Evaluating the effect of resmetirom on thyroid function: a post hoc analysis of MAESTRO-NASH, a phase 3 randomized controlled study in patients with MASH and fibrosis

POSTER 1806-P

Keith Miller,[1] Theresa Alexander,[1] Krishna Padmanabhan,[1] Geoff Rezvani,[1] Frank Tacke,[2] Christos Mantzoros[3]

[1]Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA; [2]Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Harvard Medical School, Boston, MA, USA

INTRODUCTION

- Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease with significant morbidity and mortality[1,2]
- Resmetirom is an oral, liver-directed, thyroid hormone receptor β (THR-β) agonist approved in the United States for use in conjunction with diet and exercise for the treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stages F2-F3 fibrosis)[3]
- As a liver-directed THR-β agonist that modulates thyroid hormone signaling, resmetirom warrants evaluation for potential effects on systemic thyroid function, including hypothalamic-pituitary-thyroid (HPT)-axis parameters[4]

AIM

- To evaluate the effects of resmetirom on systemic thyroid function as measured by free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH)

METHODS

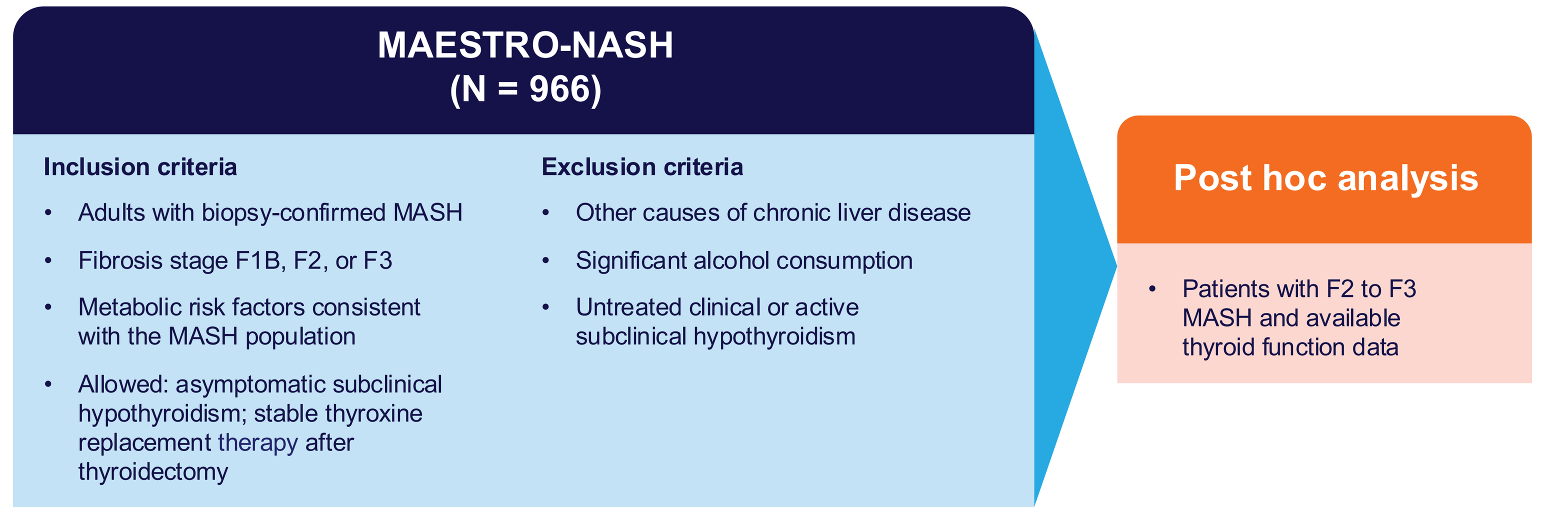
Study design

- MAESTRO-NASH is an ongoing phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of resmetirom in patients with MASH.[5] This analysis includes data through Week 52
- Patients were randomized 1:1:1 to once daily resmetirom 80 mg, resmetirom 100 mg, or placebo[5]

Population[5]

- The trial enrolled patients with biopsy-confirmed MASH (fibrosis stage F1B [mild fibrosis substage B], F2, or F3) with ≥3 metabolic risk factors
- Patients with other causes of chronic liver disease or with a history of significant alcohol consumption were excluded
- Patients with untreated clinical or active subclinical hypothyroidism (TSH >10 mIU/L without symptoms or TSH >7 mIU/L with symptoms) were excluded
- Patients with asymptomatic subclinical hypothyroidism and those with thyroidectomy receiving stable replacement thyroxine doses >75 μg/d were allowed
- This post hoc analysis included patients with fibrosis stage F2 or F3 (comprising a modified intention-to-treat population) and available thyroid function data (**Figure 1**)

FIGURE 1. Analysis population



F, fibrosis stage (F1B: mild fibrosis [substage B: dense zone 3 perisinusoidal fibrosis], F2: moderate fibrosis, F3: advanced fibrosis); MASH, metabolic dysfunction–associated steatohepatitis.

