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# Effects of Resmetirom on Metabolic-Dysfunction Associated Steatohepatitis in Patients With Weight Loss and/or Diabetes Taking Glucagon-Like Peptide-1 Receptor Agonists and Other Diabetes Therapies: A Secondary Analysis of the MAESTRO-NASH Trial

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## ABSTRACT

**Background:** MAESTRO-NASH, a randomised, double-blind, placebo-controlled, 54-month phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed metabolic-dysfunction associated steatohepatitis (MASH) and liver fibrosis achieved primary endpoints of MASH resolution with no worsening of fibrosis, and ≥1-stage improvement in fibrosis with no worsening of MASH at 52-weeks.

**Aims:** The effects of resmetirom (80 or 100 mg) versus placebo were evaluated on Week 52 histological and biomarker endpoints in relation to background treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i), GLP-1 receptor agonists (GLP-1 RA), and/or ≥5% weight loss at Week 52.

**Methods:** At baseline, 13%–17% of patients (all with type 2 diabetes mellitus [T2DM]) were on stable GLP-1 RA or SGLT2i therapy. Changes in liver histology, MRI-proton density fat fraction (MRI-PDFF), and liver stiffness were examined after 52 weeks of treatment.

**Results:** No weight loss above baseline occurred with GLP-1 RA or SGLT2i therapy. SGLT2 and GLP-1 RA treated patients showed similar rates of MASH resolution and fibrosis improvement in combination with resmetirom as patients not on these therapies. Resmetirom-treated patients (100 mg) with weight loss (≥5%) compared with those with weight loss <5% had higher rates of MASH resolution (56.6% vs. 33.8%), fibrosis improvement (40.6% vs. 31.5%), MRI-PDFF reduction (−69% vs. −46%), and liver stiffness reduction after 52 weeks of treatment (−4.6 kPa vs. −2.3 kPa).

**Conclusions:** The efficacy of resmetirom on multiple MASH endpoints was not impacted by background SGLT2i or GLP-1 RA treatment. Weight loss (≥5%) enhanced the efficacy of resmetirom.

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**Trial Registration:** MAESTRO-NASH ClinicalTrials.gov number, NCT03900429

## 1 | Introduction

Metabolic dysfunction-associated steatohepatitis (MASH, formerly known as nonalcoholic steatohepatitis [NASH] [1]) is the active, progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as nonalcoholic fatty liver disease [NAFLD]), defined as the presence of 5% or more hepatic steatosis with inflammation and hepatocyte injury (e.g., ballooning), with or without fibrosis [2]. MASH is associated with increased cardiovascular risk, including cardiovascular death [3]. Additionally, patients with MASH with more advanced fibrosis (F3, F4) have increased liver-related morbidity and mortality, especially in the setting of cirrhosis, where the development of hepatocellular carcinoma and liver decompensation result in a common indication for liver transplantation [4–7]. MASH imparts a significant economic burden on the healthcare system, with an estimated 6.65 million patients with MASH in the United States alone [8]. The number of cases of MASH with clinically significant fibrosis in the United States is expected to increase to 11.7 million by 2050 [9].

Thyroid hormone receptor (THR)-β, which is preferentially expressed in the liver relative to THR-α [10], mediates beneficial actions in MASH such as de-lipidation of the liver, improvement in hepatic mitochondrial function and biogenesis [11], and reduction of liver inflammation and fibrosis [12]. Resmetirom, a liver-directed THR-β selective agonist [13], was approved in 2024 by the Food and Drug Administration according to subpart H criteria for the treatment of adults with MASH with moderate to advanced liver fibrosis (consistent with F2–F3), based on the resolution of MASH and improvement in liver fibrosis at Week 52 in the MAESTRO-NASH trial [14]. MAESTRO-NASH is ongoing and will assess clinical benefit at 54 months. Phase 1, 2 and 3 trials with resmetirom have demonstrated reduction of hepatic and/or circulating lipids in healthy volunteers [15], familial hypercholesterolemia [16], MASLD [17], and patients with MASH [14, 18]. These studies demonstrated resmetirom's safety, and also that selectivity for THR-β and liver targeting led to the absence of toxicities on heart and bone associated with THR-α.

Glucagon-like peptide-1 (GLP-1) receptor agonists (RA) such as liraglutide [19] and semaglutide [20], and other GLP-1 RA combinations (e.g., with glucose-dependent insulinotropic polypeptide [21] or glucagon [22] receptor agonists) have been investigated in phase 2 trials with positive effects in patients with MASH and fibrosis. Semaglutide recently demonstrated improvements in both resolution of steatohepatitis and fibrosis reduction in a phase 3 MASH trial [23] and recently received accelerated approval by the Subpart H mechanism in the US for the treatment of noncirrhotic MASH with moderate to advanced liver fibrosis. Because GLP-1 receptors are not expressed in liver [24], the potential mechanism of action in MASH relates to indirect actions to reduce body weight, insulin resistance, and metabolic dysfunction [25]. Beneficial effects of weight loss through lifestyle modification or bariatric surgery on biomarkers and histology have been shown across the spectrum of MASLD/MASH [26–28]. Other T2DM therapies including SGLT2i and pioglitazone have shown beneficial effects in patients with MASH [29, 30].

In this randomised, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed MASH and fibrosis, a pre-specified analysis of the effects of resmetirom (80 or 100 mg) or placebo on a background of stable GLP-1 baseline therapy (for at least 6 months prior to randomization) or sodium-glucose cotransporter 2 inhibitors (SGLT2i) therapy and the effect of ≥ 5% weight loss on liver histology endpoints was evaluated.

## 2 | Methods

### 2.1 | Clinical Trial Information

This study used liver biopsy samples from the Phase 3, double-blinded, randomised, placebo-controlled MAESTRO-NASH trial (NCT03900429) in adults with biopsy-confirmed MASH. The design, eligibility criteria, and results have been reported elsewhere. Briefly, patients were selected for screening based on having three or more metabolic risk factors and a FibroScan VCTE of ≥ 8.5 or an eligible recent liver biopsy. As defined in the statistical analysis plan, the primary analysis population included 966 patients with baseline fibrosis stages of F1B (moderate fibrosis), F2 (moderate fibrosis), or F3 (advanced fibrosis) and meeting criteria for NASH (NAFLD Activity Score ≥ 4) based on central pathologist scoring from two readers [31]. As noted [14], the protocol, which is available along with the statistical analysis plan with the full text of this article at NEJM.org, was approved by the institutional review board and ethics committee at each participating site. The trial was and continues to be conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all relevant regulations. All patients provided written informed consent. Of the 966 randomised patients, 647 had type 2 diabetes mellitus (T2DM) and 319 did not. Weight was required to be stable (< 5% change in 3 months). Doses of GLP-1 RA and SGLT2i were required to be stable for ≥ 6 months and ≥ 30 days, respectively, prior to eligibility biopsy. All patients on GLP-1 RA or SGLT2i were on doses approved for T2DM during the conduct of the trial. The study population is shown in Figure 1.

