Durability of resmetirom response in patients with MASLD with up to two years of treatment in MAESTRO-NAFLD-OLE

POSTER #A16

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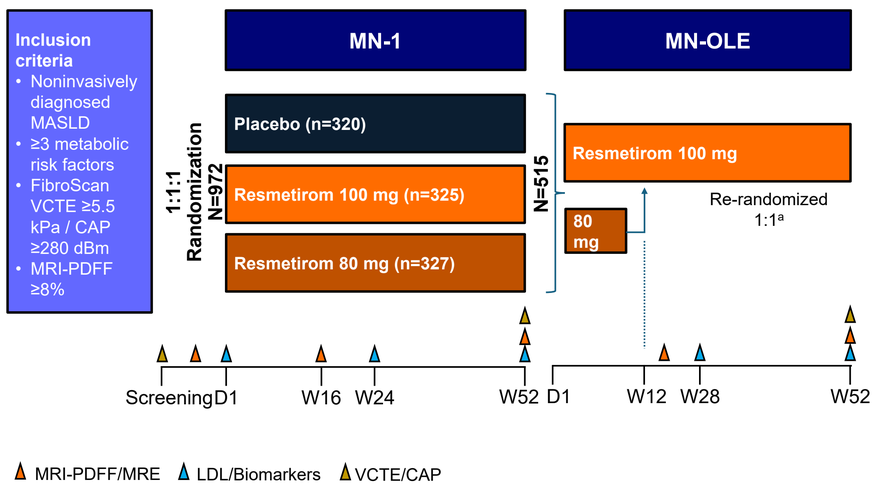
INTRODUCTION

- MASLD is the most common chronic liver disease globally and may progress to serious complications including MASH, cirrhosis, and hepatocellular carcinoma[1]
- Resmetirom is a once-daily oral selective THR-β–selective agonist approved for the treatment of adults with MASH and liver fibrosis consistent with F2 to F3 stages in the United States[2]
- Here, we report long-term results from a Phase 3 trial evaluating resmetirom in patients with MASLD

METHODS

- MAESTRO-NAFLD-1 (**MN-1**; NCT04197479) was a 52-weekPhase 3 study consisting of randomized, placebo-controlled, double-blind arms. Patients completing treatment were offered to enroll in an open-label extension study (MAESTRO-NAFLD-OLE [**MN-OLE**; NCT04951219]), in which they received resmetirom for 52 weeks (**Figure 1**)[3,4]

FIGURE 1. MAESTRO-NAFLD-1 and -OLE study design.[3]



[a]MN-OLE included a 12-week run-in period during which patients were randomized to resmetirom 80 mg or 100 mg. After Week 12, all patients received 100 mg of resmetirom for the duration of the trial.

- After a mean (SD) treatment interruption of 111 (78) days, 515 patients from the double-blind arms of MN-1 enrolled in MN-OLE, including 172 from the placebo arm, 175 from the resmetirom 100-mg arm, and 168 from the resmetirom 80-mg arm
- Patients who enrolled in MN-OLE received either 80 mg or 100 mg resmetirom for the first 12 weeks and 100 mg from Weeks 12 through 52
- Data from baseline to up to 2 years of treatment were analyzed by assigned treatment group in MN-1
- For patients in the placebo arm of MN-1, both data from baseline in MN-1 and re-baselined data from start of MN-OLE were analyzed
- Descriptive statistics based on observed data were used

RESULTS

- At baseline in MN-1, 52% and 29% of the MN-OLE population were female and Hispanic, respectively, with mean (SD) age of 57 (11.5) years, BMI of 35.2 (6.03) kg/m^2, and VCTE of 7.4 (4.74) kPa (**Table 1**)
  - Baseline prevalence of metabolic risk factors was high (type 2 diabetes in 56%; hypertension in 79%; dyslipidemia in 77%)

