Artificial Intelligence to Measure Fibrosis Change on Liver Biopsy in MAESTRO-NASH, a Phase 3 52-Week Serial Liver Biopsy Study in 966 Patients With NASH Treated With Resmetirom or Placebo

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INTRODUCTION

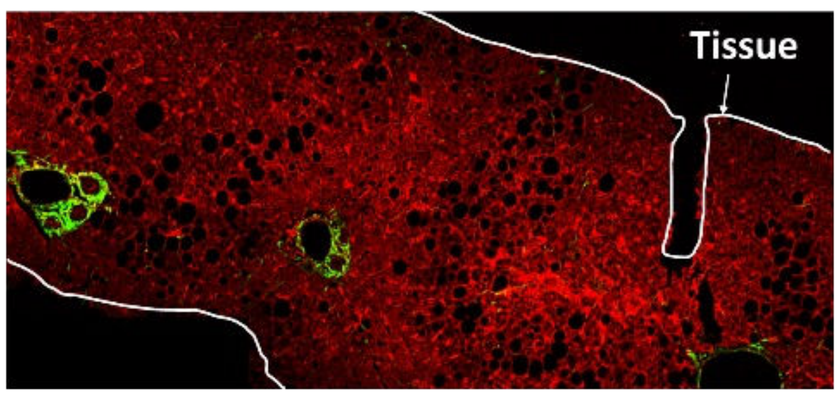
- MAESTRO-NASH (NCT03900429) is an ongoing 54-month, Phase 3, registrational, double blind, placebo-controlled non-cirrhotic nonalcoholic steatohepatitis (NASH) clinical trial to study the effect of once-daily 80 mg or 100 mg resmetirom as compared with placebo in 966 patients with NASH and liver fibrosis
- NASH resolution and fibrosis reduction endpoints on liver biopsy at 52 weeks were achieved at both resmetirom doses, including at least a 1-stage reduction in fibrosis without worsening of NASH of 24% and 26% (mITT) at 80 and 100 mg doses compared with placebo (14%)
- All biopsies were read independently by 2 central pathologists. Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both liver biopsy endpoints

AIM

- As an exploratory endpoint, artificial intelligence (AI) slide reading technologies were employed to measure the effect on fibrosis on serial liver biopsy using both continuous and quantitative scoring

METHOD

- Fibrosis was estimated as a continuous and categorical variable using second harmonic generation (SHG) (qFibrosis)/two-photon excited fluorescence[1] of 768 paired biopsy samples from MAESTRO-NASH
- A separate unstained slide was analyzed for qFibrosis (normalized by tissue area and then corrected for qSteatosis [tissue area–steatosis area])
- qFibrosis can incorporate normalization procedures to account for steatosis area reduction



To correct for qSteatosis

$$= \frac{qFibrosis\ Continuous\ Value}{Tissue\ area - Steatosis\ area}$$

RESULTS

- The exploratory analyses were based on a total of 768 slide pairs, including a baseline and Week 52 slide that were received and met criteria for quality (<10% missing pairs; <3% excluded for quality)
- Based on a continuous qSteatosis score, the % change from baseline in steatosis was 80 mg, –36%; 100 mg, –46%, placebo, –10%, P<0.0001 for both doses; the continuous change from baseline in corrected qFibrosis score was 80 mg, –22%; 100 mg, –20%; placebo, 3%, P<0.0001 for both doses
- The categorical qFibrosis stage aligned with pathologist scoring (F1, F2, F3) with the exception that qFibrosis estimated a high fraction ~20% as F4 stage fibrosis at baseline (F4 stage scored at baseline by central pathologists were excluded from this study)
- Based on categorical change in qFibrosis score, there was a significant improvement in fibrosis stage (1-stage or 2-stage improvement) at 80 and 100 mg relative to placebo, and less worsening of fibrosis in the resmetirom treatment groups compared with placebo (**Table 1**)

Table 1. Categorical Change in qFibrosis Stage

	80 mg	100 mg	Placebo
≥1-stage improvement	58%	56%	34%
P-value	<0.0001	<0.0001	--
≥2-stage improvement	19%	25%	7%
P-value	<0.0001	<0.0001	--
Worsened	11%	11%	35%
P-value	<0.0001	<0.0001	--

- The percentage showing improvement in qFibrosis (≥1-stage) was higher than scored by pathologists and identified 90% of resmetirom responders determined by pathologists
- Significant correlations were observed between reduction in qFibrosis and reduction in proton density fat fraction, alanine aminotransferase, aspartate aminotransferase, and enhanced liver fibrosis score

CONCLUSIONS

- **Measurements of fibrosis change using qFibrosis on either a continuous or categorical scale demonstrated a clear improvement and less worsening in fibrosis in resmetirom-treated NASH patients as compared with placebo after 52 weeks of treatment**

REFERENCES

1. Liu F, et al. *Hepatology* 2020;71:1953–66.

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