

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 resmetirom¹
 - 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 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 study¹
- 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 Imaging⁴

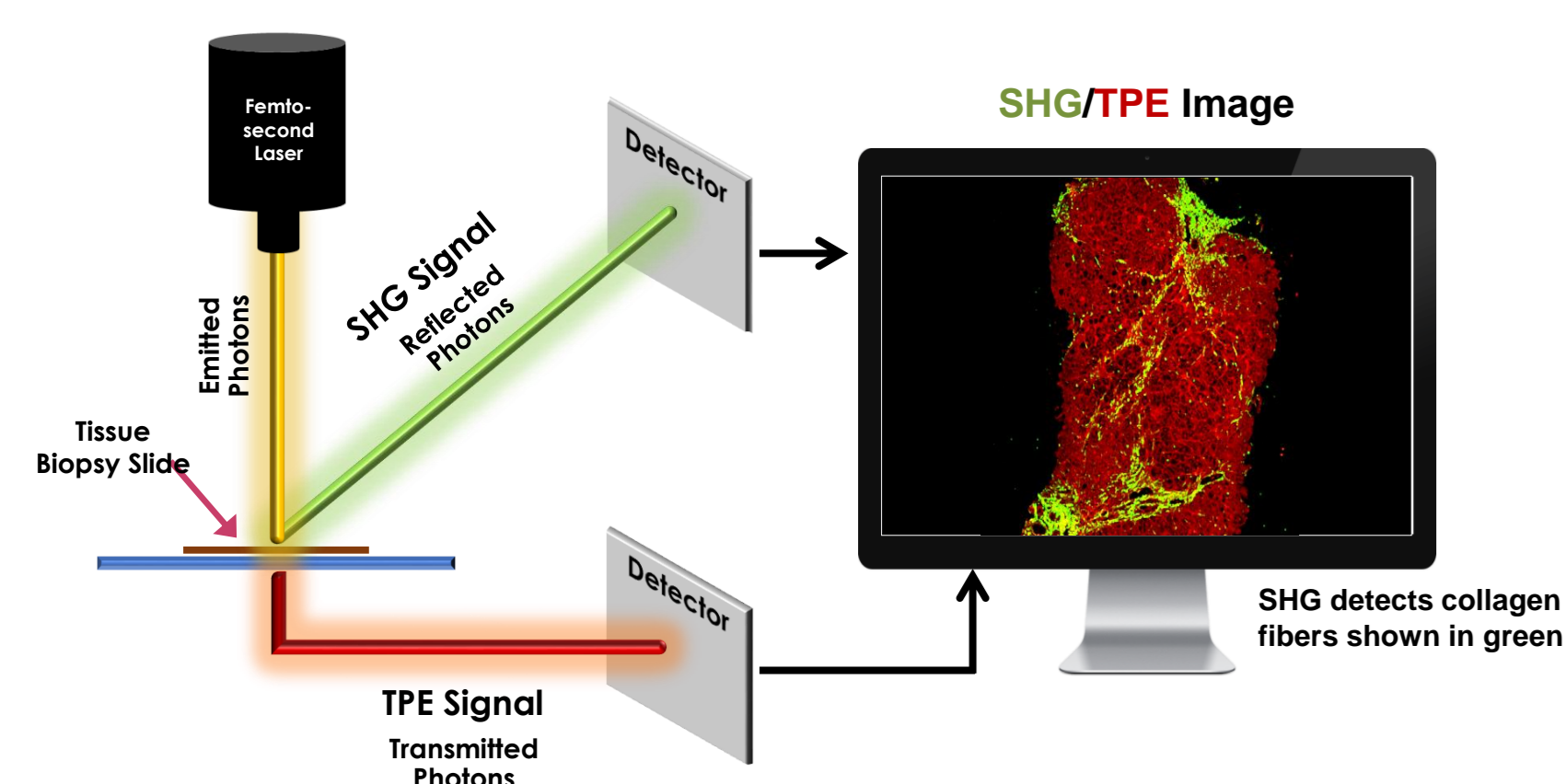
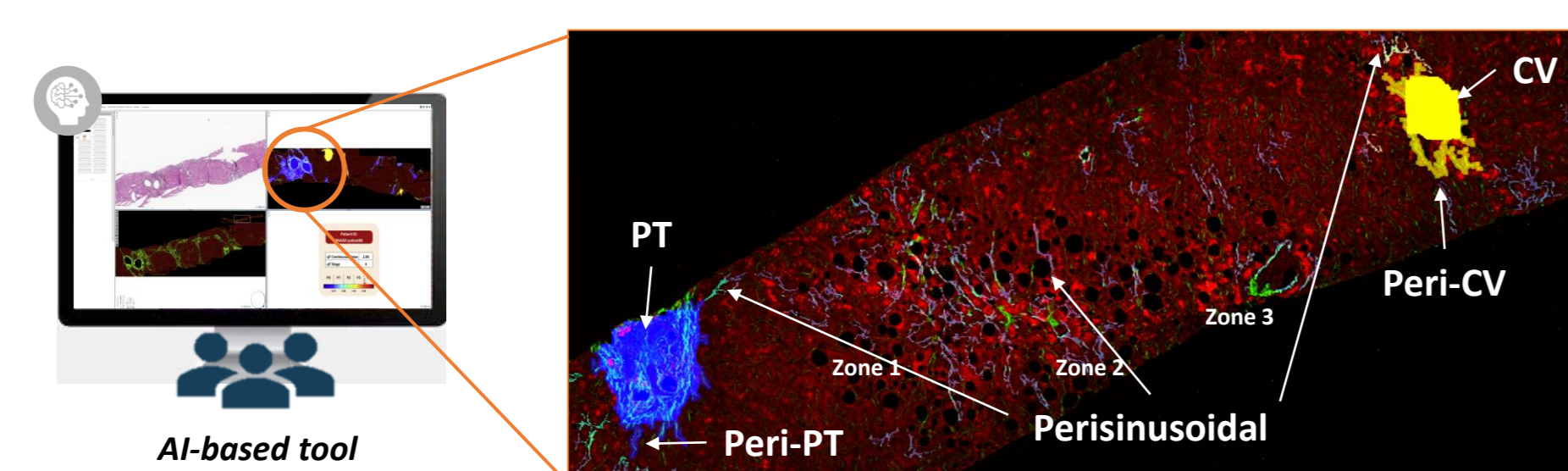


