Assessment of resmetirom-mediated reductions of steatosis and concomitant ballooning utilizing quantitative SHG imaging

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INTRODUCTION

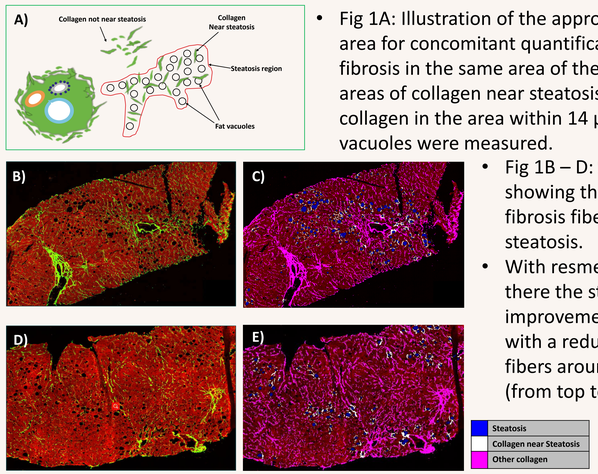
- Resmetirom, an oral, liver-targeted thyroid hormone receptor-β selective agonist, has been shown to achieve NASH resolution and fibrosis reduction endpoints on liver biopsy at 52 weeks in an ongoing Phase 3 registrational non-cirrhotic NASH trial.
- A previous exploratory analysis of qSteatosis and qFibrosis in the phase 2 36-Week study of resmetirom in patients with NASH demonstrated that reduction of collagen near steatosis associates with steatosis improvement in Zone 2.
- The aim of this analysis was to study the association between ballooning reduction and steatosis reduction in the resmetirom versus placebo group using second harmonic generation (SHG)/ two-photon excited fluorescence (TPEF) microscopy imaging of paired biopsy samples with artificial intelligence (AI)-based algorithms. The interaction between steatosis and concomitant fibrosis reduction will also be shown.

METHODS

- 103 paired biopsy samples from a 36-week, randomized, double-blind, placebo-controlled Phase 2 study with resmetirom (NCT02912260) were imaged using SHG/TPEF.
- Ballooning and steatosis were estimated as a continuous variable using an AI-based algorithm as previously described.[1]
- Resmetirom-mediated changes of ballooning in relation to steatosis reduction were evaluated by simultaneous measurement of ballooning and hepatic fat in selected areas around the fat vacuoles in liver regions: portal tract (Zone 1), central vein (Zone 3), and transitional (Zone 2).

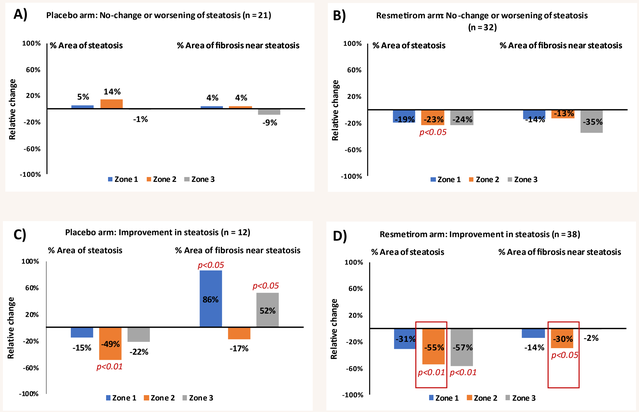
RESULTS

Figure 1. Co-localisation analysis of qSteatosis and qFibrosis.



- Fig 1A: Illustration of the approach for selecting the area for concomitant quantification of steatosis and fibrosis in the same area of the liver lobule. Multiple areas of collagen near steatosis, which refers to the collagen in the area within 14 µm around fat vacuoles were measured.
- Fig 1B – D: SHG/TPEF images showing the detection of fibrosis fibers associated with steatosis.
- With resmetirom treatment, there the steatosis improvement was associated with a reduction of collagen fibers around the fat vacuoles (from top to bottom row).

