P-3202

FIBROSIS REGRESSION AFTER TIRZEPATIDE TREATMENT OF NON-CIRRHOTIC MASH FOR 52 WEEKS OCCURED IN A ZONE-DEPENDENT MANNER

A.J. SANYAL[1], V. RATZIU[2], C.A. BEHLING[3], O.W. CUMMINGS[4], Y. CHOUDHURY[5], E. CHNG[5], Y. TANG[6], D. TAI[5], M.L. HARTMAN[6], R. LOOMBA[7]

1. Virginia Commonwealth University, Virginia, USA; 2. Sorbonne Université, Paris, France; 3. Pacific Rim Pathology, San Diego, USA; 4. Indiana University School of Medicine, Indiana, USA; 5. HistoIndex Pte. Ltd, Singapore; 6. Eli Lilly and Company, Indiana, USA; 7. University of California – San Diego, California, USA

OBJECTIVE

- This post hoc analysis of the SYNERGY-NASH phase 2 trial explored zonal changes in liver fibrosis using quantitative second harmonic generation (SHG)/two-photon excited fluorescence (TPEF) microscopy imaging with an artificial intelligence (AI) - based algorithm.

CONCLUSION

- Fibrosis regression associated with tirzepatide treatment of MASH for 52 weeks occurred in zones 1 and 2 but not in zone 3 of the liver lobule, which was different from fibrosis regression seen with placebo treatment.
- These results suggest the potential for distinct mechanisms of fibrosis regression with tirzepatide, to be evaluated in longer studies.

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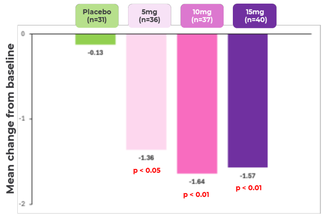
BACKGROUND

- Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease characterized histologically by steatosis, inflammation and hepatocyte injury (ballooning), with or without fibrosis[1,2]
- Tirzepatide, a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist, has been shown to induce substantial weight reduction in placebo-controlled trials in people with obesity and/or type 2 diabetes (T2D)[3-5]
- In the phase 2 SYNERGY-NASH trial,
  - up to 73% of participants treated with tirzepatide achieved resolution of MASH without worsening of fibrosis[6], and
  - the proportion of participants who completed treatment and achieved ≥1-stage fibrosis improvement without worsening of MASH was 32.5% for placebo, and 59.2%, 53.4% and 54.3% for tirzepatide 5, 10 and 15 mg, respectively.

KEY RESULTS: CHANGES IN LIVER FIBROSIS BY SHG/TPEF MICROSCOPY WITH AI ALGORITHM

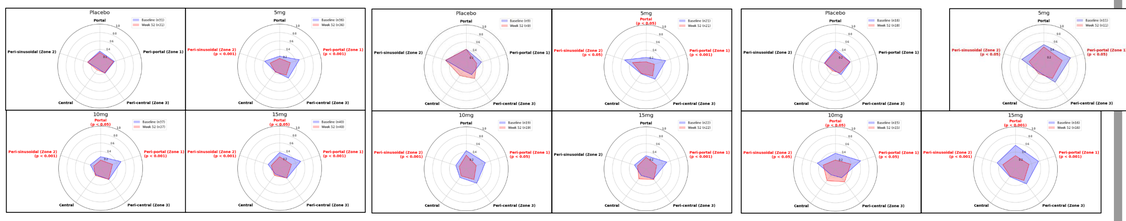
Changes in qFibrosis (steatosis-corrected) at Week 52



p values vs placebo were obtained with Student's t-tests.

Steatosis-corrected qFibrosis scores at Week 52 were significantly decreased with all tirzepatide doses compared with placebo

Radar plots showing zonal changes in fibrosis (steatosis-corrected)

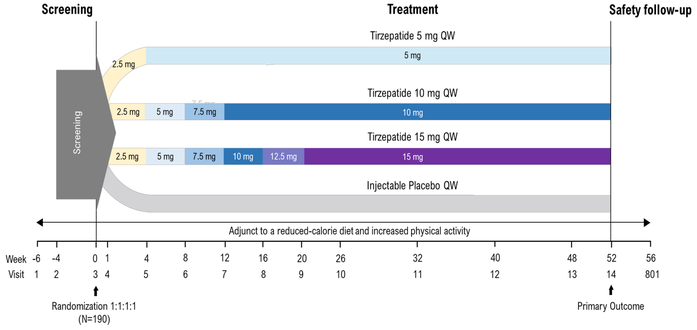


When zonal analysis of collagen area was applied, statistically significant fibrosis regression between baseline and Week 52 (denoted in red) was seen with tirzepatide in zone 1 and zone 2 with 5 mg, and in zone 1, zone 2, and the portal zone with 10 mg and 15 mg but not with placebo. No significant changes were observed in zone 3 and the central zone.