### 2.2 | Statistical Analysis

Descriptive statistics (percentages, means with standard deviation [SD], medians [Q1, Q3], and least squared [LS] means with 95% confidence intervals [CI]) were provided to summarise data. A mediation analysis was conducted to separate the contributions of percent change in weight at Week 52 and study treatment (resmetirom vs. placebo) for NASH resolution and fibrosis improvement. Odds ratios and 95% confidence intervals were estimated for percent change in body weight and direct treatment effect and their combined effect using the logistic regression method described by Samoilenko et al. [32] using the

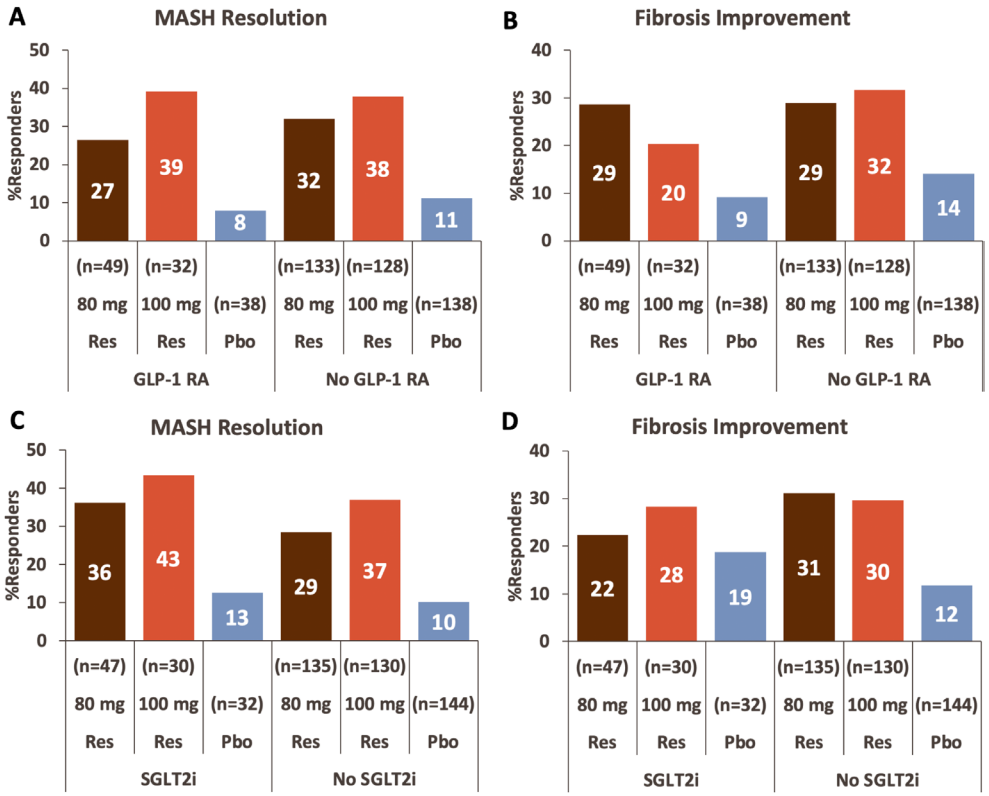


**FIGURE 1** | MASH resolution with no worsening of fibrosis and fibrosis improvement (reduction by at least one stage with no worsening of the MASH) in T2DM patients in presence or absence of GLP-1 RA (A and B) or SGLT2i (C and D). Pbo, placebo; Res, resmetirom.

R package 'ExactMed'. Baseline characteristics are provided for the primary population. Tables show effects in the primary population and the biopsy completer population (patients with both a baseline and week 52 biopsy).

## 3 | Results

### 3.1 | Patients

The demographic and clinical characteristics of randomised patients ($n = 966$) at baseline according to T2DM and T2DM treatments GLP-1 RA, SGLT2i, insulin, and pioglitazone use are shown in Table 1. Patients taking GLP-1 RAs were required to be on stable doses for at least 6 months; doses of other T2DM medications could be modified up to 30 days prior to randomization in order to achieve optimal HbA1c control. Mean HbA1c was 7.0% at baseline in the patients with T2DM, and there was little change during the study [14]. At baseline, 13%–17% of patients (all of whom had T2DM) in the treatment groups were on stable T2DM doses of GLP-1 RA (80 mg resmetirom, $n = 54$; 100 mg resmetirom, $n = 41$; placebo, $n = 42$). The most common were various doses of liraglutide (~15%), 0.5 to 1 mg semaglutide (~25%), and 0.75 to 1.5 mg dulaglutide (~33%). Another T2DM therapy associated with weight loss and potential benefit in MASH included 11%–17% of patients on SGLT2i (80 mg resmetirom, $n = 55$; 100 mg resmetirom, $n = 39$; placebo, $n = 36$), with stable treatment. In the randomised population, 39 patients were on both a GLP-1 RA and SGLT2i, 34 of whom had biopsies at Week 52 (biopsy completers). Approximately 18% of patients with T2DM were on insulin, and very few were on pioglitazone. At baseline, patients on GLP-1 RA and SGLT2i had a higher percentage of F3 patients (67.9, 67.7 vs. 52.7%) with more metabolic (HbA1c: 7.1 or 7.2 vs. 5.7%) and cardiovascular features (hypertension: 84.7, 87.7 vs. 67.4%; dyslipidemia: 85.4 or 84.6 vs. 54.2%); more common statin use (61.3 or 66.2 vs. 30.4%); and at baseline, lower LDL-C and liver enzymes (ALT: 45.6 or 48.3 vs. 62.1 U/L; AST: 34.3 or 34.7 vs. 45.7 U/L) than non-diabetic patients. There were no differences in baseline body weight (103.7 vs. 99.7 kg) or MRI-PDFF (16.5 vs. 16.1%), and no meaningful differences in other baseline characteristics between patients on GLP-1 RA or SGLT2i therapy. Patients on insulin therapy had generally poorer T2DM control, with only 30% achieving HbA1c ≤ 7% at baseline compared to 57% in the combined population of patients with T2DM.

### 3.2 | Effects of T2DM Treatments on Week 52 Histology and MRI-PDFF Endpoints

An intention-to-treat analysis in which patients with missing Week 52 biopsies are considered non-responders demonstrated consistent relative responses (Tables in Supplement) and did not demonstrate an increase in discontinuations in any group.

Patients on GLP-1 RA ($n = 81$) had 26.5% (placebo-corrected % difference [95% CI], 16.9% [1.9%, 31.9%]) and 39.1% (30.5% [12.8%, 48.3%]) response rates for MASH resolution in the resmetirom 80 and 100 mg treatment groups, respectively (Figure 1A; Table S1), compared with resmetirom patients not on GLP-1 RA ($n = 261$): 32.0% (21.3% [12.4%, 30.1%]) and 37.9% (28.3%

