# Resmetirom Improves the Lipid/Lipoprotein Profile in Patients With Nonalcoholic Fatty Liver Disease

Naim Alkhouri,[1] Rebecca Taub,[2] Guy W. Neff,[3] K. Jean Lucas,[4] Dominic Labriola,[2] Sam E. Moussa,[5] Mustafa R. Bashir,[6] Stephen A. Harrison[7]

[1]Arizona Liver Health, Tucson, AZ, USA; [2]Madrigal Pharmaceuticals, Conshohocken, PA, USA; [3]Covenant Metabolic Specialists, Sarasota, FL, USA; [4]Lucas Research, Morehead City, NC, USA; [5]University of Arizona for Medical Sciences, Tucson, AZ, USA; [6]Duke University Medical Center, Durham, NC, USA; [7]University of Oxford, Oxford, United Kingdom and Pinnacle Clinical Research, San Antonio, TX, USA

## BACKGROUND

- Patients with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) are at increased risk of cardiovascular disease (CVD)[1]
- Resmetirom is an oral, liver-targeted thyroid hormone receptor-β selective agonist in clinical development for treatment of NASH[2]
- In addition to significantly reducing hepatic fat in patients with NAFLD/NASH, resmetirom has been shown to significantly reduce atherogenic lipid and lipoprotein levels (low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides [TG])[3-5]

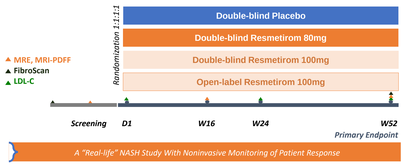
## OBJECTIVE

- To evaluate the effect of resmetirom treatment on additional components of the lipid/lipoprotein profile in patients with NAFLD/presumed NASH

## METHODS

- MAESTRO-NAFLD-1 (NCT04197479) was a randomized, double-blind, placebo-controlled Phase 3 trial to evaluate the safety of resmetirom over 52 weeks of treatment in adults with NAFLD/presumed NASH (**Figure 1**)

### Figure 1. MAESTRO-NAFLD-1 Trial Design




- Eligible patients had ≥3 metabolic risk factors, liver stiffness ≥5.5 kPa, and ≥8% hepatic fat
- The first 30 patients were enrolled in the open-label resmetirom arm prior to initiation of 1:1:1:1 randomization to the 3 double-blind arms (resmetirom 100mg, resmetirom 80mg, or placebo) or the open-label arm (resmetirom 100mg). Randomization to the open-label arm was discontinued when the target number of patients was achieved (01Jul2020). Thereafter, patients were randomized 1:1:1 to the 3 double-blind arms
- The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs) over 52 weeks
- Secondary endpoints included percent change from baseline in lipid, lipoprotein, and lipid particle levels at Weeks 24 and 48

## RESULTS

- Overall, 972 patients were randomized to the double-blind arms (resmetirom 100mg [n=325], resmetirom 80mg [n=327], or placebo [n=320]) and 171 patients to the open-label resmetirom 100mg arm
- Across the 4 treatment arms, demographic and baseline characteristics were generally comparable (**Table 1**)

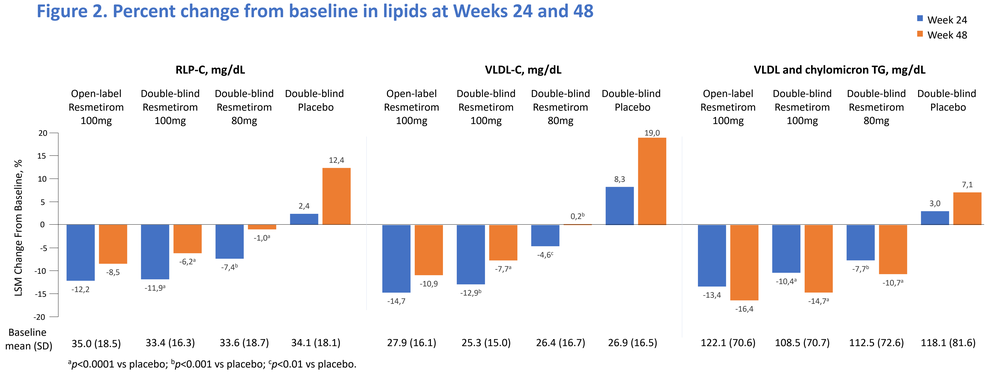
### Table 1. Demographic and baseline characteristics (safety population)