Among participants with ≥1 NASH CRN stage decrease in fibrosis, statistically significant fibrosis regression with tirzepatide was seen in zone 1, zone 2 and the portal zone with 5 mg, zones 1 and 2 with 10 mg and zone 1 with 15 mg (denoted in red). No significant changes were observed in zone 3 and the central zone.

Participants with no change in NASH CRN fibrosis stage showed statistically significant fibrosis regression in zone 1 and zone 2 with tirzepatide 5 mg, and in zone 1, zone 2, and the portal zone with tirzepatide 10 mg and 15 mg (denoted in red). No significant changes were observed in zone 3 and the central zone.

STUDY DESIGN

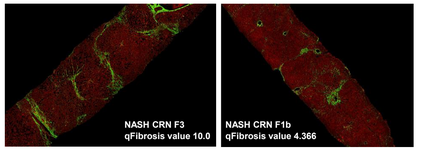


SYNERGY-NASH key inclusion criteria[6,7]

- Adults aged 18-80 years
- BMI ≥27 kg/m^2 and ≤50 kg/m^2 with or without T2D
- Diagnosis of MASH, F2-3 fibrosis and NAS of ≥4, with ≥1 point for steatosis, ballooning, and lobular inflammation

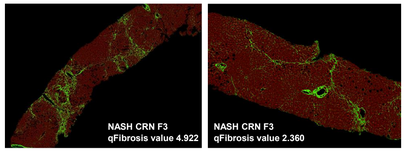
RESULTS: Case Examples

1. NASH CRN fibrosis stage regression (F3 to F1b) with decrease in qFibrosis continuous value



Baseline — Week 52
Tirzepatide 15 mg

2. No change in NASH CRN fibrosis stage F3 with decrease in qFibrosis continuous value



Baseline — Week 52
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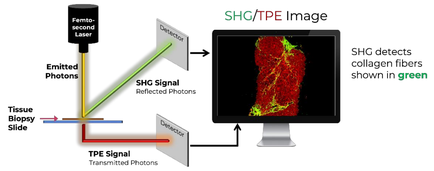
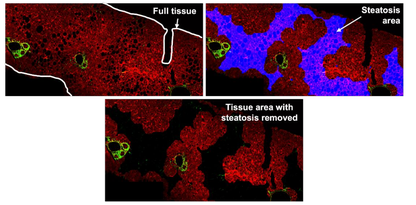
Case example figures demonstrate SHG/TPEF/AI ability to detect zonal changes in fibrosis and to quantify changes in fibrosis within a NASH CRN stage. In example 1 (left), the total amount of collagen is decreased with disappearance of collagen in zone 1 and persistence of collagen in zones 2 and 3. In example 2 (right), NASH CRN staging demonstrated bridging fibrosis in both baseline and 52-week biopsies (stage F3). However, the SHG/TPEF/AI analysis demonstrates a decrease in the total amount of collagen despite persistence of architectural bridges.

METHODS: Post Hoc Analysis using SHG/TPEF Microscopy with AI Algorithm

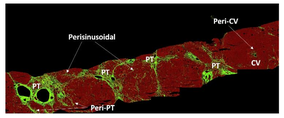
- Of 190 participants randomized in SYNERGY-NASH, 157 had end-of-treatment biopsies, and 144 had evaluable paired biopsy samples (baseline [BL] and week 52) for SHG/TPEF microscopy



- Because fibrosis burden may be underestimated in the setting of steatosis and tirzepatide induced large liver fat reductions, a steatosis correction was applied: the steatosis area (by SHG/TPEF) was subtracted from the total liver tissue area to remove the confounding effect of changes in steatosis



- Changes in fibrosis were assessed for the whole sample (qFibrosis) and for 5 zones: portal, peri-portal (zone 1), peri-sinusoidal (zone 2), central, and peri-central (zone 3).



