Reducing CV risk in patients with MASH independent of baseline statin use: Lp(a) and LDL-C lowering by resmetirom

POSTER #3508

Meena Bansal,[1] Rebecca Taub,[2] Dominic Labriola,[2] David Soergel,[2] Yestle Kim,[2] Naim Alkhouri,[3] Mazen Noureddin,[4] Seth Baum,[5] Rohit Loomba[6]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA; [3]Summit Clinical Research, San Antonio, TX, USA; [4]Pinnacle Clinical Research, San Antonio, TX, USA; [5]Florida Atlantic University, Boca Raton, FL, USA; [6]UC San Diego School of Medicine, San Diego, CA, USA

INTRODUCTION

- Patients with metabolic dysfunction–associated steatohepatitis (MASH) have high cardiovascular (CV) morbidity and mortality and commonly present with dyslipidemia, diabetes, obesity, and hypertension[1]
- Resmetirom, a selective thyroid hormone receptor β agonist, is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis)[2,3]
- Resmetirom has been shown to significantly reduce atherogenic lipids and lipoproteins, including low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and lipoprotein(a) (Lp[a])[4,5]

AIM

- To evaluate the effects of resmetirom on MASH efficacy parameters, atherogenic lipids and lipoproteins, and safety over 52 weeks according to baseline statin use in MAESTRO-NASH

METHODS

Study design and data source

- This was a secondary analysis of the phase 3 MAESTRO-NASH clinical trial. Supportive pharmacokinetic analyses of statin exposure were derived from MAESTRO-NAFLD-1
  - MAESTRO-NASH (NCT03900429) is an ongoing, phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of resmetirom in adults with biopsy-confirmed MASH and fibrosis (F1 to F3)[4]
  - MAESTRO-NAFLD-1 (NCT04197479) was a 52-week, randomized, double-blind, placebo-controlled phase 3 trial evaluating the safety and metabolic effects of resmetirom in adults with metabolic dysfunction–associated steatotic liver disease (MASLD) and presumed MASH using noninvasive diagnostic criteria[5]

Study population

- The modified intention-to-treat population from MAESTRO-NASH included patients with fibrosis stages F1B (mild fibrosis [substage B]), F2 (moderate fibrosis), and F3 (advanced fibrosis) at baseline who were randomly assigned to receive resmetirom 80 mg, 100 mg, or placebo[4]

Baseline characteristics

- Baseline demographic, clinical, imaging, and lipid parameters are summarized by baseline statin use

Outcomes

- Prespecified analyses stratified outcomes by baseline statin use over 52 weeks
  - Efficacy endpoints included Week 52 histologic outcomes (MASH resolution and fibrosis improvement) and change in liver fat by magnetic resonance imaging proton density fat fraction (MRI-PDFF)
  - Lipid endpoints included percentage change from baseline in LDL-C, ApoB, triglycerides (TGs), and Lp(a)
  - Safety assessments included treatment-emergent adverse events
- Statin pharmacokinetics were not analyzed in MAESTRO-NASH because the study remains ongoing and double-blind. To assess potential effects of concomitant treatment, statin exposure was evaluated in MAESTRO-NAFLD-1, a similar noncirrhotic MASLD population

RESULTS

Patient characteristics

- Approximately half (n = 473; 49%) of MAESTRO-NASH participants were on statins at baseline (**TABLE 1**)
- Atorvastatin was the most commonly used statin (47.1%), and 26.9% of statin-treated patients were receiving high-intensity statin therapy
- Baseline characteristics were generally similar across statin subgroups; however, a greater proportion of patients receiving statins, compared with those not receiving statins, had diabetes (79.5% vs 55.0%), dyslipidemia (100% vs 43.8%), and advanced fibrosis (F3: 64.3% vs 56.6%) at baseline