**TABLE 1** | Demographic and clinical characteristics of primary population and subgroups at baseline.

| | No T2DM (*N* = 319) | T2DM (*N* = 647) | GLP-1 RA (*N* = 137) | SGLT2i (*N* = 130) | Insulin (*N* = 118) | ≥ 5% Weight loss at week 52 (*N* = 141) | < 5% Weight loss at week 52 (*N* = 695) |
|---|---|---|---|---|---|---|---|
| Age (years) Mean (SD) | 53.7 (12.3) | 58.1 (9.9) | 56.2 (9.2) | 58.3 (8.6) | 58.2 (9.4) | 56.8 (10.8) | 56.6 (10.7) |
| Female *n* (%) | 170 (53.3) | 372 (57.5) | 84 (61.3) | 69 (53.1) | 68 (57.6) | 88 (62.4) | 380 (54.7) |
| White *n* (%) | 294 (92.2) | 569 (87.9) | 123 (89.8) | 111 (85.4) | 108 (91.5) | 126 (89.4) | 618 (88.9) |
| Hispanic or Latino *n* (%) | 63 (19.7) | 141 (21.8) | 23 (16.8) | 30 (23.1) | 21 (17.8) | 29 (20.6) | 149 (21.4) |
| T2DM *n* (%) | 0 | 647 (100) | 137 (100) | 130 (100) | 118 (100) | 100 (70.9) | 457 (65.8) |
| Duration of T2DM (years) Median (Q1, Q3) | 0 | 6.2 (2.9, 11.9) | 8.7 (5.0, 14.1) | 9.0 (5.2, 15.7) | 11.6 (6.4, 20.2) | 6.8 (2.0, 10.5) | 6.8 (3.1, 12.3) |
| Hypertension *n* (%) | 215 (67.4) | 539 (83.3) | 116 (84.7) | 114 (87.7) | 101 (85.6) | 103 (73.0) | 559 (80.4) |
| Dyslipidemia *n* (%) | 173 (54.2) | 516 (79.8) | 117 (85.4) | 110 (84.6) | 105 (89.0) | 99 (70.2) | 499 (71.8) |
| Thyroxine replacement *n* (%) | 40 (12.5) | 90 (13.9) | 25 (18.2) | 17 (13.1) | 17 (14.4) | 21 (14.9) | 87 (12.5) |
| Statin *n* (%) | 97 (30.4) | 376 (58.1) | 84 (61.3) | 86 (66.2) | 83 (70.3) | 64 (45.4) | 349 (50.2) |
| GLP-1 RA *n* (%) | n/a | 137 (21.2) | 137 (100) | 39 (30.0) | 44 (37.3) | 20 (14.2) | 103 (14.8) |
| SGLT2i *n* (%) | n/a | 130 (20.1) | 39 (28.5) | 130 (100) | 38 (13.6) | 15 (10.6) | 100 (14.4) |
| GLP-1 RA and SGLT2i *n* (%) | 0 | 39 (6.0) | 39 (28.5) | 39 (30.0) | 16 (13.6) | 4 (2.8) | 31 (4.5) |
| Duration of GLP-1 RA or SGLT2i (days) Median (Q1, Q3) | n/a | n/a | 660 (375, 1229) | 651 (284, 811) | n/a | n/a | n/a |
| Pioglitazone *n* (%) | 0 | 11 (1.7) | 1 (0.7) | 3 (2.3) | 1 (0.8) | 1 (0.7) | 8 (1.2) |
| Insulin *n* (%) | 0 | 118 (18.2) | 44 (32.1) | 38 (29.2) | 118 (100) | 9 (6.4) | 92 (13.2) |
| Weight (kg) Mean (SD) | 101.5 (22.8) | 100.3 (22.7) | 103.7 (24.3) | 99.7 (22.4) | 102.6 (22.8) | 100.3 (24.4) | 99.9 (21.9) |
| BMI (kg/m$^2$) Mean (SD) | 35.4 (6.8) | 35.8 (6.8) | 36.6 (6.9) | 35.4 (6.1) | 36.3 (6.4) | 35.6 (7.2) | 35.4 (6.5) |
| LDL-C (mg/dL) Mean (SD) | 118.5 (38.4) | 99.0 (36.9) | 93.8 (34.6) | 94.6 (39.0) | 95.9 (40.1) | 106.4 (40.3) | 105.2 (38.6) |
| HOMA-IR Mean (SD) | 9.4 (8.8) | 12.0 (11.7) | 12.9 (12.0) | 9.3 (5.9) | 11.7 (11.4) | 13.9 (16.9) | 10.5 (9.0) |

(Continues)

**TABLE 1** | (Continued)

| | No T2DM ($N=319$) | T2DM ($N=647$) | GLP-1 RA ($N=137$) | SGLT2i ($N=130$) | Insulin ($N=118$) | ≥5% Weight loss at week 52 ($N=141$) | <5% Weight loss at week 52 ($N=695$) |
|---|---|---|---|---|---|---|---|
| HbA1c (%) Mean (SD) | 5.7 (0.6) | 7.0 (1.0) | 7.4 (1.0) | 7.2 (1.0) | 7.6 (0.9) | 6.6 (1.1) | 6.5 (1.1) |
| HbA1c ≤ 7% *n* (%) | 0 | 370 (57.2) | 71 (51.8) | 62 (47.7) | 35 (29.7) | 63 (63.0) | 258 (56.5) |
| 10-year ASCVD Risk Score Mean (SD) | 9.5 (7.4) | 17.5 (12.7) | 14.5 (10.8) | 16.0 (10.6) | 18.4 (13.6) | 14.8 (11.3) | 14.8 (11.9) |
| Creatinine (mg/dL) Mean (SD) | 0.81 (0.2) | 0.78 (0.2) | 0.75 (0.2) | 0.77 (0.2) | 0.78 (0.2) | 0.79 (0.20) | 0.78 (0.19) |
| eGFR (mL/min/1.73$^2$) Mean (SD) | 97.8 (22.6) | 98.5 (23.0) | 100.5 (23.5) | 99.4 (23.1) | 97.9 (23.5) | 96.1 (24.0) | 99.1 (22.7) |
| hsCRP (mg/L) Median (Q1, Q3) | 3.5 (1.7, 6.6) | 3.4 (1.5, 7.0) | 3.3 (1.4, 6.2) | 3.9 (1.7, 6.0) | 4.3 (1.9, 7.2) | 3.4 (1.6, 8.0) | 3.3 (1.5, 6.5) |
| ELF Mean (SD) | 9.7 (0.9) | 9.5 (0.8) | 9.5 (0.8) | 9.7 (0.8) | 9.7 (0.8) | 9.8 (0.9) | 9.7 (0.9) |
| FibroScan VCTE (kPa) Median (Q1, Q3) | 11.0 (9.1, 14.6) | 12.0 (9.7, 15.5) | 12.0 (9.8, 15.5) | 11.2 (9.6, 13.9) | 11.9 (9.6, 14.6) | 11.9 (9.2, 14.7) | 11.4 (9.4, 14.9) |
| FibroScan CAP (dB/m) Mean (SD) | 342.1 (39.6) | 350.3 (36.4) | 351.8 (36.2) | 348.8 (36.1) | 355.6 (34.8) | 346.1 (39.1) | 347.9 (38.0) |
| MRI-PDFF (%) Mean (SD) | 18.4 (7.0) | 17.4 (6.6) | 16.5 (6.0) | 16.1 (6.5) | 16.4 (6.1) | 17.6 (6.8) | 17.8 (6.7) |
| MRE (kPa) Median (Q1, Q3) | 3.3 (2.7, 3.9) | 3.5 (2.9, 4.2) | 3.4 (3.0, 4.0) | 3.4 (3.0, 4.1) | 3.3 (2.9, 4.0) | 3.4 (3.0, 4.0) | 3.4 (2.8, 4.0) |
| ALT (U/L) Mean (SD) | 61.2 (36.3) | 51.3 (29.4) | 45.3 (22.2) | 47.9 (23.1) | 45.6 (22.1) | 54.2 (29.5) | 54.6 (32.3) |
| AST (U/L) Mean (SD) | 45.1 (25.3) | 38.2 (21.8) | 33.7 (16.4) | 34.4 (14.2) | 35.1 (16.8) | 40.0 (19.9) | 40.3 (23.6) |
| NAS at screening, ≥ 5 *n* (%) | 263 (82.4) | 544 (84.1) | 110 (80.3) | 101 (77.7) | 99 (83.9) | 121 (85.8) | 578 (83.2) |
| Fibrosis stage at baseline *n* (%) | | | | | | | |
| 1B | 16 (5.0) | 33 (5.1) | 6 (4.4) | 4 (3.1) | 8 (6.8) | 7 (5.0) | 35 (5.0) |
| 2 | 130 (40.8) | 189 (29.2) | 35 (25.5) | 37 (28.5) | 32 (27.1) | 42 (29.8) | 225 (32.4) |
| 3 | 168 (52.7) | 415 (64.1) | 93 (67.9) | 88 (67.7) | 77 (65.3) | 92 (65.2) | 422 (60.7) |
| 4 | 5 (1.6) | 10 (1.5) | 3 (2.2) | 1 (0.8) | 1 (0.8) | 0 | 13 (1.9) |

Abbreviations: ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; HbA1c, haemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; kPa, kilopascals; LDL-C, low-density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, NAFLD activity score; T2DM, type 2 diabetes mellitus; VCTE, vibration controlled transient elastography.

