Impact of Resmetirom-Mediated Reductions in Liver Volume and Steatosis Compared With Placebo on the Quantification of Fibrosis Using Second Harmonic Generation in a Serial Liver Biopsy Study

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BACKGROUND

- Resmetirom (MGL-3196) is a liver-targeted, oral thyroid hormone receptor-beta selective agonist in clinical development for treatment of nonalcoholic steatohepatitis (NASH) with significant fibrosis

- In the Phase 2 serial liver biopsy study, the primary endpoint (relative reduction in hepatic fat based on magnetic resonance imaging-proton density fat fraction [MRI-PDFF] at Week 12) was achieved with resmetirom[1]
  - The reduction in hepatic fat was sustained at Week 36
  - Dose-dependent 50% reduction in hepatic fat at 80-mg dose of resmetirom

- Key secondary and exploratory liver biopsy endpoints were achieved
  - Statistically significant reduction and resolution of NASH as compared with placebo

- Liver volume is markedly elevated in patients with NASH and well-compensated NASH cirrhosis even after correcting for size and body mass index[2,3]

- In a secondary analysis, the impact of resmetirom treatment on liver volume (measured by MRI-PDFF) was assessed
  - Liver volume was reduced ~20% with resmetirom treatment as compared with placebo by Weeks 12 and 36 (p<0.0001)
  - Only a fraction of the liver volume reduction was explained by steatosis reduction

OBJECTIVE

- To investigate the impact of resmetirom-mediated reductions in liver volume and steatosis compared with placebo on NASH fibrosis by quantifying and correcting for fibrosis changes using qFibrosis, an artificial intelligence (AI)-based algorithm

- **Hypothesis: qFibrosis can incorporate liver volume normalization procedures to account for liver volume reduction and steatosis area, thereby improving the detection of fibrosis changes**

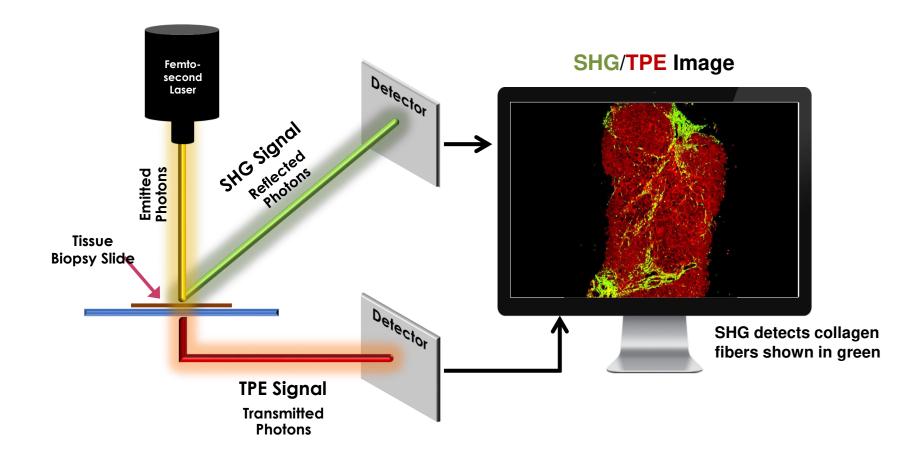- Retrospective analysis was conducted on 102 paired biopsy samples from the resmetirom Phase 2 serial liver biopsy study[1]

- Based on liver volume and hepatic fat reduction (measured by serial MRI-PDFF), corrections of qFibrosis were made for liver volume and hepatic fat reduction
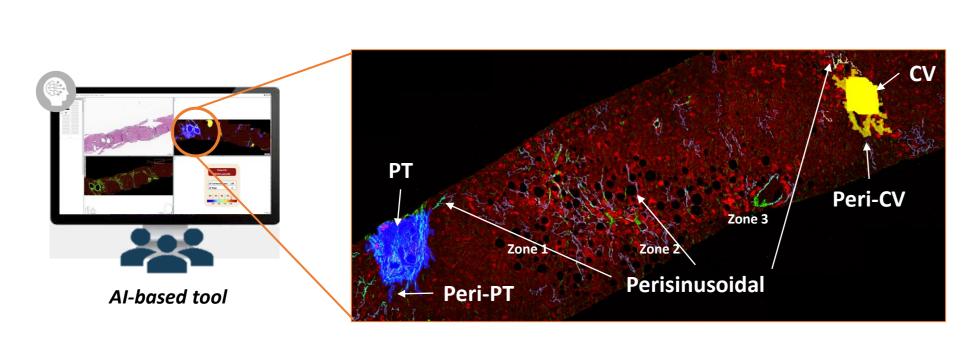
METHODS