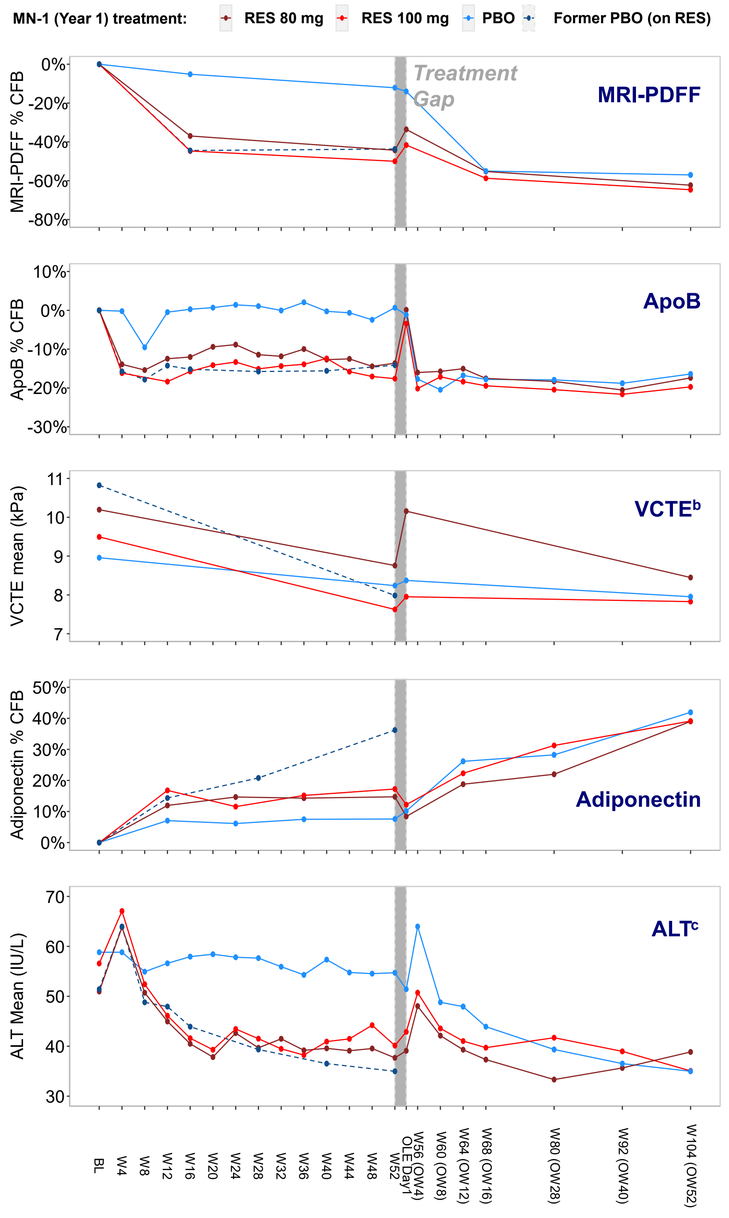
TABLE 1. Baseline characteristics at randomization in MN-1 in the MN-OLE population (Groups shown as Year 1 Treatment/Year 2 Treatment)

Characteristic[a]	PBO/RES (n=172)	100RES/RES (n=175)	80RES/RES (n=168)	Overall (N=515)
Age, years	58 (12.0)	56 (11.4)	58 (11.1)	57 (11.5)
Female, n (%)	85 (49.4)	92 (52.6)	91 (54.2)	268 (52.0)
White, n (%)	152 (88.4)	154 (88.0)	151 (89.9)	457 (88.7)
Hispanic, n (%)	57 (33.1)	46 (26.3)	45 (26.8)	148 (28.7)
BMI, kg/m^2	34.8 (5.29)	35.2 (6.57)	35.4 (6.17)	35.2 (6.03)
VCTE, kPa	7.3 (2.41)	7.5 (5.41)	7.5 (5.72)	7.4 (4.74)
VCTE, kPa (patients with baseline VCTE ≥7.2 kPa)	9.0 (3.02) n=69	9.5 (8.28) n=68	10.2 (9.30) n=56	9.5 (7.22) n=193
CAP, dB/m	344 (34.1)	342 (34.0)	343 (32.5)	343 (33.5)
MRI-PDFF, %	18.4 (7.44)	18.0 (6.91)	17.0 (6.28)	17.8 (6.90)
Type 2 diabetes, n (%)	98 (57.0)	93 (53.1)	95 (56.5)	286 (55.5)
Hypertension, n (%)	137 (79.7)	135 (77.1)	137 (81.5)	409 (79.4)
Dyslipidemia, n (%)	144 (83.7)	130 (74.3)	122 (72.6)	396 (76.9)
MRE, kPa	2.6 (0.50)	2.6 (0.57)	2.7 (0.52)	2.7 (0.53)
LDL, mg/dL	108 (35.1)	112 (34.0)	109 (37.6)	110 (35.5)
Triglycerides, mg/dL	186 (91.0)	178 (90.7)	175 (93.8)	180 (91.8)
ApoB, mg/dL	96 (25.8)	98 (24.0)	96 (25.0)	97 (24.9)
ALT, U/L	40 (34.1)	39 (29.4)	36 (22.4)	38 (29.1)
ALT, U/L (patients with baseline ALT ≥30 U/L)	59 (39.2) n=87	57 (32.9) n=87	51 (22.8) n=83	56 (32.5) n=257
AST, U/L	28 (18.2)	26 (13.9)	25 (13.5)	26 (15.4)
GGT, U/L	50 (64.6)	43 (35.9)	42 (35.5)	45 (47.4)
Adiponectin, µg/mL	4.6 (2.75)	4.8 (2.79)	5.0 (3.08)	4.8 (2.87)

[a]Values are mean (SD) unless otherwise specified. PBO/RES, 100RES/RES and 80RES/RES corresponds to patients who received placebo, resmetirom 100 mg and resmetirom 80 mg, respectively, in MN-1 (Year 1) and resmetirom in MN-OLE (Year 2).