[19.4%, 37.3%]). Resmetirom patients on GLP-1 RA had 28.6% (18.5% [3.8%, 33.2%]) and 20.3% (10.5% [−4.2%, 25.2%]) response rates for fibrosis improvement compared with resmetirom patients not on GLP-1 RA: 28.9% (14.9% [6.1%, 23.7%]) and 31.6% (17.6% [8.8%, 26.4%]), (Figure 1B). Patients on SGLT2i ($n = 77$) had 36.2% (24.3% [6.0%, 42.5%]) and 43.3% (31.1% [11.6%, 50.6%]) response rates for MASH resolution in the 80 and 100 mg resmetirom groups, respectively, compared with resmetirom patients not on SGLT2i ($n = 265$): 28.5% (18.5% [10.1%, 26.8%]) and 36.9% (28.4% [19.7%, 37.2%]), Figure 1C, Table S2. Resmetirom patients on SGLT2i had 22.3% (3.3% [−13.0%, 19.7%]) and 28.3% (9.2% [−9.1%, 27.5%]) response rates for fibrosis improvement compared with resmetirom patients not on SGLT2i: 31.1% (19.3% [10.8%, 27.7%]) and 29.6% (18.1% [9.8%, 26.4%]), (Figure 1D). In the 80 and 100 mg resmetirom groups, respectively, patients on insulin ($n = 93$) compared to those not on insulin ($n = 425$) had somewhat lower response rates for MASH resolution (15.6% and 28.1% vs. 33.7% and 40.6%) and fibrosis improvement (20.3% and 25.0% vs. 30.7% and 30.5%, Table S3). Thirty-nine patients were on both GLP-1 RA and SGLT-2i and showed no meaningful differences in response from patients with T2DM on either alone or on background therapy.

Resmetirom's fibrosis and MASH responses on biopsy correlated with MRI-PDFF reduction [14]. Comparison of resmetirom's efficacy to decrease MRI-PDFF in patients without T2DM versus patients with T2DM, patients on or not on GLP-1 RA, SGLT2i, or insulin had similar decreases in MRI-PDFF in all comparisons (Figure 2; Table S4).

### 3.3 | Safety and Tolerability Evaluated in Patients According to GLP-1 RA Therapy

No notable differences in safety and tolerability were observed between treatment groups on a GLP-1RA or not on a GLP-1RA. Expected gastrointestinal adverse events such as diarrhoea and nausea were generally higher in the resmetirom groups independent of GLP-1RA use (Table S5).

### 3.4 | Impact of Weight Loss on Week 52 Histology, MRI-PDFF and VCTE Endpoints

Weight loss has been shown to improve responses on liver biopsy in patients with MASH, including patients treated with resmetirom [14, 18]. Reflecting that GLP-1 RA therapy was stable (at least 6 months), the percentages of patients on GLP-1 RA treatment in MAESTRO-NASH with ≥5% (14%) and <5% (16%) weight loss were equivalent. Week 52 median body weight changes in patients on GLP-1 RA were −1.8%, −1.5% and −1.9% in placebo, 80 mg, and 100 mg, respectively. Week 52 median body weight changes in patients on SGLT2i were −1.9%, −0.5%, and −2.3% in placebo, 80 and 100 mg, respectively. Patients on insulin had a numerically smaller fraction (~10%) who lost ≥5% body weight.

The numbers of patients who lost ≥5% weight in the study according to treatment were evaluated. The percentages of patients with ≥5% weight loss in the placebo, 80 and 100 mg of resmetirom groups were 12.7% (35 of 276), 17.1% (44 of 258), and 21.4% (53 of 248), respectively. The median weight loss was 7% in the ≥5% weight loss groups.

In the 80 and 100 mg resmetirom groups, respectively, patients achieving ≥5% weight loss had 50.0% (placebo-corrected % difference [95% CI], 22.0% [2.9%, 41.2%]) and 56.6% (28.4% [10.3%, 46.5%]) response rates for MASH resolution (Figure 3A; Table S6) compared to resmetirom patients with <5% weight loss who had 27.6% (20.4% [14.1%, 26.7%]) and 33.8% (26.5% [20.1%, 32.9%]) response rates for MASH resolution (Figure 3B). In the 80 and 100 mg resmetirom groups, respectively, patients achieving ≥5% weight loss had 38.6% (11.2% [−6.8%, 29.1%]) and 40.6% (12.0% [−5.0%, 29.0%]) response rates for fibrosis improvement compared to patients with <5% weight loss who had 27.6% (13.0% [6.3%, 19.7%]) and 31.5% (16.7% [9.9%, 23.5%]) response rates for fibrosis improvement. Achieving ≥5% weight loss in the placebo group resulted in 31.4% and 27.1% response rates for MASH resolution and fibrosis improvement, respectively, compared to placebo patients with <5% weight loss who had 7.9% and 14.9% response rates for MASH resolution and fibrosis improvement, respectively.

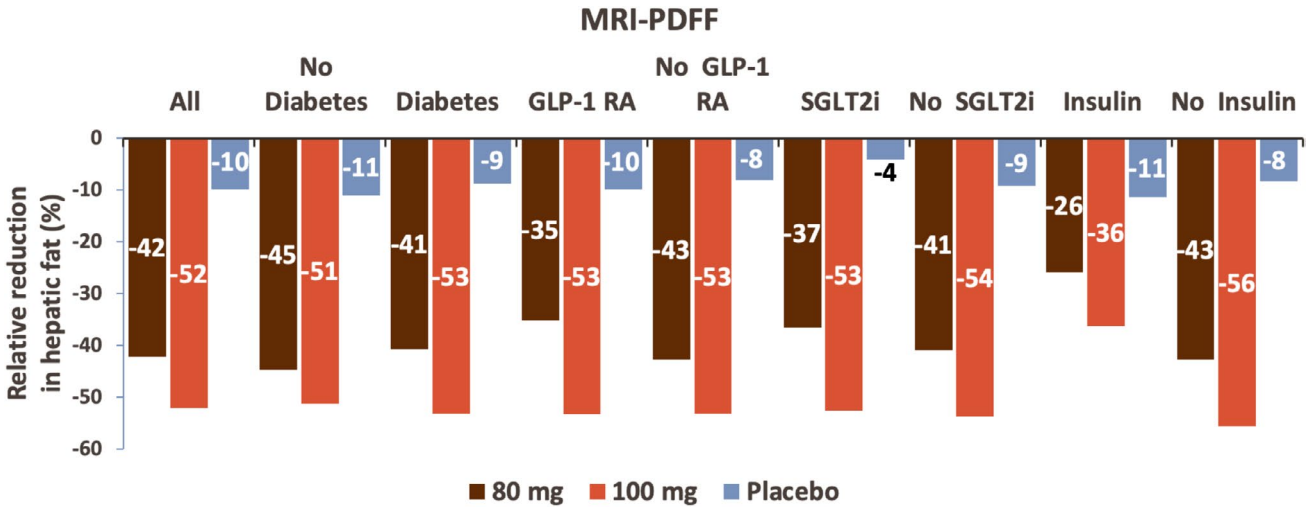


**FIGURE 2** | Relative (median) hepatic fat reduction at Week 52 in various subgroups of patients on resmetirom (80 or 100 mg) or placebo. See Table S4 for Ns.

A mediation analysis revealed that the percent change in weight at Week 52 does not contribute to the benefits of resmetirom relative to placebo on MASH resolution (odds ratio [95% CI], 1.08 [1.00, 1.17]) or fibrosis improvement (1.04 [0.99, 1.09], Figure 3C and Table 2). Both doses of resmetirom maintained favorable differences on MASH resolution and fibrosis improvement with < 5% weight gain (Table S7). The small numbers of patients with ≥ 5% weight gain precluded an assessment; however, the 100 mg dose appeared to maintain a difference from placebo for MASH and fibrosis improvement.

Both doses of resmetirom elicited reductions in MRI-PDFF relative to placebo, independent of weight loss (Table S8). Patients achieving ≥ 5% weight loss showed additional reductions in MRI-PDFF between Weeks 16 and 52 irrespective of treatment (Figure 4A; Table S8), whereas patients who achieved < 5% weight loss showed no further reductions in MRI-PDFF at Week 52 compared with Week 16 in any treatment groups (Figure 4C). In the resmetirom groups, 90.9% and 97.7% of patients (40 of 44 and 52 of 53 patients in the 80 and 100 mg groups, respectively) who achieved ≥ 5% weight loss had a ≥ 30% reduction in MRI-PDFF (Figure 4B). In the resmetirom groups, 72.7%–87.8% of patients (32 of 44 and 47 of 53 patients in the 80 and 100 mg groups, respectively) who achieved ≥ 5% weight loss had a ≥ 50% reduction in MRI-PDFF (Table S6) by Week 52.