References: 1. Rinella ME, et al. Hepatology 2023;78(6):1966-1986. 2. Rinella ME, et al. Hepatology 2023;77(5):1797-1835. 3. Rosenstock J, et al. The Lancet 2021;398(10295):143-155. 4. Jastreboff AM, et al. NEJM 2022;387(3):205-216. 5. Garvey WT, et al. The Lancet 2023;402(10402):613-626. 6. Loomba R, et al. NEJM 2024; Jul 25;391(4):299-310. 7. Vuppalanchi R, et al. APT 2024; Jul;60(1):17-32. **Abbreviations:** CRN = clinical research network; qFibrosis = quantitative assessment of liver fibrosis; MASH = metabolic dysfunction-associated steatohepatitis; NAS = non-alcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; SHG = second harmonic generation; TPEF = two-photon excitation fluorescence. **Acknowledgments:** We thank the clinical trial participants and their caregivers, without whom this work would not be possible. We thank Eli Lilly and Company employee Eric A. Rodriguez for medical writing and editorial support.. **Disclosures:** Disclosure forms provided by AJS, CAB, OWC, YT, MLH, and RL are available at Loomba R, et al. NEJM 2024; Jul 25;391(4):299-310. VR has received support from Histoindex Inc. YC, EC, and DT are employees and shareholders of Histoindex Inc.

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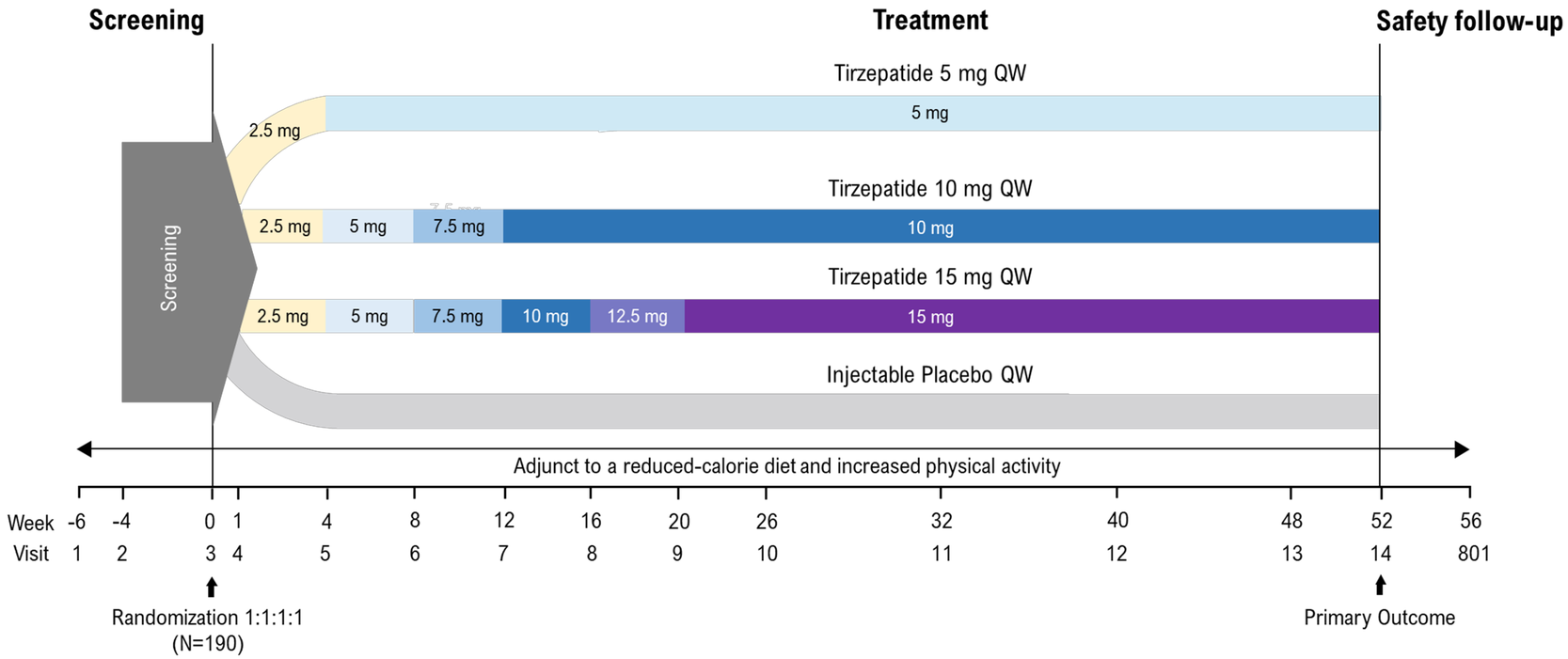