Figure 2. qFibrosis: AI-based Tool for Liver Volume Correction

- 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

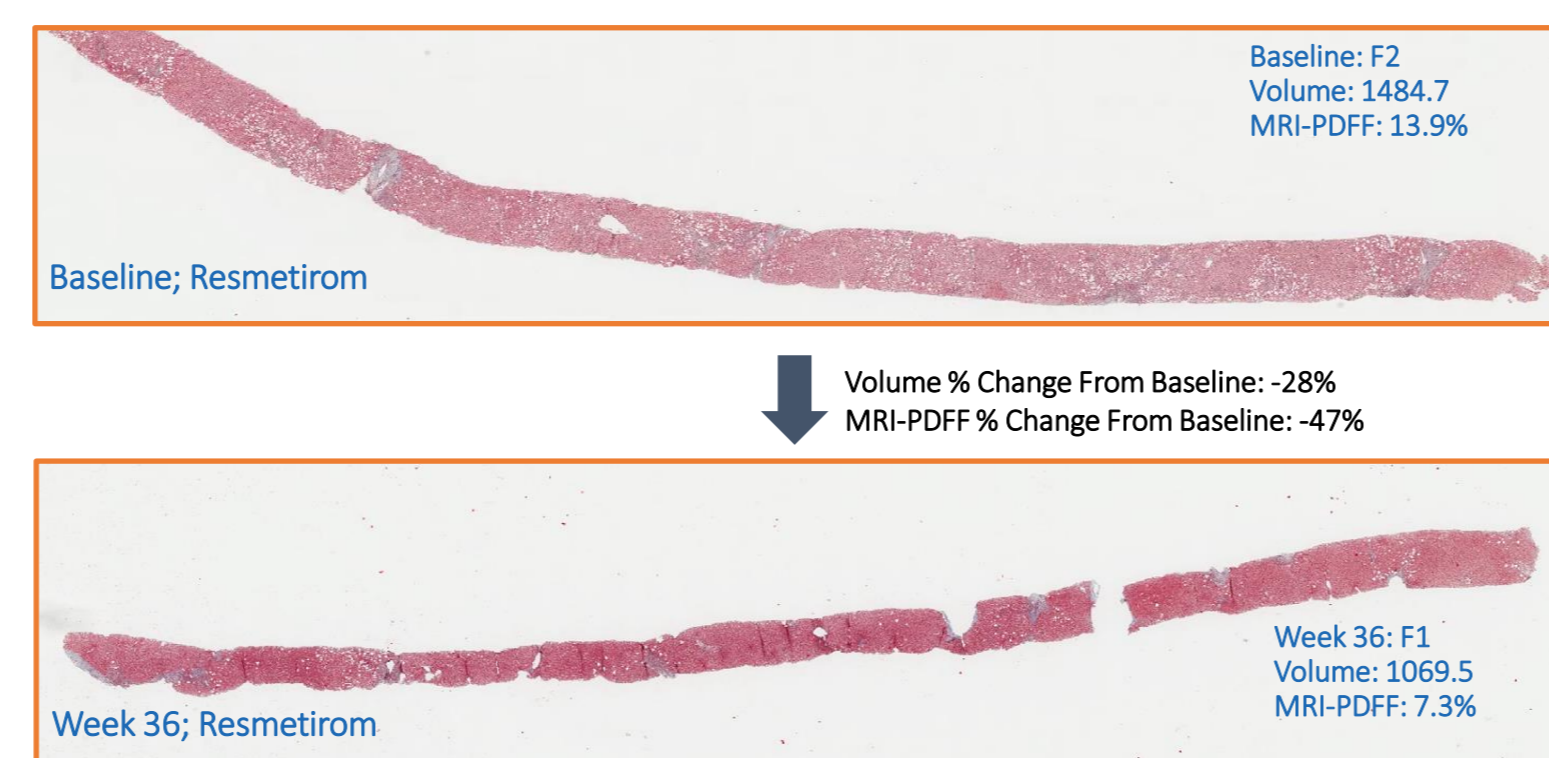


Figure 3b. Percentage Zone 2 Area Calculation