Both doses of resmetirom elicited reductions in liver stiffness measurements (VCTE) relative to placebo, independent of weight loss [14], but percentages with reductions were greater in patients who achieved ≥ 5% weight loss (Figure 5A; Table S9). A responder analysis for patients achieving ≥ 5% weight loss showed that 43.9% (18 of 41 patients), 64.7% (33 of 51 patients), and 54.5% (18 of 33 patients) in the 80 mg resmetirom, 100 mg resmetirom, and placebo groups, respectively, achieved a 25% reduction in VCTE (Figure 5B). For patients achieving < 5% weight loss, 43.9% (86 of 196 patients), 44.8% (82 of 183 patients), and 25.3% (56 of 221 patients) in the 80 mg resmetirom, 100 mg resmetirom, and placebo groups, respectively, achieved a ≥ 25% reduction in VCTE.

Evaluation of other markers such as hsCRP, which is elevated in patients with obesity and MASH (Table 1), showed a trend to reduction in hsCRP in patients with ≥ 5% weight loss relative to patients without 5% weight loss that was independent of treatment with any T2DM agent, resmetirom, or placebo.

## 4 | Discussion

Approximately 2/3 of patients with biopsy-confirmed MASH with moderate to advanced liver fibrosis also have T2DM [33], as reflected in the MAESTRO-NASH baseline population

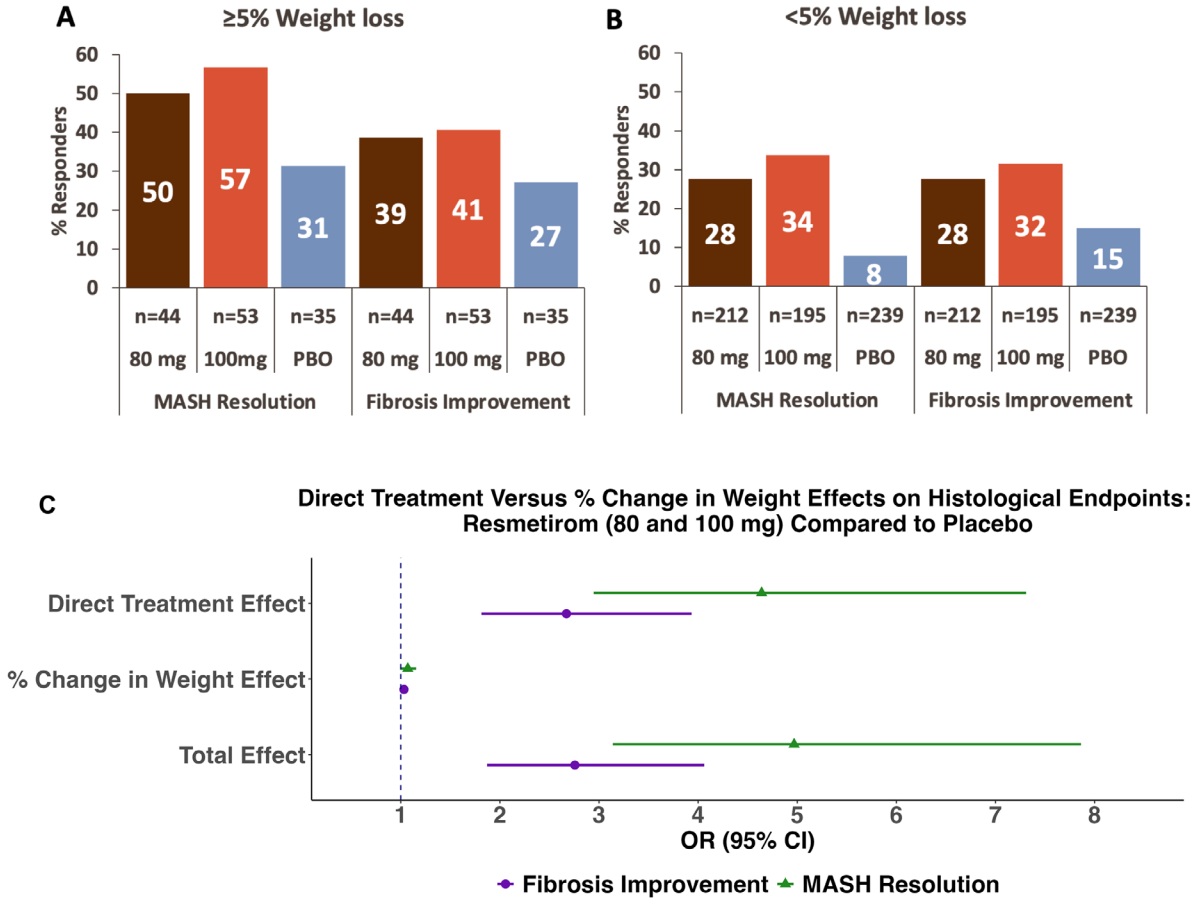


**FIGURE 3** | MASH resolution with no worsening of fibrosis and fibrosis improvement (reduction by at least one stage with no worsening of MASH) in patients with (A) or without (B) ≥ 5% weight loss, and mediation analysis: Odds ratios (OR) with 95% confidence intervals for the total effect of resmetirom versus placebo, as well as the direct treatment effect and the indirect effect mediated through the percent change in weight at Week 52 on both MASH resolution and fibrosis improvement (C). CI, confidence interval; OR, odds ratio; Pbo, placebo.

characteristics. Of those patients with T2DM in MAESTRO-NASH, 21% were on stable treatment with a GLP-1 RA, 20% with an SGLT2i, a small number were on both, and about 18% were on insulin. T2DM was reasonably controlled at baseline and throughout the 52-week study with a mean HbA1c at baseline of 7.0% and 57% with baseline HbA1c ≤7% [14] and there were no differences between the resmetirom and placebo groups. Of note, given the long duration of the MAESTRO-NASH trial, the eligible and enrolled population were excluded from having advanced cardiovascular or renal disease, including heart failure or renal failure. Nonetheless, ASCVD risk scores were high, denoting significant CV risk, a known comorbidity of MASH. Resmetirom significantly lowers atherogenic lipids as well as steatosis and inflammation and has the potential to provide CV benefit in MASH patients, particularly those with T2DM who have elevated CV risk. Both SGLT2i and GLP-1 RA have been shown to provide long-term CV and renal benefits, including lowering of events in cardiovascular outcome trials and reducing progression of heart failure and renal disease [34, 35]. The safe and efficacious use of combinations of these agents with resmetirom is an important outcome of this subpopulation analysis.

Once MASH progresses to clinically significant fibrosis (stages F2 and F3), the risk of adverse clinical outcomes markedly increases [4–6], especially among patients with T2DM [36]. In MAESTRO-NASH, a sizable proportion of patients on stable GLP-1 RA treatment still had significant MASH (80% with NAS ≥5) and clinically meaningful fibrosis (26% were F2, 68% were F3). Baseline hepatic fat content was not different in patients on GLP-1 RA or SGLT2i therapy. Patients in MAESTRO-NASH were on SGLT2i or GLP-1 RA doses used for T2DM (most T2DM doses of semaglutide or dulaglutide per week). No weight loss above background was observed in the GLP-1 RA or SGLT2i treated patients, and GLP-1 RA and SGLT2i treated patients with T2DM showed similar MASH resolution and fibrosis improvement rates and MRI-PDFF responses in combination with resmetirom as patients with T2DM not on these agents. These results demonstrate that the addition of resmetirom to GLP-1 RA (T2DM doses) or SGLT2i treatment with stable weight has no additional benefits beyond the significant benefits of resmetirom alone.