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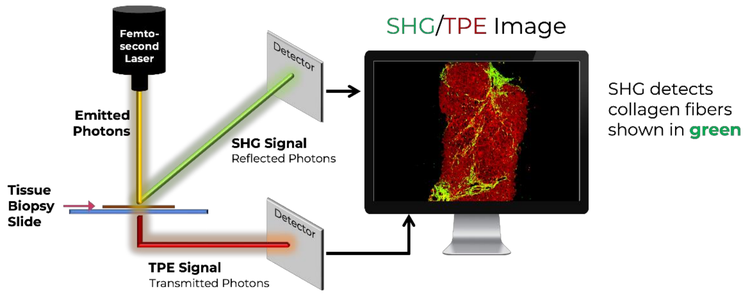
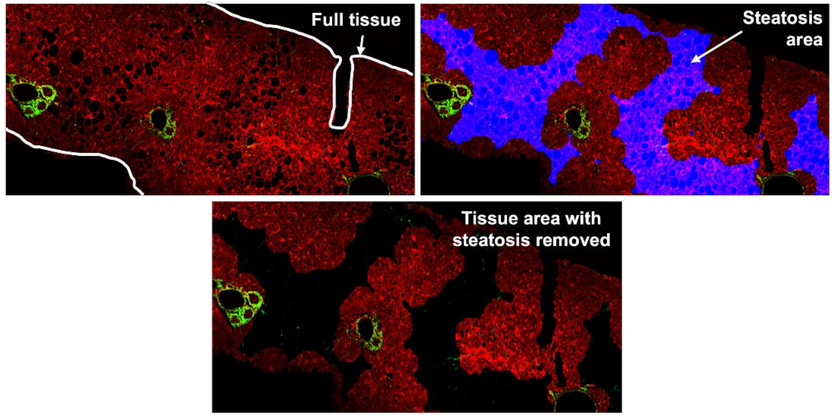
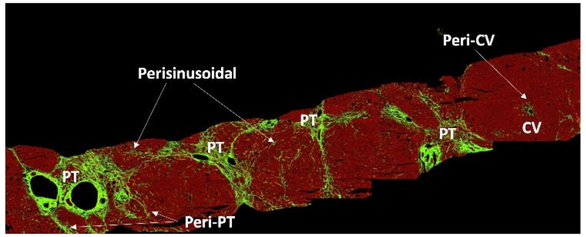
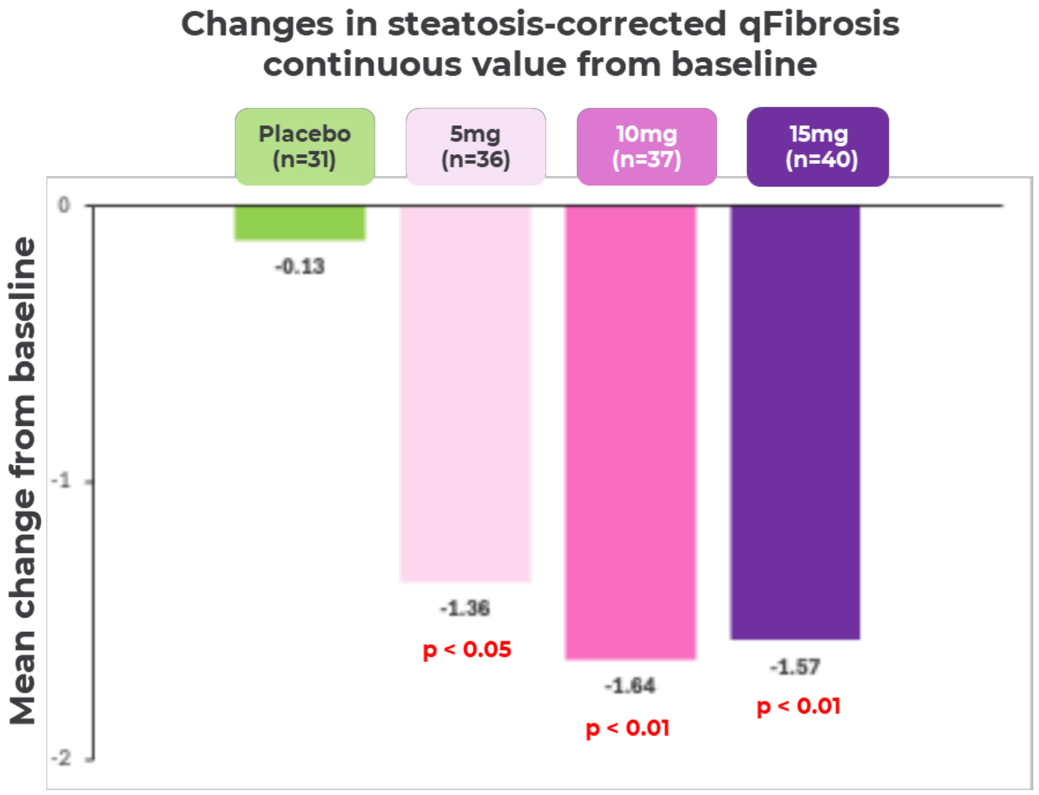