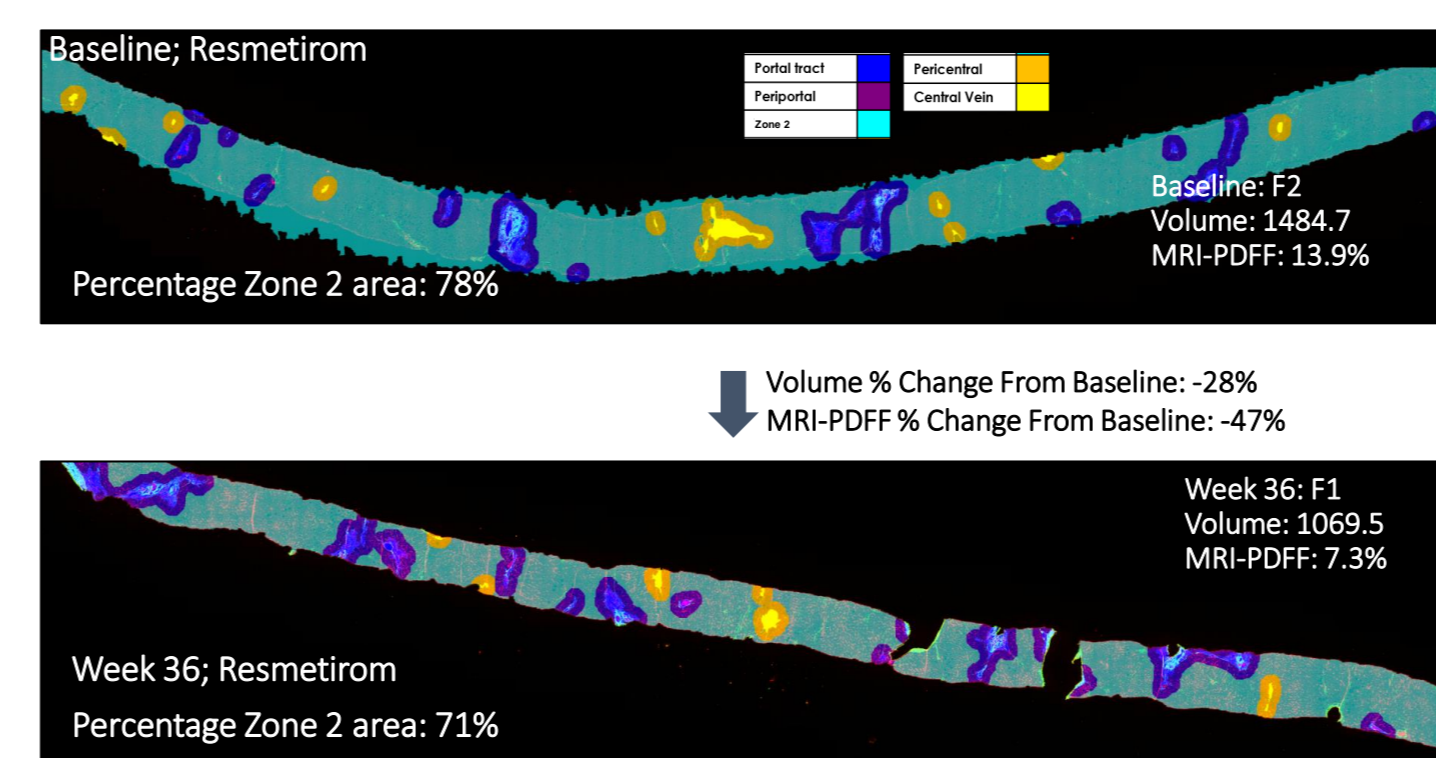
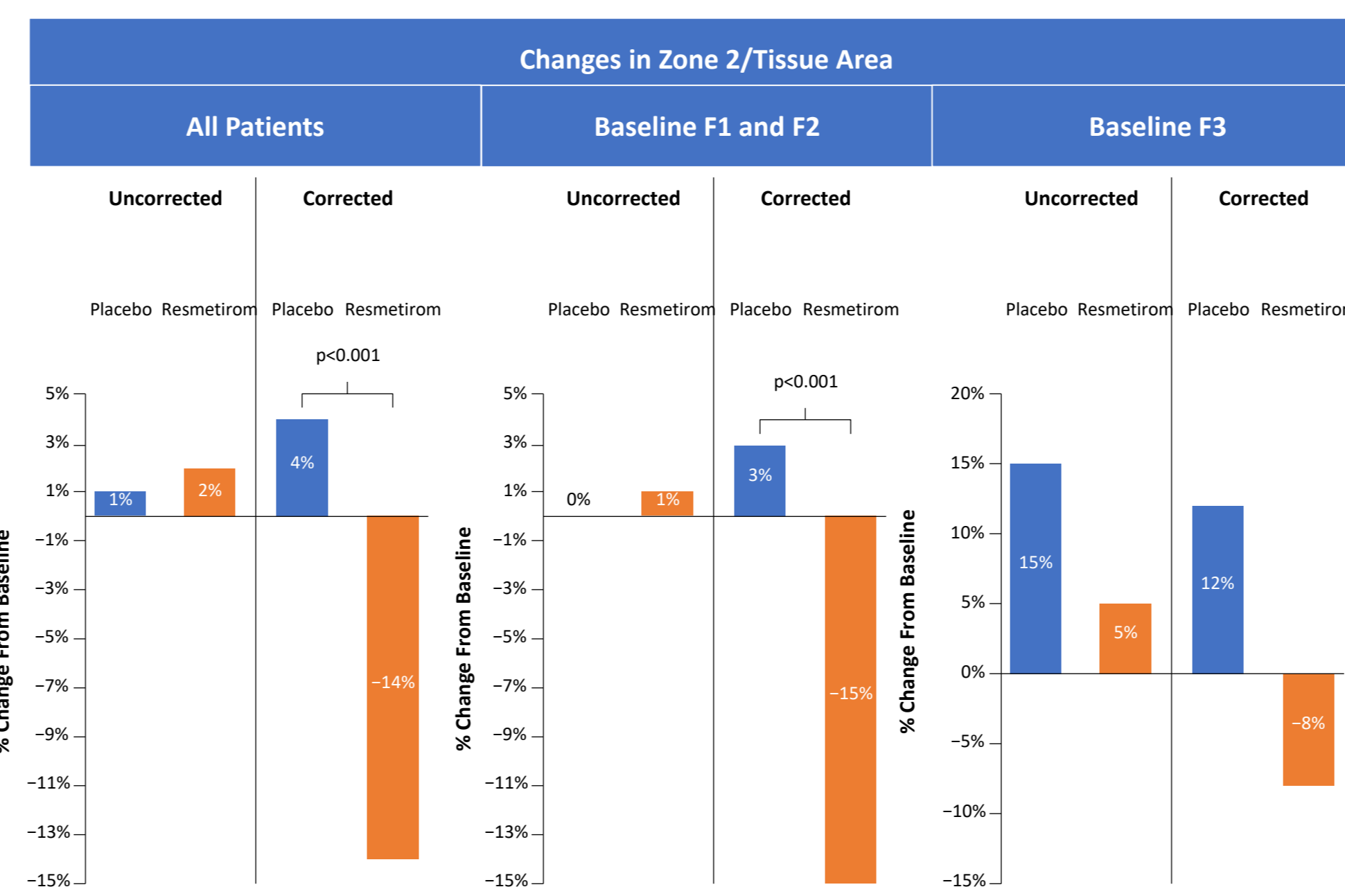