Outcomes

- This post hoc analysis evaluated systemic thyroid function biomarker (FT4, FT3, TSH, and rT3) change from baseline through Week 52 after resmetirom initiation
  - Changes in thyroid parameters were assessed as least squares (LS) mean change from baseline by treatment group relative to placebo
  - Outcomes were stratified by baseline thyroxine use (receiving vs not receiving replacement therapy)

RESULTS

Patient characteristics

- In total, 966 patients were randomized in MAESTRO-NASH and 888 patients had stages F2-F3 fibrosis
- Baseline characteristics were similar to the primary analysis population[5] and across the 3 treatment groups (**Table 1**)

TABLE 1. Baseline demographic and clinical characteristics

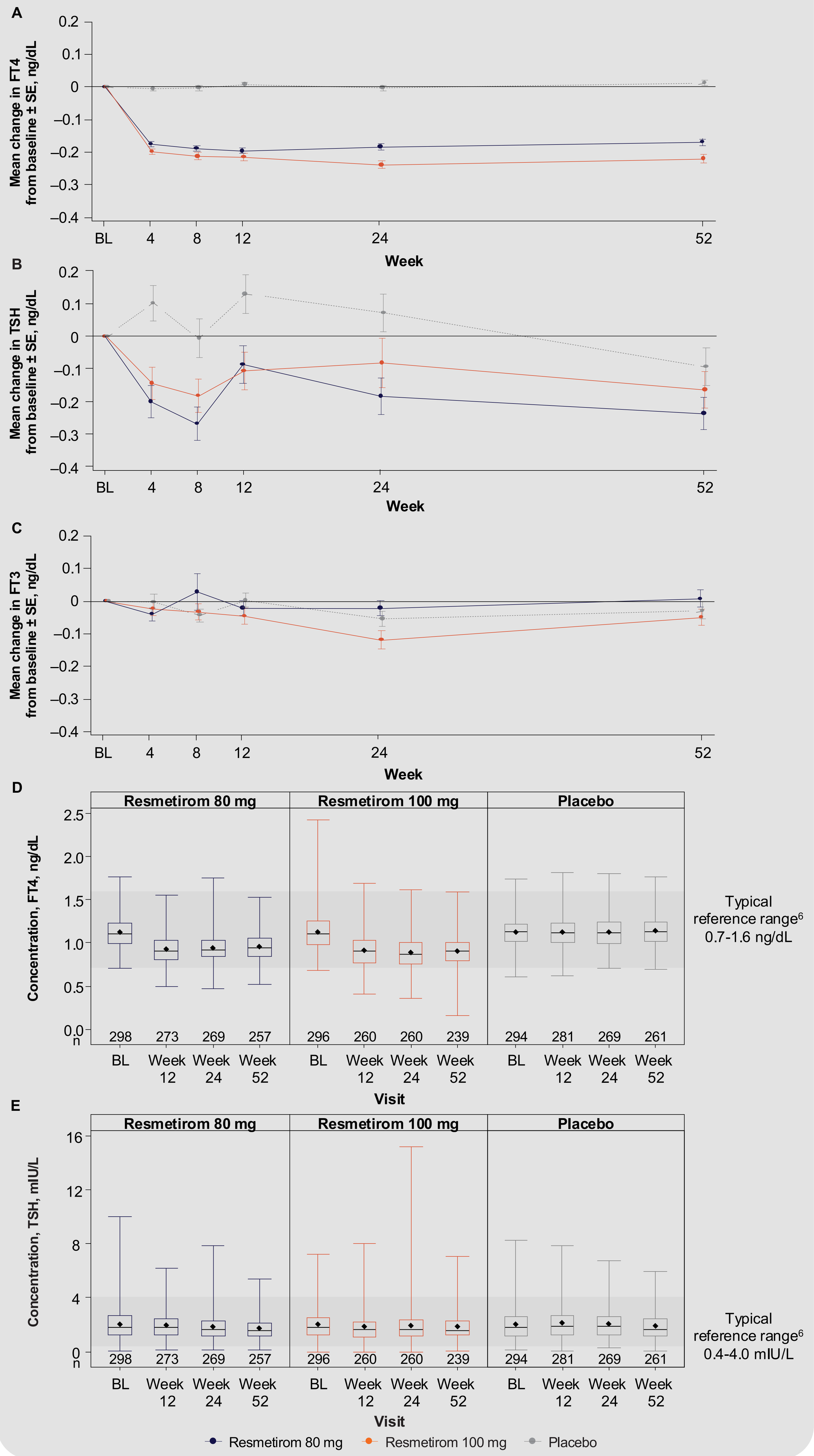
Characteristic	Resmetirom 80 mg n = 298	Resmetirom 100 mg n = 296	Placebo n = 294
Age, mean ± SD, years	55.8 ± 11.4	57.6 ± 10.5	57.2 ± 10.9
Sex, male	132 (44.3)	126 (42.6)	133 (45.2)
Race, White	268 (89.9)	267 (90.2)	255 (86.7)
Ethnicity, Hispanic or Latino	64 (21.5)	76 (25.7)	46 (15.6)
Body weight, mean ± SD, kg	99.9 ± 22.1	101.7 ± 22.9	100.3 ± 22.6
BMI, mean ± SD	35.5 ± 6.5	36.1 ± 7.3	35.5 ± 6.4
Type 2 diabetes	208 (69.8)	202 (68.2)	198 (67.3)
Hypertension	225 (75.5)	238 (80.4)	237 (80.6)
Dyslipidemia	211 (70.8)	217 (73.3)	205 (69.7)
History of ASCVD	17 (5.7)	21 (7.1)	14 (4.8)
LDL-C, mean ± SD, mg/dL	106.6 ± 37.6	102.4 ± 37.0	106.3 ± 41.4
Fibrosis stage			
F2	110 (36.9)	108 (36.5)	110 (37.4)
F3	188 (63.1)	188 (63.5)	184 (62.6)
Patients on thyroid replacement therapy at screening	37 (12.4)	43 (14.5)	44 (15.0)
Thyroxine dose ≤75 mcg/day	27 (9.1)	30 (10.1)	35 (11.9)
Thyroxine dose >75 mcg/day	9 (3.0)	12 (4.1)	9 (3.1)
Dose level unknown	1 (0.3)	1 (0.3)	0
FT4, mean ± SD, ng/dL[a]	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
FT3, mean ± SD, ng/L[b]	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.4
TSH, mean ± SD, mIU/L[c]	2.0 ± 1.2	2.0 ± 1.1	2.0 ± 1.2
rT3, mean ± SD, ng/dL[d]	18.5 ± 5.5	19.4 ± 6.3	18.6 ± 5.7
Baseline pulse rate, mean ± SD, bpm[e]	73.4 ± 10.9	72.3 ± 11.7	73.5 ± 11.7
Systolic BP, mean ± SD, mm Hg[e]	129.5 ± 14.0	129.4 ± 15.7	130.3 ± 13.7
Diastolic BP, mean ± SD, mm Hg[e]	79.9 ± 8.9	78.5 ± 9.3	80.7 ± 9.2

