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

Naim Alkhouri[1], Rebecca Taub[2], Xiaomin Lu[2], Matthew Dauphin[2], Jeannie Lucas[3], Sam E. Moussa[4], Rashmee Patil[5]

[1]Summit Clinical Research, San Antonio, TX, United States; [2]Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, United States; [3]Lucas Research, Morehead City, NC, United States; [4]University of Arizona for Medical Sciences, Tucson, AZ, United States; [5]Pinnacle Clinical Research, San Antonio, TX, United States

POSTER #4003

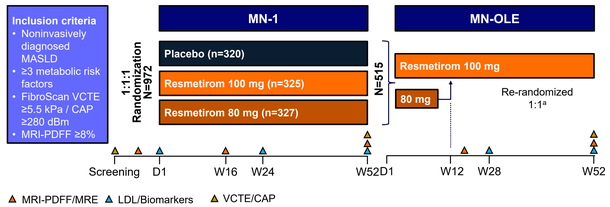
INTRODUCTION

- 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-week Phase 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%)

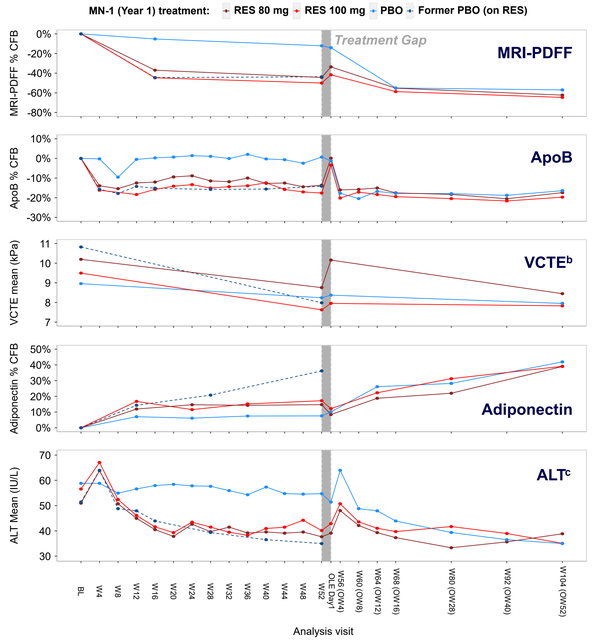
TABLE 1. Baseline characteristics at randomization in MN-1 in the MN-OLE population (Groups shown as Year 1 Treatment/ Year 2 Treatment)

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

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.

- 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 in MASLD,[5] showed a mean (SE) % increase at 1 (16 [2]%) and 2 (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

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

Biomarker	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.

CONCLUSIONS

- **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.

DISCLOSURES AND ACKNOWLEDGEMENTS

NA reports speaking and teaching roles with Madrigal, Novo Nordisk, Echosens, Ipsen, and Intercept and consulting roles with Novo Nordisk, Perspectum, Cima, Fibronostics, Madrigal, Boehringer Ingelheim, Ipsen, Gilead, Perspectum, Cima, and 89bio; has received grant/research support from Novo Nordisk, Corcept, 89bio, Inventiva, Merck, Pfizer, Arbutus, GSK, Regeneron, AstraZeneca, Madrigal, Akero, Boehringer Ingelheim, Eli Lilly, Gilead, Galectin, and Boston Pharma; has received research funding from Madrigal, Novo Nordisk, Inventiva, Boehringer Ingelheim, Corcept, Ipsen, Gilead, and Perspectum; and reports advisory roles with Cima and 89bio. RT is employed by (executive role) and has stock ownership in Madrigal Pharmaceuticals (publicly traded). XL and MD are employees and shareholders of Madrigal Pharmaceuticals. JL, SEM, and RP do not report any disclosures. This study was funded by Madrigal Pharmaceuticals, Inc.

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.

SCAN QR CODE FOR DIGITAL POSTER

Madrigal