Figure 4. Liver Volume Correction – Zone 2 Impact for F1, F2 vs F3 Baseline Biopsies

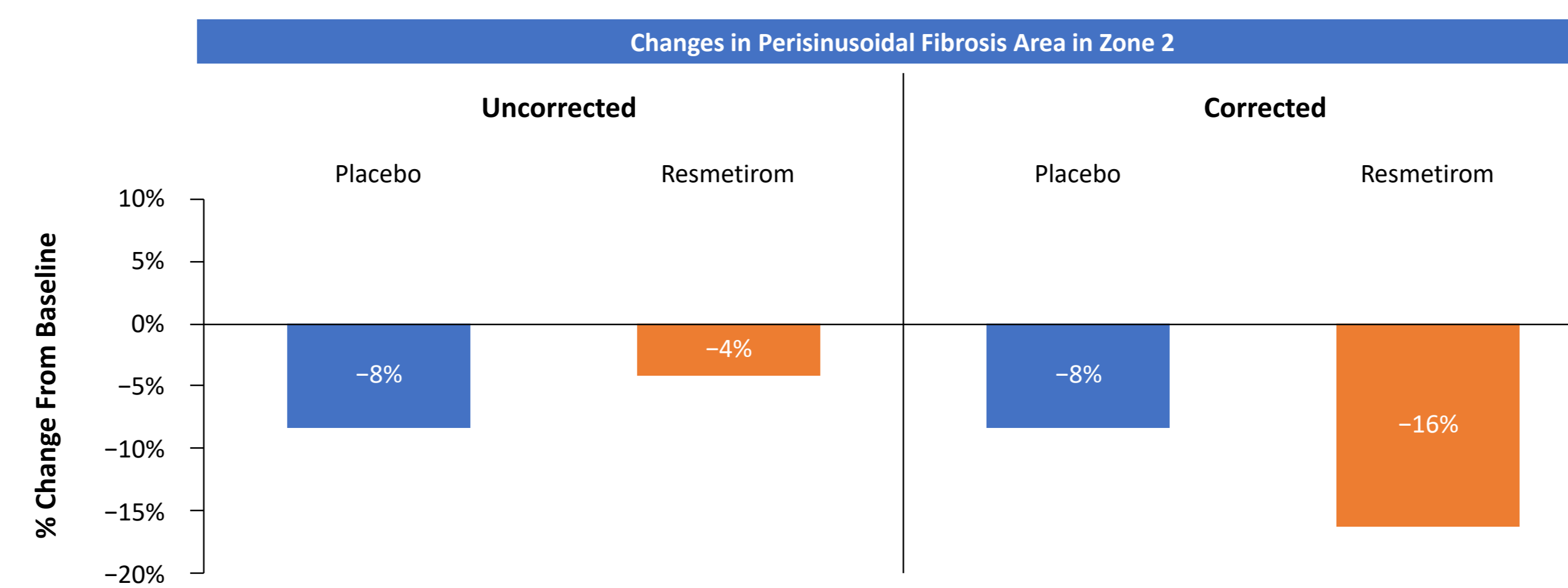
- Resmetirom-treated F3 biopsies showed a reduction in fibrosis relative to placebo even without volume correction using SHG technology
- Before liver volume was corrected, the changes in zone 2 tissue area were indistinguishable between the resmetirom and placebo groups



Baseline parameter: no correction; end-of-treatment parameter (corrected): correction coefficient x parameter value.

