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Digital pathology; MAESTRO-NASH; qFibrosis

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

Stephen A. Harrison,[1] Rebecca Taub,[2] Dominic Labriola,[2] Elaine Chng,[3] Yayun Ren,[3] Dean Tai[3]

[1] Pinnacle Research, San Antonio, TX, USA
[2] Madrigal Pharmaceuticals, Conshohocken, PA, USA
[3] Histoindex Pte. Ltd., Singapore

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1 INTRODUCTION

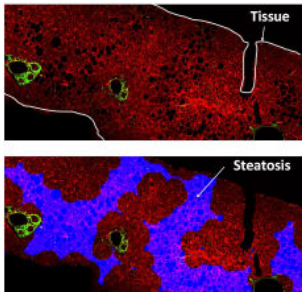
- MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial to evaluate the effect of once-daily 80 or 100mg resmetirom in 966 patients with noncirrhotic NASH and liver fibrosis
- The dual primary endpoints at Week 52 (NASH resolution and fibrosis reduction based on liver biopsy) were achieved with both resmetirom doses, including a ≥1-stage reduction in fibrosis without worsening of NASH in 24% and 26% of patients with 80 and 100mg resmetirom, respectively, compared with 14% of patients with placebo (mITT)
- All liver biopsies were read independently by two central pathologists. Each pathologist's scores showed a similar statistically significant magnitude of response at both doses of resmetirom for both primary endpoints

2 AIM

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

3 METHODS

- 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



$$\text{To correct for qSteatosis} = \frac{qFibrosis\ Continuous\ Value}{Tissue\ area\ -\ Steatosis\ area}$$

4 RESULTS

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

Table 1: Categorical change in qFibrosis stage

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

- The percentage showing improvement in qFibrosis (≥1-stage) was higher than scored by central pathologists, and identified 90% of resmetirom responders determined by the pathologists
- Significant correlations were observed between reduction in qFibrosis and reduction in PDFF, ALT, AST, and ELF

5 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 patients compared with placebo-treated patients with NASH after 52 weeks of treatment

6 ACKNOWLEDGMENTS

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7 REFERENCE

1. Liu F, et al. *Hepatology* 2020;71:1953-1966.

8 CONTACT INFORMATION

Stephen A. Harrison: stephenharrison87@gmail.com

LBP-17

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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[1]Pinnacle Research, United States, *[2]Madrigal Pharmaceuticals, R&D, United States*, *[3]Histoindex, Singapore*

Email: rebeccataub@yahoo.com

Background and Aims: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, Phase 3, registrational double blind, placebo-controlled non-cirrhotic 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 one stage reduction in fibrosis without worsening of NASH of 24%, 26% (mITT) at 80 and 100 mg doses compared with placebo (14%). As an exploratory endpoint, artificial intelligence 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 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)). Relative changes in 184 fibrosis parameters were determined.

Results: The 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). 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 PDFF, ALT, AST, and ELF.

Conclusion: 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.

Figure:

Categorical change in qFibrosis stage						
	>=1-stage improvement	p-value	>=2-stage improvement	p-value	worsened	p-value
80 mg	58%	<0.0001	19%	<0.0001	11%	<0.0001
100 mg	56%	<0.0001	25%	<0.0001	11%	<0.0001
PBO	34%		7%		35%	