TABLE 1. Baseline demographic and clinical characteristics

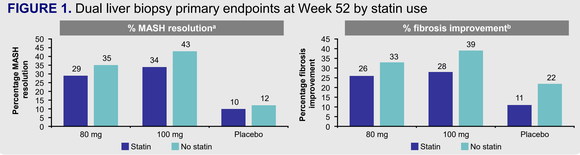
Characteristic	BL statin (N = 473)	No BL statin (N = 493)
Age, mean (SD), years	59.3 (9.4)	54.1 (11.7)
Sex, male, n (%)	224 (47.4)	200 (40.6)
Race, White, n (%)	414 (87.5)	449 (91.1)
Ethnicity, Hispanic or Latino, n (%)	94 (19.9)	110 (22.3)
BMI, mean (SD)	35.9 (6.8)	35.4 (6.7)
T2D, n (%)	376 (79.5)	271 (55.0)
Hypertension, n (%)	407 (86.0)	347 (70.4)
Dyslipidemia, n (%)	473 (100.0)	216 (43.8)
Hypothyroidism, n (%)	70 (14.8)	60 (12.2)
ASCVD, n (%)	38 (8.0)	19 (3.9)
ASCVD risk score, mean (SD)	16.0 (11.7)	14.0 (12.0)
LSM by FibroScan VCTE, kPa		
Mean (SD)	13.9 (7.4)	12.7 (5.5)
Median (min, max)	12.0 (3.8, 75.0)	11.4 (4.0, 66.4)
CAP by FibroScan, mean (SD), dB/m	350.4 (36.7)	344.8 (38.4)
% liver fat by MRI-PDFF, mean (SD)	16.8 (6.5)	18.6 (6.9)
LSM by MRE, kPa		
Mean (SD)	3.6 (1.0)	3.5 (1.0)
Median (min, max)	3.5 (1.8, 9.2)	3.3 (1.9, 9.9)
ELF score, mean (SD)	9.8 (0.9)	9.7 (0.9)
Baseline liver biopsy, n (%)		
NAS ≥5 at screening	393 (83.1)	414 (84.0)
F1B	32 (6.8)	17 (3.4)
F2	128 (27.1)	191 (38.7)
F3	304 (64.3)	279 (56.6)
On GLP-1 therapy, n (%)	84 (17.8)	53 (10.8)
Statin use, n (%)		
Atorvastatin	223 (47.1)	N/A
Atorvastatin ≥40 mg	84 (17.8)	N/A
Lovastatin	7 (1.5)	N/A
Pitavastatin	3 (0.6)	N/A
Pravastatin	63 (13.3)	N/A
Pravastatin ≥40 mg	25 (5.3)	N/A
Rosuvastatin	114 (24.1)	N/A
Rosuvastatin ≥20 mg	42 (9.3)	N/A
Simvastatin ≤20 mg	64 (13.5)	N/A
Statin intensity, n (%)		
High	127 (26.9)	N/A
Moderate	288 (61.0)	N/A
Low	56 (11.9)	N/A
Other lipid therapy	137 (29.0)	103 (20.9)
Baseline lipids		
LDL-C, mean (SD), mg/dL	87.7 (32.3)	122.5 (36.3)
LDL-C ≥100 mg/dL, n (%)	136 (28.8)	373 (75.7)
LDL-C ≥70 mg/dL, n (%)	336 (71.0)	461 (93.5)
HDL-C, mean (SD), mg/dL	43.0 (12.9)	44.7 (12.9)
TGs, mean (SD), mg/dL	194.2 (135.8)	180.8 (127.5)
TGs ≥150 mg/dL, n (%)	266 (56.2)	262 (53.1)
ApoB, mean (SD), mg/dL	86.7 (24.8)	107.6 (29.5)
Lp(a), mean (SD), nmol/L	6.1 (4.0)	6.1 (4.2)

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BL, baseline; BMI, body mass index; CAP, controlled attenuation parameter; dB, decibel; ELF, enhanced liver fibrosis test; F, fibrosis stage (F1B: mild fibrosis [substage B]; F2: moderate fibrosis, F3: advanced fibrosis); GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; kPa, kilopascal; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; T2D, type 2 diabetes; TG, triglyceride; VCTE, vibration-controlled transient elastography.

Efficacy measures by baseline statin use

- The dual primary endpoints remained directionally consistent with the overall MAESTRO-NASH results and were nominally statistically significant for both resmetirom 80 mg and 100 mg versus placebo, regardless of baseline statin use (**FIGURE 1**)

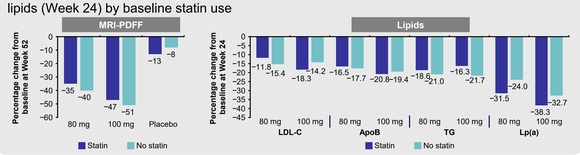
FIGURE 1. Dual liver biopsy primary endpoints at Week 52 by statin use



[a]Resolution of MASH is defined as achievement of a hepatocellular ballooning score of 0, inflammation score of 0 or 1, and ≥2-point reduction in NAS with no worsening of fibrosis.[6] [b]Fibrosis improvement is defined as achievement of ≥1-stage reduction in fibrosis with no worsening of NAS. A 1-point improvement in fibrosis would be a change to F1A or F1C from F2 (a change of F2 to F1B is not considered a 1-point improvement)[6]
F, fibrosis stage (F1A: mild fibrosis [substage A], F1B: mild fibrosis [substage B], F1C: mild fibrosis [substage C], F2: moderate fibrosis); MASH, metabolic dysfunction–associated steatohepatitis; NAS, nonalcoholic fatty liver disease activity score.