**TABLE 2** | Mediation analysis of the impact of percent change in weight at Week 52 on MASH resolution and fibrosis improvement comparing resmetirom (combined doses) to placebo treatment.

| Effect on MASH resolution | Resmetirom compared to placebo | |
|---|---|---|
| | OR (95% CI) | Nominal *p* |
| Weight loss independent | 4.64 (2.95, 7.31) | <0.0001 |
| Weight loss dependent | 1.07 (0.99, 1.15) | 0.0762 |
| Total effect | 4.97 (3.14, 7.86) | <0.0001 |
| **Effect on fibrosis improvement** | | |
| Weight loss independent | 2.67 (1.81, 3.93) | <0.0001 |
| Weight loss dependent | 1.03 (0.99, 1.07) | 0.1340 |
| Total effect | 2.76 (1.87, 4.06) | <0.0001 |

*Note:* $N = 777$, five subjects (two in 80 mg resmetirom and three in placebo) were missing Week 52 body weight data.
Abbreviations: CI, confidence interval; OR, odds ratio.

The beneficial effects of weight loss through lifestyle modification on biomarkers and liver histology have been shown across the entire spectrum of MASLD [26, 27]; hence, nutrition and exercise counselling remain part of current non-pharmacological recommendations for the treatment of MASLD/MASH [37]. The observation that patients treated with placebo or resmetirom with ≥5% weight loss had higher response rates for both histological endpoints (compared with patients with <5% weight loss) is in line with evidence that lifestyle modification provides histological benefits. Mediation analysis indicated that resmetirom's improvement in NASH and fibrosis relative to placebo is not mediated by percent change in weight at Week 52. However, in the overall study, ≥5% weight loss was observed more frequently in patients treated with resmetirom when compared with placebo-treated patients, representing approximately 22% of those treated with resmetirom compared with 12% treated with placebo.

For patients treated with resmetirom, a ≥5% weight loss was associated with higher rates of MASH resolution and fibrosis improvement in resmetirom-treated patients compared with resmetirom-treated patients without weight loss, suggesting that relatively small amounts (≥5%) of weight loss enhance the effects of resmetirom on MASH resolution and liver fibrosis improvement. The effects on MRI-PDFF in ≥5% resmetirom weight loss patients were also noteworthy, with more than 95% achieving ≥30% liver fat reduction, a predictive marker for both fibrosis improvement and NASH resolution in resmetirom-treated patients. Non-invasive tests and surrogates for fibrosis improvement, including liver stiffness reduction, also showed robust responses, particularly in patients with ≥5% weight loss on resmetirom. Although the mechanism of resmetirom-mediated enhancement of weight loss relative to placebo is unknown, a hypothetical reduction in the hepatic inflammasome that is elevated in MASH patients [38] could potentiate weight loss. For example, it is known that the anti-inflammatory effects of some diets [39] or medications [40, 41] can help facilitate weight loss.

The 72-week readout of ESSENCE, a phase 3 trial in patients with MASH and F2/F3 fibrosis, demonstrated that a weekly dose of 2.4 mg semaglutide achieved both NASH resolution and fibrosis improvement endpoints [23]. Approximately 10% weight loss was achieved in the semaglutide arm associated with approximately 50% of patients with a 30% reduction of PDFF. In alignment with resmetirom-treated patients who had ≥5% weight loss in MAESTRO-NASH, the combination of resmetirom and higher weight-loss doses of GLP-1 RA may have the potential to achieve additional benefits on MASH with fibrosis compared with either therapy alone.

Limitations of the study that may impact the generalizability of the findings include a relatively small number of subjects in each treatment group on GLP-1 RA, specifically semaglutide, or SGLT2i, and small numbers of patients with weight loss. In addition, only patients stably dosed with SGLT2 or GLP-1 therapies

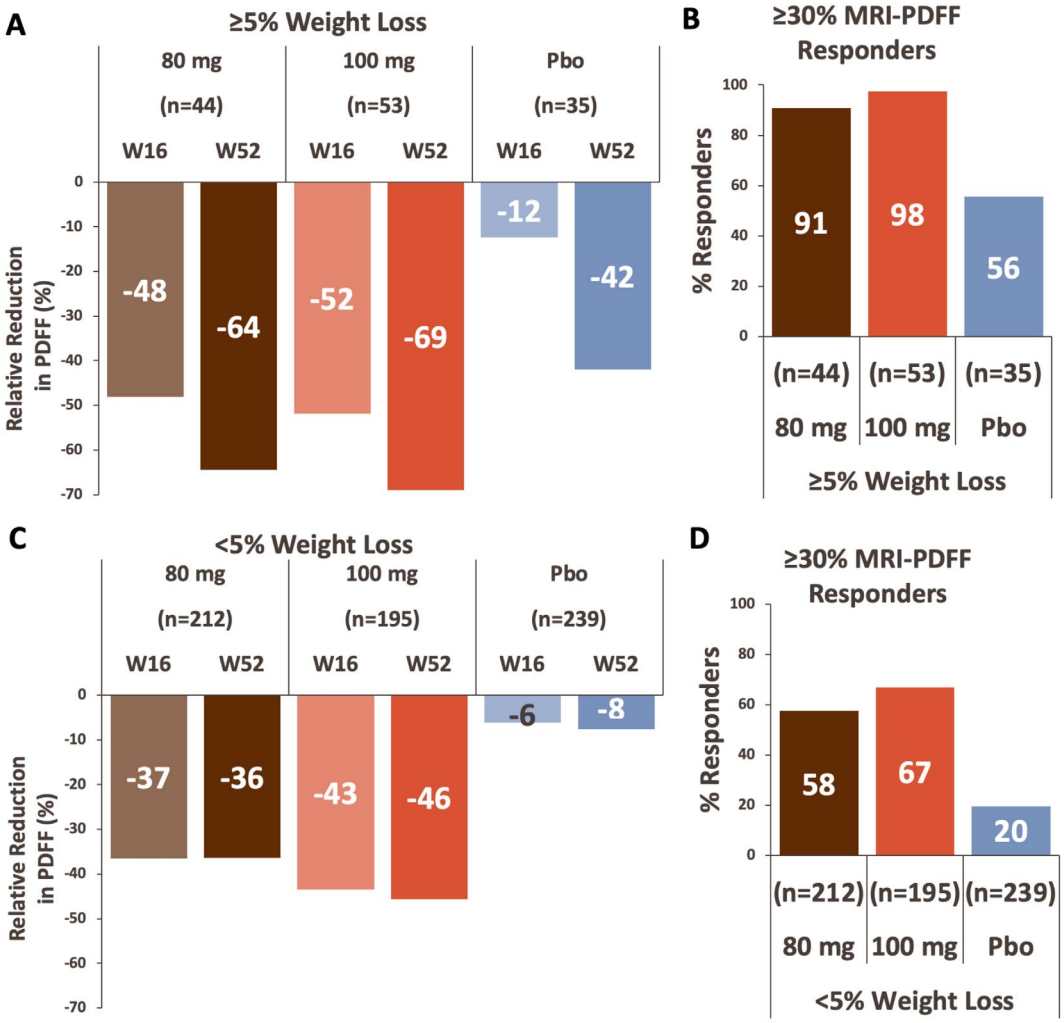


**FIGURE 4** | Relative (median) hepatic fat reduction at weeks 16 and 52 and percentage of patients achieving 30% reduction in hepatic fat in patients on resmetirom (80 or 100 mg) or placebo with ≥ 5% weight loss (A and B) or < 5% weight loss (C and D) at Week 52. Pbo, placebo; W, week.