KEY RESULTS

Changes in qFibrosis (steatosis-corrected) at Week 52



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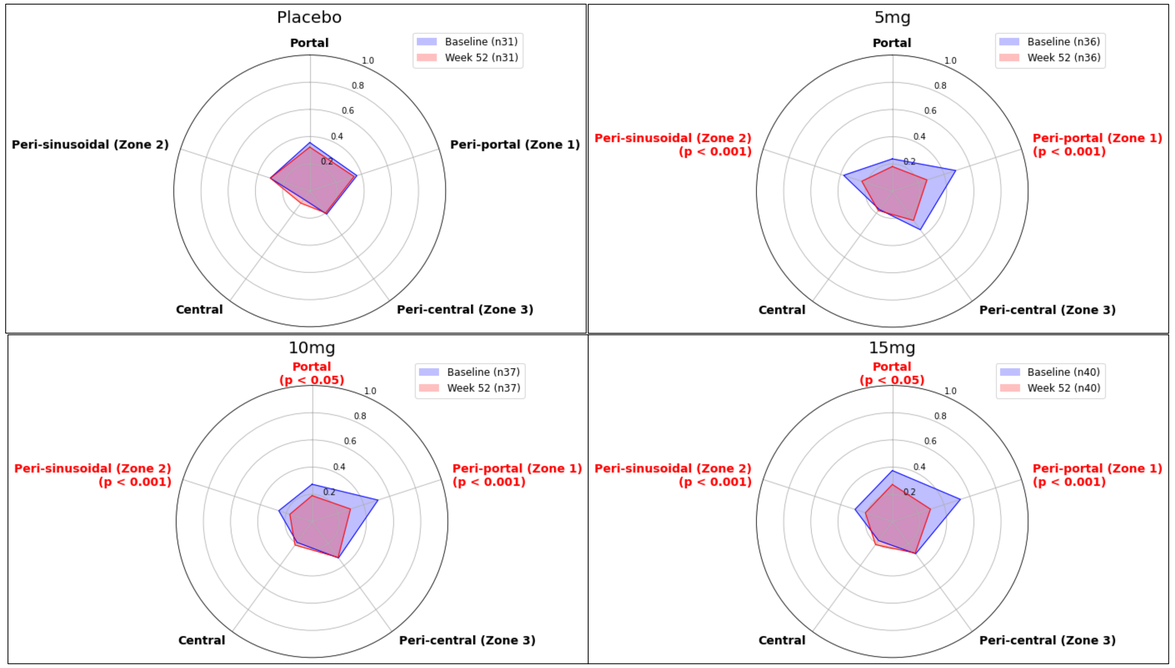
p values vs placebo were obtained with student's t tests.