Figure 1. qFibrosis: Stain-free Imaging[4]

- Fibrosis is estimated as a continuous variable (qFibrosis) using second harmonic generation (SHG) imaging of unstained tissue sections

- SHG imaging provides visual mapping of collagen burden/distribution and permits measurement of quantifiable collagen fibrillar properties

Figure 2. qFibrosis: AI-based Tool for Liver Volume Correction

- This AI-based tool can automatically identify and annotate zonal regions, portal tracts, central vein, and other morphological features with subsequent quantification of qFibrosis parameters within these zones

$$\text{Correction coefficient:} \left(\frac{\text{End of Treatment } volume}{\text{Baseline } volume}\right)^{2/3}$$

- Liver volume correction is then applied to changes in fibrosis

- By using liver volume data, a correction coefficient was developed to correct the end-of-treatment parameters impacted by these volume changes

RESULTS

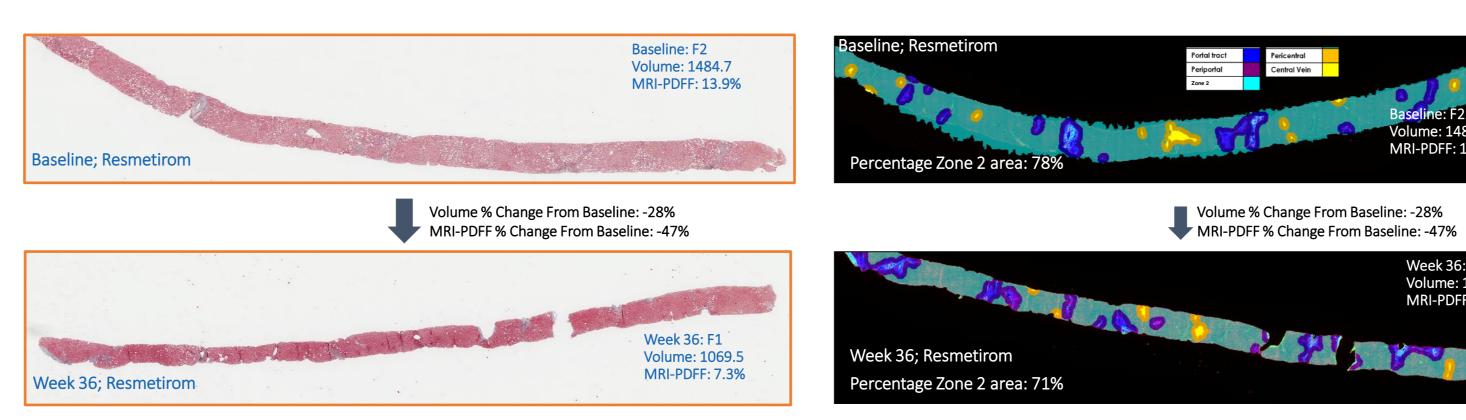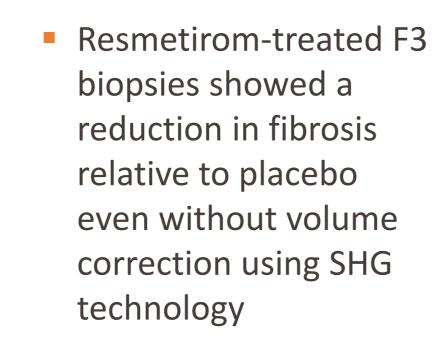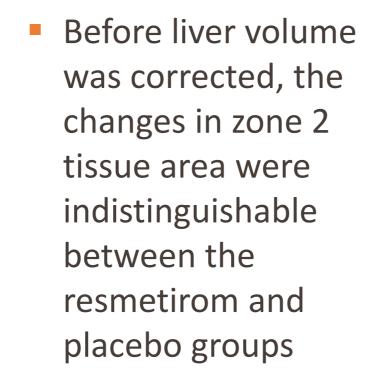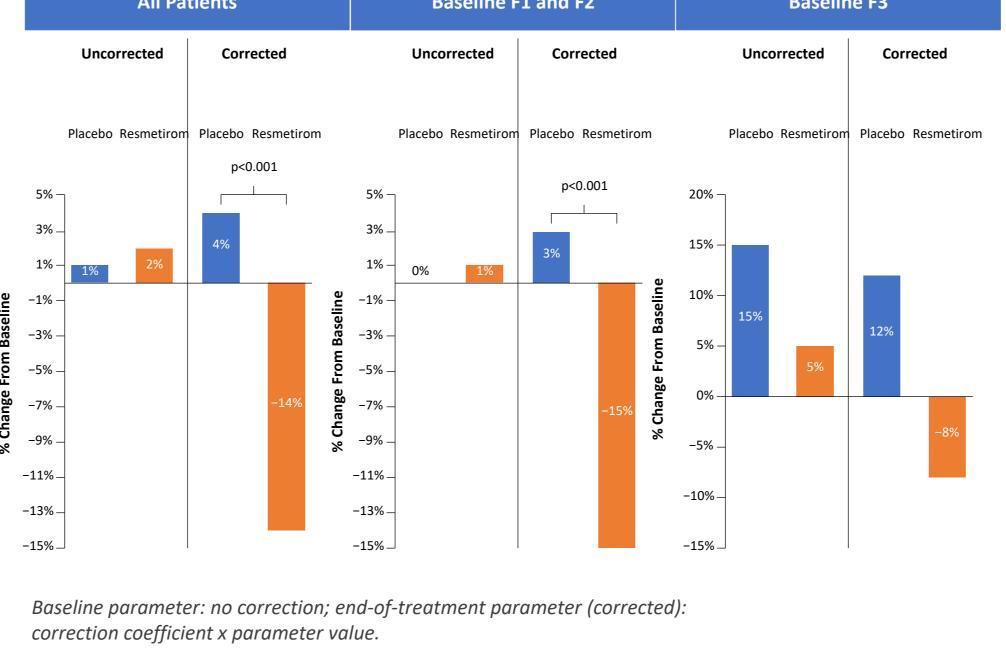### Figure 3a. Liver Volume Reduction Assessment on Stained Images