- A numerically greater reduction in liver fat as measured by MRI-PDFF at Week 52 was also observed with resmetirom compared with placebo, irrespective of baseline statin use (**FIGURE 2**)
- At Week 24, placebo-corrected reductions were observed for LDL-C, ApoB, TGs, and Lp(a) across statin and non-statin subgroups (**FIGURE 2**)

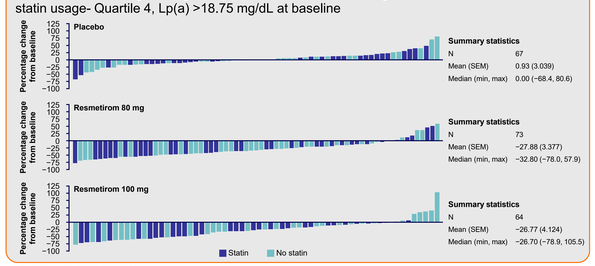
FIGURE 2. Percentage change from baseline in MRI-PDFF (Week 52, % liver fat content) and lipids (Week 24) by baseline statin use



ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MRI-PDFF, magnetic resonance imaging proton density fat fraction; TG, triglyceride.

- In patients on statins, 44.4% with LDL-C ≥70 mg/dL at baseline shifted to LDL-C <70 mg/dL with 100 mg resmetirom; 36.3% and 37.5% with Lp(a) ≥30 or ≥50 mg/dL at baseline shifted to <30 or <50 mg/dL with 100 mg resmetirom (**FIGURE 3** and **TABLE 2**)
- Patients in the highest CV risk quartile of baseline Lp(a) showed significant reductions in Lp(a) with resmetirom, independent of statin use (**FIGURE 3**)

FIGURE 3. Percentage change in Lp(a) from baseline according to resmetirom treatment and statin usage- Quartile 4, Lp(a) >18.75 mg/dL at baseline



Lp(a), lipoprotein(a); SEM, standard error of the mean.

TABLE 2. Shift in Lp(a) and LDL-C risk categories at Week 52

Characteristic	Resmetirom 80 mg		Resmetirom 100 mg		Placebo	
	Statin	No statin	Statin	No statin	Statin	No statin
Lp(a) ≥30 mg/dL						
Baseline, n (%)	32 (25.8)	30 (21.0)	22 (17.1)	22 (17.9)	30 (21.4)	20 (14.4)
Week 52, n (%)	22 (17.7)	19 (13.3)	14 (10.9)	12 (9.8)	30 (21.4)	20 (14.4)
% shift to <30 mg/dL	31.3	36.7	36.3	45.4	0	0
Lp(a) ≥50 mg/dL						
Baseline, n (%)	21 (16.9)	16 (11.2)	16 (12.4)	8 (6.5)	17 (12.1)	7.9
Week 52, n (%)	14 (11.3)	10 (7.0)	10 (7.8)	3 (2.4)	19 (13.6)	6.5
% shift to <50 mg/dL	33.0	37.5	37.5	62.5	-11.8	18.2
LDL-C ≥70 mg/dL						
Baseline, n (%)	88 (68.2)	138 (93.9)	97 (71.9)	116 (91.3)	102 (70.8)	132 (93.6)
Week 52, n (%)	65 (50.4)	119 (81.0)	53 (39.3)	100 (78.7)	95 (66.0)	130 (92.2)
% shift to <70 mg/dL	26.1	13.8	44.4	13.8	-6.8	1.5
LDL-C ≥100 mg/dL						
Baseline, n (%)	44 (34.1)	108 (73.5)	34 (25.2)	97 (76.4)	42 (29.2)	106 (75.2)
Week 52, n (%)	25 (19.4)	60 (40.8)	15 (11.1)	47 (37.0)	38 (26.4)	99 (70.2)
% shift to <100 mg/dL	43.2	44.4	50.0	51.5	9.5	6.6

Includes patients with both baseline and Week 52 data.
LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

Adverse events by statin use

- No significant statin-related adverse events were observed

CONCLUSION

- **Resmetirom demonstrated consistent efficacy across key MASH endpoints and reduced multiple atherogenic lipids and lipoproteins regardless of baseline statin use**
- **Resmetirom demonstrated significant shifts of Lp(a) and LDL-C into potentially lower CV risk categories independent of baseline statin use**
- **Approximately half of patients were on statins and no statin or resmetirom related safety signal was observed**
- **These findings support concomitant use of resmetirom and statins in patients requiring management of both hepatic and CV metabolic risk**

DISCLOSURES

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