

• The NASCH NRN staging: staging was initially performed individually by the 3 independent pathologists, followed by a consensus reading by the committee
• A ranked assessment: The same central committee performed a ranked assessment (improvement/worsened/stable) of paired biopsies, scrambled and blinded to sequence
• Artificial Intelligence: The same slides were scanned and read using FibroNest™, a quantitative Digital Pathology image analysis and AI automated, full tissue method providing a continuous phenotypic Fibrosis Composite Severity (FCS) score that ranges from 1 to 10 for the full spectrum of fibrosis severity observed in the liver. This allows identifying fibrosis improvement that may be missed by staging methods as well as statistical quantification of change from baseline. A 0.3 reduction in FCS (4-fold higher than the analytical variability) identified any reduction in fibrosis, a 25% relative decline in FCS, a strong reduction in fibrosis.

Results
Post-baseline biopsies were performed in 51 patients (28 and 23 pts at <48 weeks and ≥48 weeks, respectively) that received Aramchol. At baseline, mean age was 59.7; 80% were females; 86% White; mean weight 88.8, mean BMI 33.2 kg/m2; 32 patients had stage 3 fibrosis; 11 stage 2, and 8 stage 1; Mean FCS was 5.0 (see Table 1). A greater fibrosis improvement with longer duration of therapy for both conventional histology and digital pathology readings was demonstrated (see Table 2). For all methods, a treatment effect was larger at ≥48 weeks compared to <48 weeks. At week 48 or more, fibrosis improvement was identified in 39%, 61% and 100% of patients according to NASCH NRN, paired and AI, respectively using a FCS absolute reduction of 0.3 (see Table 2 and Figure 2). Mean FCS reduction was −0.585 (p<0.01) at ≥14 weeks and −1.7288 (p=0.0001) at ≥24 weeks. AI evaluation was consistent with paired reading in 22/38 (57.9%) of the pts with fibrosis improvement. When analyzed by AI, 18/23 pts with unchanged NASCH NRN stages had any fibrosis response, including 9 with a strong response. Similarly, 14/18 pts with stable ranking had a fibrosis response, including 6 with a strong reduction. No pts with worse CRN stages or worsening ranking had a strong AI fibrosis reduction.

Conclusion
Aramchol resulted in a high proportion of fibrosis improvement using three separate biopsy reading methodologies, with a larger treatment effect with longer duration of therapy. Both ranked assessments and AI evaluations identified more subjects with fibrosis improvement, indicating greater sensitivity to change vs categorical scoring. Digital pathology quantification by AI reveals a high level of fibrosis improvement that would have been missed by conventional histological methodologies. AI technologies are promising for the detection of fibrosis changes in future clinical trials.