Figure 2. Co-localisation analysis of qFibrosis and steatotic changes based on pathologist's reads.



- Fig 2C, D: For patients who showed improvement in steatosis, we observed statistically significant steatosis reduction with concomitant fibrosis improvement in Zone 2 for the resmetirom arm (D), whereas the placebo arm showed a worsening of concomitant fibrosis in Zones 1 and 3.
- Fig 2A, B: For patients whose steatosis worsened, the resmetirom arm showed less worsening of fibrosis compared with placebo.

Figure 3. Co-localisation analysis of qSteatosis and qBallooning.

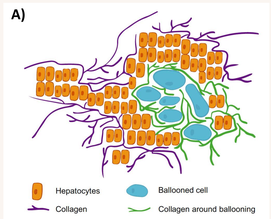


Fig 3A: Illustration of the co-localisation of ballooned hepatocytes and collagen fibers within the liver lobule. Multiple areas of collagen within 14 µm of the ballooned were measured.

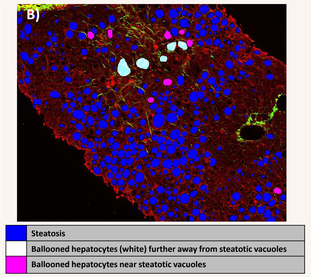
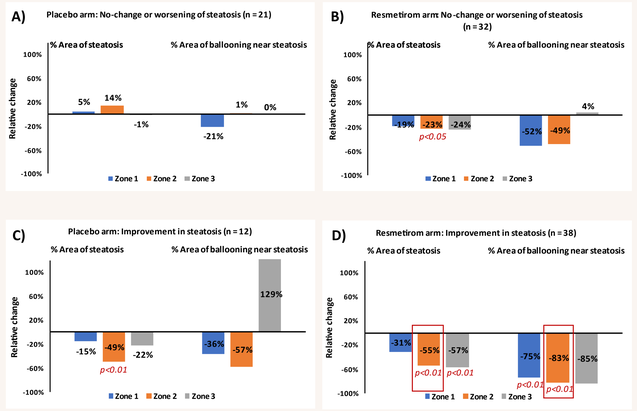


Fig 3B: SHG/TPEF image of a ROI showing the detection of ballooned hepatocytes (pink) in close proximity to steatotic vacuoles (blue), versus ballooned hepatocytes (white) further away from steatotic vacuoles.

Figure 4. Co-localisation analysis of qBallooning and steatotic changes based on pathologist's reads.



- Fig 4D: In patients whose steatosis improved, resmetirom treated patients showed a relative decrease of 55% for % area of steatosis was associated with a relative decrease of 83% for % area of ballooning near steatosis in Zone 2 ($p < 0.01$). Similar observation of concomitant reduction in ballooning (85%) near steatosis (57%) can be seen for Zone 3 too ($p<0.01$).
- Fig 4C: The placebo arm only showed some associated ballooning reduction in Zones 1 and 2 and worsening of ballooning in Zone 3, but these were not statistically significant.
- Fig 4A, B: For patients whose steatosis worsened, the resmetirom arm seemed to show less worsening of co-localized ballooning in comparison to the placebo arm.

CONCLUSION

- SHG/TPEF microscopy with AI provides greater granularity in assessing the dynamics between histological components associated with NASH.
- Qualitatively, a clear difference can be seen in the pattern of co-localization analysis of steatosis and ballooning in resmetirom-treated patients versus placebo-treated patients.
- The use of a continuous variable (qBallooning, qSteatosis) provides quantitation of zonal changes in ballooning and steatosis in serial liver biopsy studies which cannot be captured using the NASH CRN system.
- The clinical relevance of AI digital measurements of the NASH features will have to be established in future liver-related clinical outcomes study.

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REFERENCE

1) Liu F, et al. Hepatology 2020; 71: 1953–1966

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