Novel Digital Pathology quantitative image analysis and AI method detects the treatment effect of NASH drug candidates with a performance that benchmarks Imaging based measurements.

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**1 Introduction**

Manual histological evaluation of liver biopsy is the gold standard for fibrosis and steatosis staging in Non-Alcoholic Steatohepatitis (NASH), but it is limited by its inter and intra-reader variability. Quantitative Digital Pathology image analysis and AI (FibroNest™) as well as quantitative MRI signal analysis methods have the potential to overcome the limitation of these standards.

**2 Aim**

This exploratory post-hoc analysis compared FibroNest digital pathology scoring methods (Fibrosis and Steatosis) with NASH-CRN categorical stages and imaging-based scores (MRI Mean Liver Stiffness and MRI Mean Proton Density Fat Fraction (MRI-PDFF)) in patients with NASH from the Phase 2a FALCON study (NCT348699).

**3 Method**

- N=197 adults were 18-75 years of age with NASH and stage 3 fibrosis (NASH-CRN).
- 48-week double-blind treatment period, 10mg, 20mg, or 40mg PGBF subcutaneous or placebo once weekly.
- Liver biopsies (N=396) more than 50% of the biopsy were available for analysis. 24 weeks into the treatment phase, 111 biopsies were evaluated.
- NASH-CRN categorical stages (F0 to F4) were adjudicated for each biopsy.
- MRI imaging results were adjudicated by radiologists. The results are compared to the FibroNest digital pathology scoring methods.
- NASH-CRN Saint and imaging scores were compared using paired t-test (same performance as PDFF).
- A post-hoc analysis compared FibroNest digital pathology scoring methods with imaging results.

**4 Results**

- Patients with biopsies with a DBA lower than 5 (non-adjudicated, ~10% of the cohort) were not included.
- Groups sizes ranged from 27 to 40 patients per group.
- The quantification of the antifibrotic effect of the treatments is similar using the mean change from baseline of the Ph-FCS and MRI-PDFF (Fig. A).
- SQRT(A%) highly correlates to PDFF (N=334) and quantifies the anti-steatotic effects for each group with the same performance as PDFF (Fig. A, Table B).
- Responders were identified with a relative reduction from baseline as summarized in Table F.
- The experimental error of the FibroNest method (related to staining and tissue processing variability) was estimated between 5% and 7% [1]. A 25% relative reduction from baseline is chosen for fibrosis, and 30% for steatosis to fully align to MRI-PDFF.

**5 Conclusions**

Combined to AI algorithms, quantitative digital pathology image analysis provides continuous read-outs of the histological parameters for severity and steatosis. These read-outs are sensitive to subtle changes providing a more granular and accurate way to assess drug effects in clinical trials.

**6 Contact Information**

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