Data are n (%) unless otherwise specified.
[a]Reference range, 0.7-1.6 ng/dL.
[b]Reference range, 2.0-4.4 ng/L.
[c]Reference range, 0.4-4.0 mIU/L.
[d]Reference range, 9.0-27.0 ng/dL.
[e]Data from New Drug Application safety update.
ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; bpm, beats per minute; F, fibrosis stage (F2: moderate fibrosis, F3: advanced fibrosis); FT3, free triiodothyronine; FT4, free thyroxine; LDL-C, low-density lipoprotein cholesterol; rT3, reverse triiodothyronine; TSH, thyroid-stimulating hormone.

Outcomes

- Both doses of resmetirom produced modest decreases in FT4 without compensatory increases in TSH or FT3 over 52 weeks (**Figure 2**)
  - TSH remained generally stable over 52 weeks, indicating preserved HPT axis feedback
  - Minimal changes in FT3 were observed over 52 weeks; levels remained within the normal range

FIGURE 2. Levels of (A) FT4, (B) TSH, and (C) FT3 by treatment group over time, and distribution of (D) FT4 and (E) TSH levels by treatment group and visit



For plots in D and E, boxes represent interquartile range and whiskers represent minimum and maximum values.
BL, baseline; FT3, free triiodothyronine; FT4, free thyroxine; SE, standard error; TSH, thyroid-stimulating hormone.

- At Week 52, thyroid parameters showed minimal changes from baseline overall, regardless of baseline thyroxine replacement therapy status (**Table 2**)