Figure 3b. Percentage Zone 2 Area Calculation

Figure 4. Liver Volume Correction – Zone 2 Impact for F1, F2 vs F3 Baseline Biopsies

- Resmetirom-treated F3 biopsies showed a reduction in fibrosis relative to placebo even without volume correction using SHG technology

- Before liver volume was corrected, the changes in zone 2 tissue area were indistinguishable between the resmetirom and placebo groups

Baseline parameter: no correction; end-of-treatment parameter (corrected): correction coefficient x parameter value.
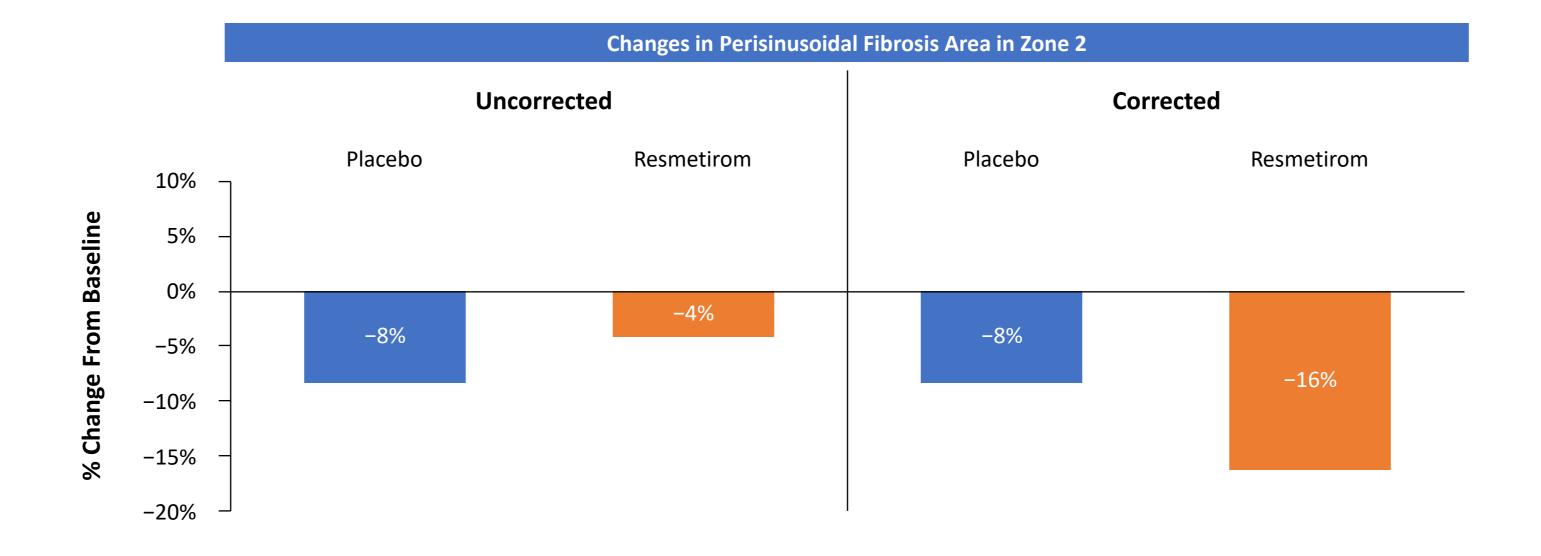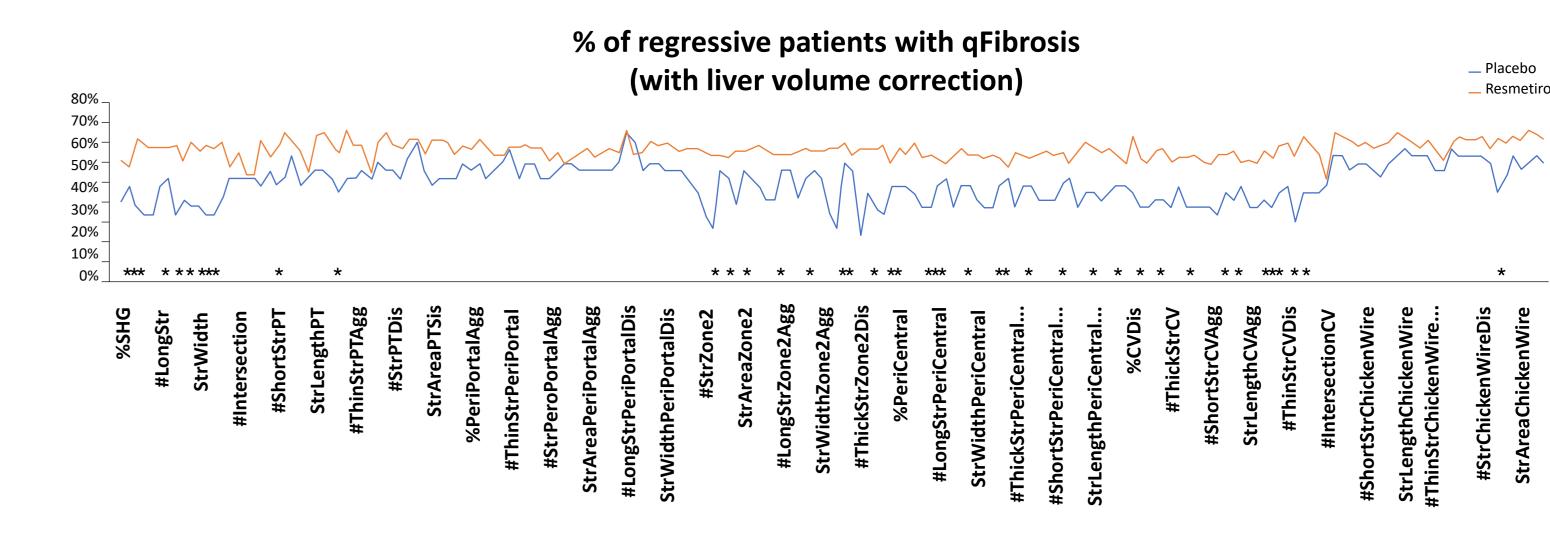
- After correcting for liver volume reduction, zone 2 tissue area was clearly reduced in the resmetirom group despite different stages of fibrosis