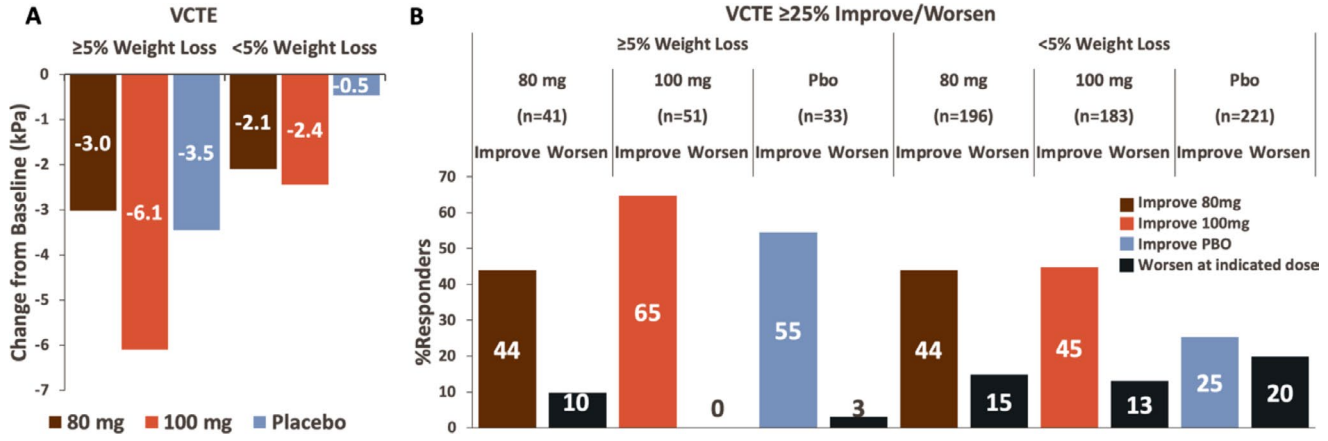


**FIGURE 5** | Absolute Fibroscan VCTE reduction (A) and percentage of patients achieving a ≥ 25% improvement or worsening in VCTE (B) in patients with ≥ 5% or < 5% weight loss at Week 52 according to treatment.

were studied. This was not a combination study in which the simultaneous concomitant de novo treatment of resmetirom and a T2DM agent was tested. Therefore, the effect of weight loss on MASH/fibrosis due to the GLP-1 RA (or SGLT2i) plus resmetirom was not evaluated.

In summary, for patients with T2DM, the rates of MASH resolution and fibrosis improvement were comparable between those who were treated with GLP-1 RA and SGLT2i and resmetirom and those who received resmetirom alone. Relatively small amounts (≥ 5%) of weight loss enhance the effects of resmetirom

on MASH resolution, liver fibrosis improvement, and non-invasive tests of efficacy, suggesting a potential complementary mechanism to increase response rates to resmetirom treatment.

### Author Contributions

**Mazen Noureddin:** writing – review and editing, supervision, conceptualization. **Mary Rinella:** writing – review and editing, supervision. **Rebecca Taub:** conceptualization, methodology, writing – original draft, writing – review and editing, visualization, supervision. **Dominic Labriola:** data curation, formal analysis, visualization, supervision, writing – review and editing. **Raul C. Camacho:** visualization, writing – original draft, writing – review and editing. **Naim Alkhouri:** writing – review and editing, supervision. **Rohit Loomba:** writing – review and editing, supervision, conceptualization. **Meena B. Bansal:** writing – review and editing, supervision.


### Acknowledgements

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### Ethics Statement

The MAESTRO-NASH Study protocol was approved by the institutional review board and ethics committee at each participating site. The MAESTRO-NASH trial was and continues to be conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all relevant regulations.

### Consent

All patients provided written informed consent.

### Conflicts of Interest

M.N. serves on an advisory board/consulting for Akero, Altimmune, Alligos, AstraZeneca, BI, Boston Pharma, Cytodyn, GSK, Lilly, Madrigal, Merck, Novo Nordisk, Sagimet, Terns, and Takeda and as a Principal Investigator for a Drug Study: Allergan, Altimmune, Akero, BI, BMS, Boston Pharma, Conatus, Corcept, Gilead, Galectin, Genfit, GSK, Kowa, Enanta, Madrigal, Lilly, Merck, Novartis, Novo Nordisk, Rivus, Shire, Takeda, Terns, Viking, and Zydus. M.N. is a stockholder of Rivus Pharma and Akero and serves on a speaking bureau for Madrigal. M.R. has served as a scientific consultant in the last 24 months for Akero, 89Bio, Boehringer Ingelheim, Boston Pharmaceuticals, Intercept Pharmaceuticals, Histoindex, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Eli Lilly, Sagimet Biosciences, Sonic Incytes, Cytodyn, GSK. R.T., D.L., and R.C.C. are employees and stockholders of Madrigal Pharmaceuticals Inc. N.A. has received grant/research support from 89bio, Akero Therapeutics, Arbutus Biopharma, AstraZeneca, BioAge, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, Galectin Therapeutics, Genentech, Gilead Sciences, Hepagene Therapeutics, Intercept Pharmaceuticals, Inventiva Pharma, Ionis Pharmaceuticals, Ipsen, Lilly, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, PharmaIN, Poxel, Regeneron, Viking Therapeutics, and Zydus Pharmaceuticals; reports speaker's fees from AbbVie, AstraZeneca, Echosens, Gilead Sciences, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, and Perspectum; and reports consulting for 89bio, AbbVie, Akero, Boehringer Ingelheim, Echosens, Fibronostics, Gilead Sciences, HistoIndex, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, and Regeneron. R.L. serves as a consultant to Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse bio, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet, 89 bio, Takeda, Terns Pharmaceuticals, and Viking Therapeutics. R.L. has stock options in Sagimet biosciences. In addition, his institution received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals, and is co-founder of LipoNexus Inc. M.B.B. has received Grant Support from NIH, CDC/NIOSH, Pfizer, The Kinetix Group, Histoindex, Siemens and has served as a consultant for The Kinetix Group, Madrigal, Pfizer, Fibronostics, NOVO Nordisk, GSK, Boston Pharma, Merck, Boehringer-Ingelheim, CurveBio, and mBIOTA.

### Data Availability Statement

The data underlying this study were derived from the MAESTRO-NASH Phase 3 clinical trial sponsored by Madrigal Pharmaceuticals Inc. Access to individual participant data, imaging datasets, and AI-generated qFibrosis features is subject to restrictions and is not publicly available.

### References


1. M. E. Rinella, J. V. Lazarus, V. Ratziu, et al., "A Multisociety Delphi Consensus Statement on New Fatty Liver Disease Nomenclature," *Hepatology* 78 (2023): 1966–1986.

2. A. M. Diehl and C. Day, "Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis," *New England Journal of Medicine* 377 (2017): 2063–2072.

3. E. P. Stahl, D. S. Dhindsa, S. K. Lee, P. B. Sandesara, N. P. Chalasani, and L. S. Sperling, "Nonalcoholic Fatty Liver Disease and the Heart: JACC State-Of-The-Art Review," *Journal of the American College of Cardiology* 73 (2019): 948–963.

4. P. Angulo, D. E. Kleiner, S. Dam-Larsen, et al., "Liver Fibrosis, but no Other Histologic Features, Is Associated With Long-Term Outcomes of Patients With Nonalcoholic Fatty Liver Disease," *Gastroenterology* 149 (2015): 389–397.e310.

5. P. S. Dulai, S. Singh, J. Patel, et al., "Increased Risk of Mortality by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis," *Hepatology* 65 (2017): 1557–1565.

6. H. Hagstrom, P. Nasr, M. Ekstedt, et al., "Fibrosis Stage but Not NASH Predicts Mortality and Time to Development of Severe Liver Disease in Biopsy-Proven NAFLD," *Journal of Hepatology* 67 (2017): 1265–1273.

7. M. Noureddin, A. Vipani, C. Bresee, et al., "NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications for Liver Transplant and Ethnic and Gender Variances," *American Journal of Gastroenterology* 113 (2018): 1649–1659.

8. Z. M. Younossi, R. Tampi, M. Priyadarshini, F. Nader, I. M. Younossi, and A. Racila, "Burden of Illness and Economic Model for Patients With Nonalcoholic Steatohepatitis in the United States," *Hepatology* 69 (2019): 564–572.

9. P. Le, M. Tatar, S. Dasarathy, et al., "Estimated Burden of Metabolic Dysfunction-Associated Steatotic Liver Disease in US Adults, 2020 to 2050," *JAMA Network Open* 8 (2025): e2454707.