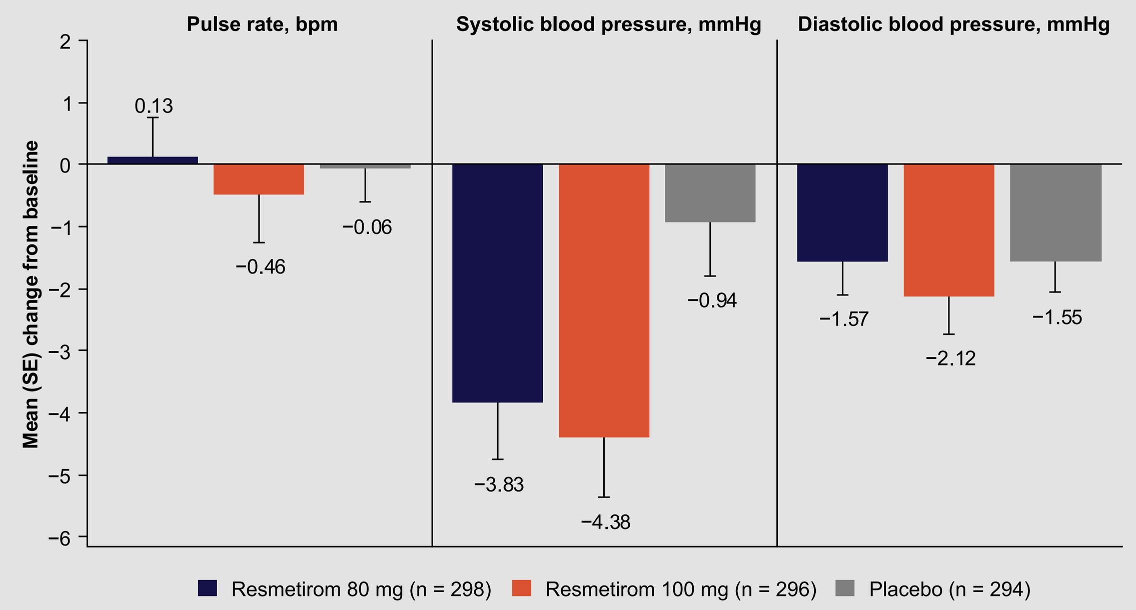
TABLE 2. Least-squares mean (LSM) change from baseline (CFB) in thyroid hormones at Week 52 by baseline thyroxine status

Hormone	LS mean CFB (SE)	LS mean CFB (SE)	LS mean CFB (SE)	LS mean difference from placebo (95% CI)	
	Resmetirom 80 mg	Resmetirom 100 mg	Placebo	Resmetirom 80 mg	Resmetirom 100 mg
Patients not on thyroxine replacement therapy at baseline					
FT3, ng/L	−0.01 (0.032) n = 248	−0.08 (0.033) n = 229	−0.02 (0.031) n = 245	0.01 (−0.06, 0.08)	−0.06 (−0.13, 0.01)
FT4, ng/L	−0.16 (0.011) n = 248	−0.21 (0.011) n = 229	0.02 (0.010) n = 245	−0.18 (−0.20, −0.16)	−0.23 (−0.25, −0.20)
TSH, mIU/L	−0.23 (0.056) n = 248	−0.20 (0.058) n = 229	−0.08 (0.055) n = 245	−0.15 (−0.27, −0.03)	−0.12 (−0.24, 0)
rT3, ng/dL	−4.5 (0.33) n = 247	−4.9 (0.34) n = 232	0.19 (0.33) n = 244	−4.5 (−5.4, −3.9)	−5.1 (−5.9, −4.8)
Patients receiving replacement thyroxine therapy at baseline					
FT3, ng/L	0.04 (0.089) n = 31	−0.03 (0.081) n = 36	−0.02 (0.079) n = 41	0.05 (0.13, 0.23)	−0.01 (−0.19, 0.17)
FT4, ng/L	−0.18 (0.041) n = 31	−0.26 (0.037) n = 36	0.02 (0.036) n = 41	−0.21 (−0.29, −0.12)	−0.29 (−0.37, −0.21)
TSH, mIU/L	−0.63 (0.27) n = 31	−0.13 (0.25) n = 36	−0.22 (0.24) n = 41	−0.41 (−0.97, 0.15)	0.09 (−0.46, 0.63)
rT3, ng/dL	−5.1 (0.94) n = 31	−6.3 (0.85) n = 37	−0.01 (0.84) n = 38	−5.1 (−7.1, −3.1)	−6.3 (−8.2, −4.4)

CFB, change from baseline; FT3, free triiodothyronine; FT4, free thyroxine; LS, least squares; rT3, reverse triiodothyronine; SE, standard error; TSH, thyroid-stimulating hormone.

- At Week 52, no clinically meaningful effects were observed in heart rate; small reductions in systolic blood pressure and diastolic blood pressure were observed (**Figure 3**)

FIGURE 3. Change from baseline in cardiovascular parameters at Week 52 by treatment group



bpm, beats per minute; SE, standard error.

CONCLUSION

- **In this post hoc analysis, resmetirom did not meaningfully affect systemic thyroid function, providing further support for its extrahepatic safety profile**
- **Cardiovascular parameters, including heart rate and blood pressure, remained generally stable across treatment groups**
- **These findings reinforce the hepatic selectivity of resmetirom with limited systemic thyroid hormone signaling effects**

DISCLOSURES

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