- Among patients originally randomized to resmetirom in MN-1, resmetirom treatment for a second year in MN-OLE resulted in persistent effects on biomarkers (**Figure 2** and **Table 2**), including:
  - Lipids (mean [SE] % change at Year 2: LDL, -15 [2]%; ApoB,-19 [1]%; triglycerides, -23 [2]%)
  - Liver enzymes (among patients with baseline ALT ≥30 U/L;
    mean [SE] % change at Year 2: ALT, -25 [3]%; AST -9 [4]%;
    GGT -27 [3]%)
  - MRI-PDFF: median (IQR) % reduction of 63 (37, 76)% at Year 2
  - VCTE (among patients with baseline VCTE ≥7.2 kPa): median (IQR) % change of 18 (-10, 34)% at Year 2
- Responses were similar in patients originally randomized to placebo in MN-1 who received resmetirom for 1 year in MN-OLE (**Figure 2** and **Table 2**)
  Adiponectin, a biomarker that inversely correlates with fibrosis stage (39 [4]%) years in those randomized to resmetirom in MN-1
- The treatment gap between Year 1 and 2 resulted in loss of effect on several biomarkers in patients who received resmetirom in MN-1, which was recovered with reinitiation of resmetirom (**Figure 2**)
- Resmetirom was well tolerated; reinitiation of resmetirom therapy did not generally result in recurrence of gastrointestinal AEs in patients who received resmetirom in MN-1

FIGURE 2. Changes in biomarkers: Year 1 (MN-1) vs Year 2 (MN-OLE).[a]



[a]Median for MRI-PDFF and mean for others; the dashed line shows the year of RES treatment in MN-OLE for patients who were on PBO in MN-1. [b]For patients with baseline VCTE ≥7.2 kPa. [c]For patients with baseline ALT ≥30 IU/L.

TABLE 2. Changes from baseline to Year 2 in biomarkers.

	PBO/RES (n=172)[a]	100RES/RES (n=175)[a]	80RES/RES (n=168)[a]
LDL, mean (SE) CFB (%)	-13.5 (2.3)	-16.4 (2.4)	-14.3 (2.1)
ApoB, mean (SE) CFB (%)	-16.4 (1.8)	-19.7 (1.9)	-17.4 (1.8)
Triglycerides, mean (SE) CFB (%)	-18.6 (4.6)	-23.4 (3.9)	-23.6 (2.4)
ALT, mean (SE) CFB (%)[b]	-27.9 (3.4)	-31.7 (4.2)	-19.3 (4.7)
AST, mean (SE) CFB (%)[b]	-18.9 (3.5)	-15.7 (4.6)	-2.4 (6.5)
GGT, mean (SE) CFB (%)[b]	-29 (3.5)	-29.5 (4)	-25.5 (4.9)
MRI-PDFF, median (IQR) CFB (%)	-57 (-74.7, -32.4)	-64.6 (-78.9, -40.7)	-62.3 (-72.7, -34.1)
VCTE, mean (SE) CFB[c]	-0.7 (0.60)	-1.8 (1.26)	-1.7 (1.36)
VCTE, median (IQR) CFB (%)[c]	-14.7 (-37.1, 6.5)	-17.8 (-33.9, 12)	-18.3 (-34.5, 5.7)
Adiponectin, mean (SE) CFB (%)	41.9 (5.3)	39.1 (5.1)	39 (4.8)

[a]Represents originally assigned treatment in MN-1. [b]For patients with baseline ALT ≥30 IU/L. [c]For patients with baseline VCTE ≥7.2 kPa.

CONCLUSION

- **In a 52-week OLE of a Phase 3 trial in patients with MASLD and high metabolic risk, resmetirom treatment for a second year resulted in durable effects on biomarkers, including:**
  - **Reductions in atherogenic lipids, VCTE, and MRI-PDFF**
  - **Improvements in markers of liver injury and fibrosis**
- **Patients who were originally randomized to placebo in MN-1 showed similar improvements in biomarkers upon switching to resmetirom, regardless of the baseline used (ie, MN-1 vs MN-OLE)**

ABBREVIATIONS

AE, adverse event; ALT, alanine aminotransferase; ApoB, apolipoprotein B; AST, aspartate aminotransferase; BL, baseline; BMI, body mass index; CAP, controlled attenuation parameter; CFB, change from baseline; D, Day; GGT, gamma-glutamyl transferase; IQR, interquartile range; LDL, low-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; OLE, open-label extension; OW, OLE Week; PBO, placebo; RES, resmetirom; SD, standard deviation; SE, standard error; THR-β, thyroid hormone receptor-beta; VCTE, vibration-controlled transient elastography; W, Week.

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REFERENCES

1. Younossi ZM, Henry L. *Diabetes Spectr*. 2024;37(1):9-19. **2.** Rezdiffra [prescribing information]. Madrigal Pharmaceuticals, Inc. **3.** Harrison SA, et al. *Aliment Pharmacol Ther*. 2024;59(1):51-63. **4.** Harrison SA, et al. *Nat Med*. 2023;29(11):2919-2928. **5.** Youssef TM, et al. *QJM*. 2021;114(Suppl1):hcab100.054.

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