KEY RESULTS

Radar plots showing zonal changes in fibrosis (steatosis-corrected)

All participants



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KEY RESULTS

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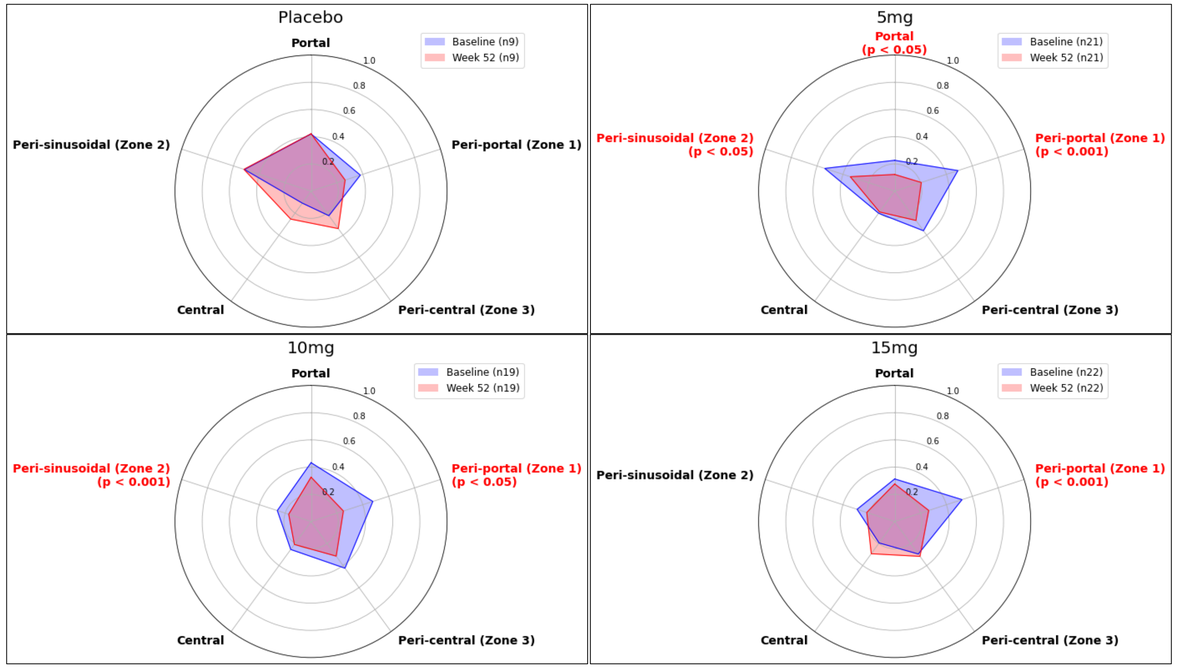
Participants with ≥1 stage decrease in fibrosis by pathologists