10. F. Saponaro, S. Sestito, M. Runfola, et al., "Selective Thyroid Hormone Receptor-Beta (TRbeta) Agonists: New Perspectives for the Treatment of Metabolic and Neurodegenerative Disorders," *Frontiers in Medicine* 7 (2020): 331.

11. J. A. Vaitkus, J. S. Farrar, and F. S. Celi, "Thyroid Hormone Mediated Modulation of Energy Expenditure," *International Journal of Molecular Sciences* 16 (2015): 16158–16175.

12. J. Zhou, M. Tripathi, J. P. Ho, et al., "Thyroid Hormone Decreases Hepatic Steatosis, Inflammation, and Fibrosis in a Dietary Mouse Model of Nonalcoholic Steatohepatitis," *Thyroid* 32 (2022): 725–738.

13. M. J. Kelly, S. Pietranico-Cole, J. D. Larigan, et al., "Discovery of 2-[3,5-Dichloro-4-(5-Isopropyl-6-Oxo-1,6-Dihydropyridazin-3-Yloxy) phenyl]-3,5-Dio Xo-2,3,4,5-Tetrahydro[1,2,4]Triazine-6-Carbonitrile (MGL-3196), a Highly Selective Thyroid Hormone Receptor Beta Agonist in Clinical Trials for the Treatment of Dyslipidemia," *Journal of Medicinal Chemistry* 57 (2014): 3912–3923.

14. S. A. Harrison, P. Bedossa, C. D. Guy, et al., "A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH With Liver Fibrosis," *New England Journal of Medicine* 390 (2024): 497–509.

15. R. Taub, E. Chiang, M. Chabot-Blanchet, et al., "Lipid Lowering in Healthy Volunteers Treated With Multiple Doses of MGL-3196, a Liver-Targeted Thyroid Hormone Receptor-Beta Agonist," *Atherosclerosis* 230 (2013): 373–380.

16. G. K. Hovingh, I. C. Klausen, E. Heggen, et al., "Resmetirom (MGL-3196) in Patients With Heterozygous Familial Hypercholesterolemia," *Journal of the American College of Cardiology* 79 (2022): 1220–1222.

17. S. A. Harrison, R. Taub, G. W. Neff, et al., "Resmetirom for Nonalcoholic Fatty Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial," *Nature Medicine* 29 (2023): 2919–2928.

18. S. A. Harrison, M. R. Bashir, C. D. Guy, et al., "Resmetirom (MGL-3196) for the Treatment of Non-Alcoholic Steatohepatitis: A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial," *Lancet* 394 (2019): 2012–2024.

19. M. J. Armstrong, P. Gaunt, G. P. Aithal, et al., "Liraglutide Safety and Efficacy in Patients With Non-Alcoholic Steatohepatitis (LEAN): A Multicentre, Double-Blind, Randomised, Placebo-Controlled Phase 2 Study," *Lancet* 387 (2016): 679–690.

20. P. N. Newsome, K. Buchholtz, K. Cusi, et al., "A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis," *New England Journal of Medicine* 382 (2020): 1113–1124.

21. R. Loomba, M. L. Hartman, E. J. Lawitz, et al., "Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis With Liver Fibrosis," *New England Journal of Medicine* 391 (2024): 299–310.

22. S. A. Harrison, S. K. Browne, J. J. Suschak, et al., "Effect of Pemvidutide, a GLP-1/Glucagon Dual Receptor Agonist, on MASLD: A Randomized, Double-Blind, Placebo-Controlled Study," *Journal of Hepatology* 82 (2025): 7–17.

23. A. J. Sanyal, P. N. Newsome, I. Kliers, et al., "Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis," *New England Journal of Medicine* 392 (2025): 2089–2099.

24. C. Pyke, R. S. Heller, R. K. Kirk, et al., "GLP-1 Receptor Localization in Monkey and Human Tissue: Novel Distribution Revealed With Extensively Validated Monoclonal Antibody," *Endocrinology* 155 (2014): 1280–1290.

25. M. J. Armstrong, D. Hull, K. Guo, et al., "Glucagon-Like Peptide 1 Decreases Lipotoxicity in Non-Alcoholic Steatohepatitis," *Journal of Hepatology* 64 (2016): 399–408.

26. D. A. Koutoukidis, N. M. Astbury, K. E. Tudor, et al., "Association of Weight Loss Interventions With Changes in Biomarkers of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis," *JAMA Internal Medicine* 179 (2019): 1262.

27. E. Vilar-Gomez, Y. Martinez-Perez, L. Calzadilla-Bertot, et al., "Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis," *Gastroenterology* 149 (2015): 367–378.

28. G. Lassailly, R. Caiazzo, D. Buob, et al., "Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients," *Gastroenterology* 149 (2015): 379–388.

29. J. Lin, Y. Huang, B. Xu, et al., "Effect of Dapagliflozin on Metabolic Dysfunction-Associated Steatohepatitis: Multicentre, Double Blind, Randomised, Placebo Controlled Trial," *BMJ* 389 (2025): e083735.

30. A. J. Sanyal, N. Chalasani, K. V. Kowdley, et al., "Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis," *New England Journal of Medicine* 362 (2010): 1675–1685.

31. D. E. Kleiner, E. M. Brunt, M. Van Natta, et al., "Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease," *Hepatology* 41 (2005): 1313–1321.

32. M. Samoilenko and G. Lefebvre, "An Exact Regression-Based Approach for the Estimation of Natural Direct and Indirect Effects With a Binary Outcome and a Continuous Mediator," *Statistics in Medicine* 42 (2023): 353–387.

33. Z. M. Younossi, P. Golabi, J. K. Price, et al., "The Global Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among Patients With Type 2 Diabetes," *Clinical Gastroenterology and Hepatology* 22 (2024): 1999–2010.

34. F. B. Rivera, L. L. A. Cruz, J. V. Magalong, et al., "Cardiovascular and Renal Outcomes of Glucagon-Like Peptide 1 Receptor Agonists Among Patients With and Without Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Placebo-Controlled Trials," *American Journal of Preventive Cardiology* 18 (2024): 100679.

35. E. M. Apperloo, B. L. Neuen, R. A. Fletcher, et al., "Efficacy and Safety of SGLT2 Inhibitors With and Without Glucagon-Like Peptide 1 Receptor Agonists: A SMART-C Collaborative Meta-Analysis of Randomised Controlled Trials," *Lancet Diabetes and Endocrinology* 12 (2024): 545–557.

36. D. Q. Huang, L. A. Wilson, C. Behling, et al., "Fibrosis Progression Rate in Biopsy-Proven Nonalcoholic Fatty Liver Disease Among People With Diabetes Versus People Without Diabetes: A Multicenter Study," *Gastroenterology* 165 (2023): 463–472.

37. M. E. Rinella, B. A. Neuschwander-Tetri, M. S. Siddiqui, et al., "AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease," *Hepatology* 77 (2023): 1797–1835.

38. T. Csak, M. Ganz, J. Pespisa, K. Kodys, A. Dolganiuc, and G. Szabo, "Fatty Acid and Endotoxin Activate Inflammasomes in Mouse Hepatocytes That Release Danger Signals to Stimulate Immune Cells," *Hepatology* 54 (2011): 133–144.

39. L. Alufer, G. Tsaban, E. Rinott, et al., "Long-Term Green-Mediterranean Diet May Favor Fasting Morning Cortisol Stress Hormone; the DIRECT-PLUS Clinical Trial," *Front Endocrinol (Lausanne)* 14 (2023): 1243910.

40. C. Paul, J. Cather, M. Gooderham, et al., "Efficacy and Safety of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients With Moderate-To-Severe Plaque Psoriasis Over 52 Weeks: A Phase III, Randomized Controlled Trial (ESTEEM 2)," *British Journal of Dermatology* 173 (2015): 1387–1399.

41. C. J. Edwards, F. J. Blanco, J. Crowley, et al., "Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients With Psoriatic Arthritis and Current Skin Involvement: A Phase III, Randomised, Controlled Trial (PALACE 3)," *Annals of the Rheumatic Diseases* 75 (2016): 1065–1073.

**Supporting Information**

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.