| | Open-label Resmetirom 100mg (n=171) | Double-blind Resmetirom 100mg (n=324) | Double-blind Resmetirom 80mg (n=327) | Double-blind Placebo (n=318) |
|---|---|---|---|---|
| Age, years, mean (SD) | 55.6 (11.5) | 55.9 (11.7) | 56.2 (11.7) | 55.7 (12.1) |
| Sex, male, n (%) | 55 (32.2) | 147 (45.4) | 145 (44.3) | 150 (47.2) |
| Race, White, n (%) | 151 (88.3) | 287 (88.6) | 290 (88.7) | 282 (88.7) |
| Ethnicity, Hispanic or Latino, n (%) | 52 (30.4) | 108 (33.3) | 108 (33.0) | 120 (37.7) |
| Body mass index, kg/m$^2$, mean (SD) | 36.1 (6.3) | 35.4 (6.4) | 35.3 (5.9) | 35.2 (5.8) |
| Type 2 diabetes, n (%) | 83 (48.5) | 156 (48.1) | 160 (48.9) | 159 (50.0) |
| Hypertension, n (%) | 119 (69.6) | 246 (75.9) | 249 (76.1) | 242 (76.1) |
| Dyslipidemia, n (%) | 152 (88.9) | 283 (87.3) | 288 (88.1) | 281 (88.4) |
| Hypothyroidism, n (%)[a] | 76 (44.4) | 34 (10.5) | 39 (11.9) | 35 (11.0) |
| ASCVD, n (%) | 10 (5.8) | 22 (6.8) | 26 (8.0) | 24 (7.5) |
| FibroScan VCTE/LSM, kPa, mean (SD) | 7.8 (3.4) | 7.3 (4.1) | 7.4 (4.4) | 7.5 (5.5) |
| FibroScan CAP, dB/m, mean (SD) | 342.3 (35.6) | 341.4 (34.0) | 339.5 (32.9) | 344.1 (34.0) |
| MRI-PDFF, % fat fraction, mean (SD) | 17.9 (7.1) | 18.1 (7.3) | 17.7 (6.7) | 17.8 (6.9) |
| LDL-C, mg/dL, mean (SD) | 115.2 (41.0) | 109.1 (36.4) | 111.7 (37.6) | 106.8 (37.2) |
| ApoB, mg/dL, mean (SD) | 101.1 (28.4) | 95.5 (25.0) | 98.1 (26.3) | 95.1 (27.1) |
| TG, mg/dL, mean (SD) | 183.6 (86.2) | 174.1 (93.5) | 177.6 (94.4) | 186.8 (119.2) |
| Baseline medication, statin, n (%) | 75 (43.9) | 143 (44.1) | 138 (42.2) | 164 (51.6) |

[a]Patients on thyroxine replacement therapy at baseline.
ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAP, controlled attenuation parameter; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; TG, triglycerides; VCTE, vibration-controlled transient elastography.

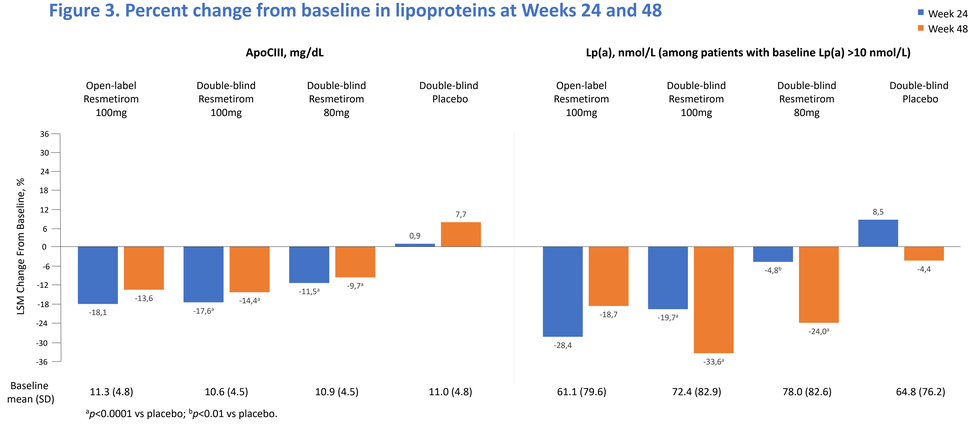
- As reported previously, 86.1%-88.4% of resmetirom-treated patients and 81.8% of placebo-treated patients reported a TEAE during the trial; the majority of TEAEs were mild or moderate in severity[5]
- At Week 24, remnant-like particle cholesterol (RLP-C), very low-density lipoprotein cholesterol (VLDL-C), and VLDL and chylomicron TG levels were significantly reduced from baseline in all resmetirom arms ($p$<0.01 vs placebo for all); these significant reductions were maintained at Week 48 (**Figure 2**)
- In addition, apolipoprotein CIII (apoCIII) and lipoprotein(a) (Lp(a)) levels were significantly reduced from baseline in the resmetirom arms at Week 24 ($p$<0.01 vs placebo for all); these significant reductions were also maintained at Week 48 (**Figure 3**)