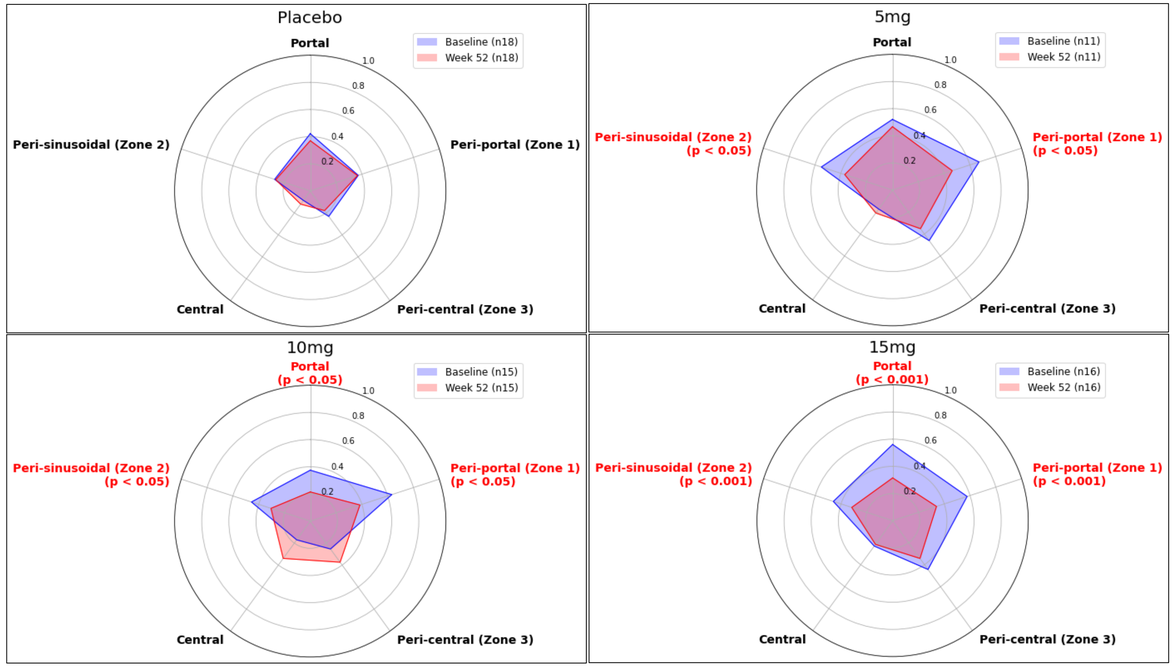


Among participants with ≥1 NASH CRN stage decrease in fibrosis, statistically significant fibrosis regression with tirzepatide was seen in zone 1, zone 2 and the portal zone with 5 mg, zones 1 and 2 with 10 mg and zone 1 with 15 mg (denoted in red). No significant changes were observed in zone 3 and the central zone.

KEY RESULTS

Radar plots showing zonal changes in fibrosis (steatosis-corrected)

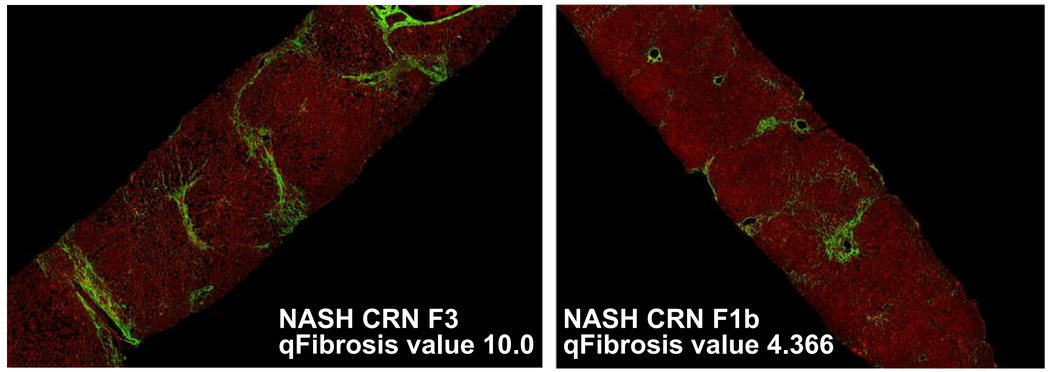
Participants with no change in fibrosis by pathologists



Participants with no change in NASH CRN fibrosis stage showed statistically significant fibrosis regression in zone 1 and zone 2 with tirzepatide 5 mg, and in zone 1, zone 2, and the portal zone with tirzepatide 10 mg and 15 mg (denoted in red). No significant changes were observed in zone 3 and the central zone.

RESULTS: Case Examples

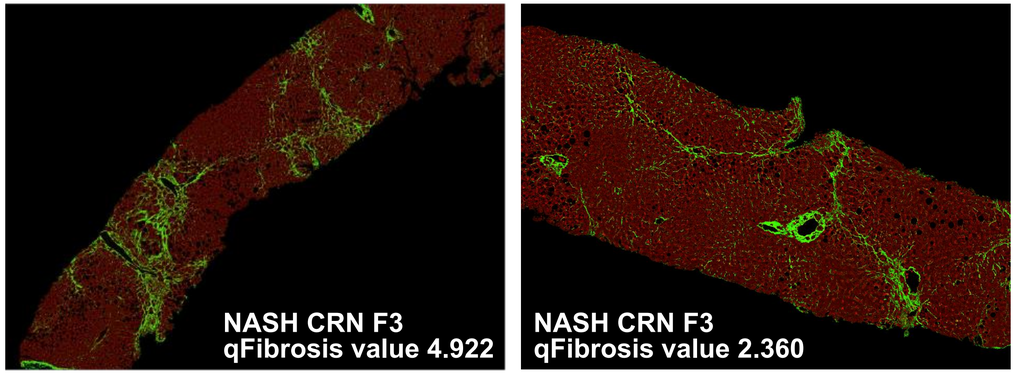
Fibrosis regression from F3 to F1b per central pathologists



Baseline Week 52

Tirzepatide 15 mg

No change in fibrosis stage (F3) per central pathologists



Baseline Week 52

Tirzepatide 15 mg

CONCLUSION

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