- The impact of liver volume was most significant for patients with F1 or F2 fibrosis at baseline

Figure 5. Liver Volume Correction – Zone 2 Changes in Perisinusoidal Fibrosis

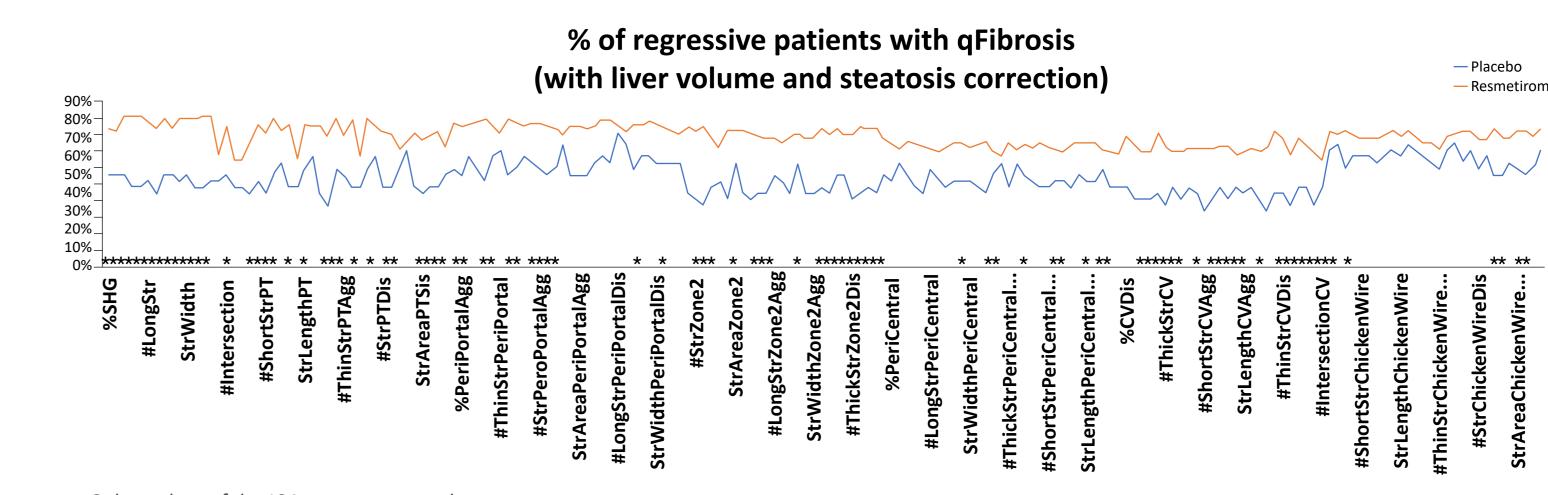- Perisinusoidal fibrosis area in zone 2 was further reduced in the resmetirom group

Figure 6. Liver Volume Correction – qFibrosis Parameter Level Analysis

% of regressive patients with qFibrosis (with liver volume correction)

Only a subset of the 184 parameters are shown

- In normal qFibrosis without correction, resmetirom treatment resulted in a significant reduction in fibrosis (≥1-point reduction) in F3 patients compared to placebo
- With liver volume correction, 45/184 regression parameters demonstrated significant changes with resmetirom treatment (p<0.05)

Figure 7. Liver Volume and Steatosis Correction – qFibrosis Parameter Level Analysis

% of regressive patients with qFibrosis (with liver volume and steatosis correction)

Only a subset of the 184 parameters are shown

- When liver volume and steatosis correction factors were combined, 111/184 regression parameters were significantly reduced with resmetirom treatment (p<0.05)

CONCLUSIONS

- **Assessment and quantification of changes in NASH fibrosis are impacted by therapeutics that potentially reduce liver volume and hepatic steatosis**

- **Impact of liver volume reduction may not be discernable by conventional means of fibrosis staging, since the percentage of zone 2 area does not change. However, with correction for liver volume reduction, the changes in zone 2 area become significant**

- **Use of qFibrosis, an AI-based algorithm, can help to assess and correct for liver volume and steatosis reduction, potentially allowing for more accurate assessment of fibrosis changes over time**

- **Further study is warranted in additional data sets to better understand the mechanism of liver volume reduction and its impact on histopathology in patients with NASH**

REFERENCES

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