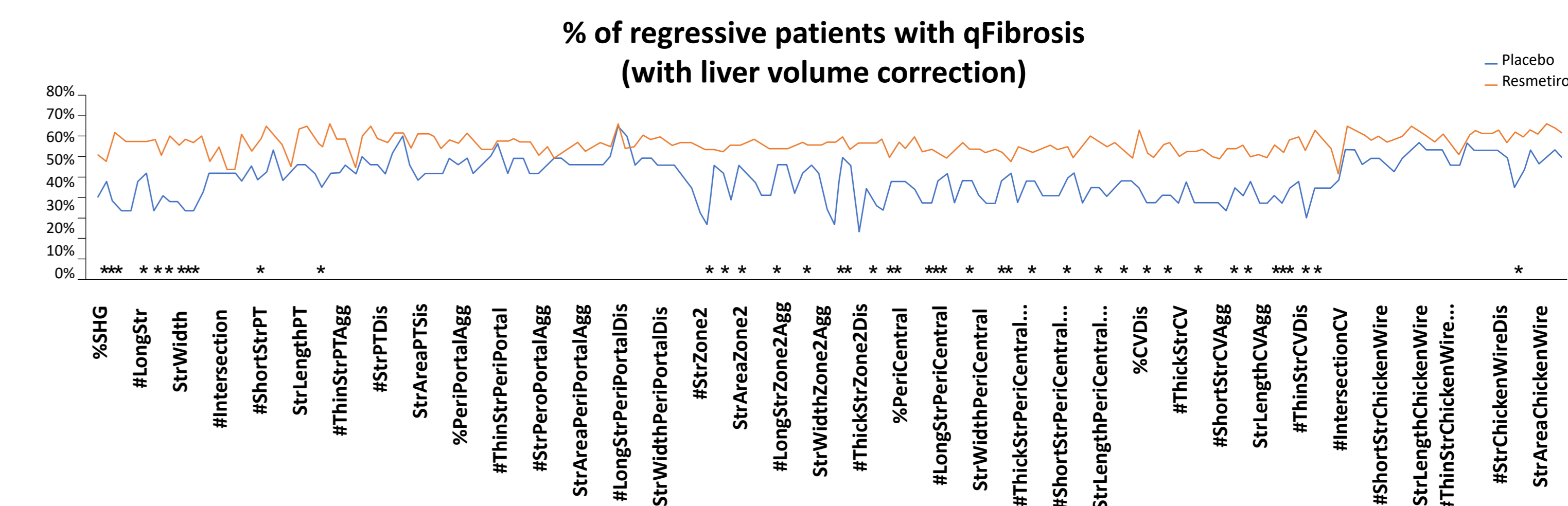
- After correcting for liver volume reduction, zone 2 tissue area was clearly reduced in the resmetirom group despite different stages of fibrosis
- The impact of liver volume was most significant for patients with F1 or F2 fibrosis at baseline

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



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

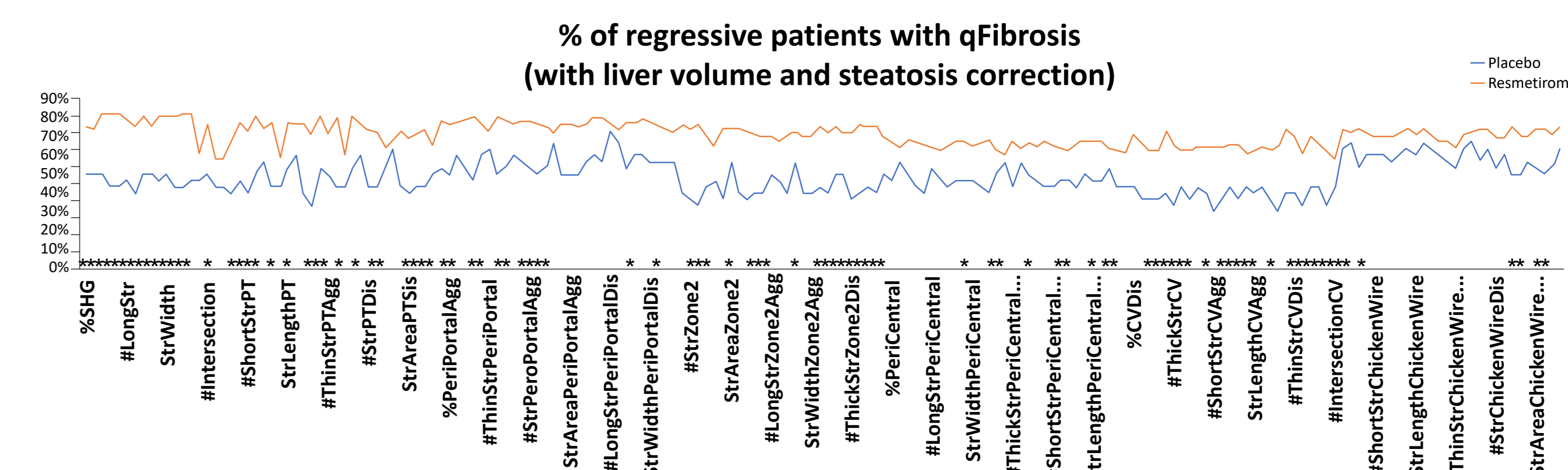
Figure 6. Liver Volume Correction – qFibrosis Parameter Level Analysis



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



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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