### Figure 2. Percent change from baseline in lipids at Weeks 24 and 48




[a]$p$<0.0001 vs placebo; [b]$p$<0.001 vs placebo; [c]$p$<0.01 vs placebo.

### Figure 3. Percent change from baseline in lipoproteins at Weeks 24 and 48




[a]$p$<0.0001 vs placebo; [b]$p$<0.01 vs placebo.

- Atherogenic lipoprotein particles, including LDL, small LDL, and VLDL and chylomicron were significantly reduced from baseline in the resmetirom arms at Week 24 ($p$<0.001 vs placebo for all) with these significant reductions maintained at Week 48 (**Table 2**)

### Table 2. Percent change from baseline in lipoprotein particles at Weeks 24 and 48

| | Open-label Resmetirom 100mg | Double-blind Resmetirom 100mg | Double-blind Resmetirom 80mg | Double-blind Placebo |
|---|---|---|---|---|
| **LDL particles,** nmol/L | | | | |
| Baseline mean (SD) | 1347.8 (449.7) | 1311.8 (394.8) | 1344.7 (399.1) | 1290.0 (430.8) |
| Week 24 LSM %CFB (SE) | −21.7 (2.1) | −16.7 (1.7)[a] | −15.5 (1.7)[a] | −3.6 (1.7) |
| Week 48 LSM %CFB (SE) | −21.0 (2.3) | −15.6 (2.0)[a] | −15.1 (2.0)[a] | −2.1 (1.9) |
| **Small LDL particles,** nmol/L | | | | |
| Baseline mean (SD) | 961.3 (356.9) | 911.6 (311.6) | 920.3 (316.2) | 923.0 (334.0) |
| Week 24 LSM %CFB (SE) | −15.6 (3.5) | −17.1 (2.9)[a] | −15.8 (2.9)[b] | −4.0 (2.9) |
| Week 48 LSM %CFB (SE) | −24.5 (2.7) | −18.3 (2.3)[a] | −18.7 (2.4)[a] | −6.7 (2.3) |
| **VLDL and chylomicron particles,** nmol/L | | | | |
| Baseline mean (SD) | 62.0 (37.1) | 53.0 (33.9) | 55.6 (37.0) | 55.2 (30.6) |
| Week 24 LSM %CFB (SE) | −1.5 (6.0) | −0.3 (5.0)[b] | 8.5 (4.9) | 18.5 (4.9) |
| Week 48 LSM %CFB (SE) | −6.4 (5.7) | −7.6 (5.0)[a] | 1.6 (5.0)[a] | 22.6 (4.9) |

[a]$p$<0.0001 vs placebo; [b]$p$<0.001 vs placebo.
CFB, change from baseline; LSM, least squares mean.

## CONCLUSIONS

- **Resmetirom significantly improved the overall lipid/lipoprotein profile in adults with NAFLD/presumed NASH**
  - **By Week 24, both resmetirom 100mg and 80mg significantly reduced atherogenic lipids/lipoproteins, including RLP-C, VLDL-C, apoCIII, and Lp(a) from baseline compared with placebo; these improvements were maintained at Week 48**
  - **Significant improvements from baseline in atherogenic lipid particles were also observed with resmetirom treatment compared with placebo at Weeks 24 and 48**
- **As CVD is the most common cause of mortality in patients with NASH, the effect of potential therapies such as resmetirom on cardiovascular risk factors, including atherogenic lipids, lipoproteins, and lipid particles, is important to consider**

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