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Impact of resmetirom on statin pharmacokinetics safety in Phase 1 and 3 studies; Safety and efficacy of resmetirom in patients on statins in MAESTRO-NASH

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Background

- Resmetirom, a THR-β agonist approved by the US FDA in March 2024, is indicated for the treatment of adults with NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3)
- In MAESTRO-NASH (NCT03900429), the pivotal Phase 3, randomized, placebo-controlled trial of resmetirom that enrolled patients with biopsy-confirmed NASH and fibrosis:
  - 49% of enrolled patients were taking statins at baseline (**Tables 1 and 2**)
  - 13% were receiving high-intensity statin therapy (rosuvastatin 20 mg or atorvastatin 40 mg)
  - 36% were receiving moderate or low-intensity statin therapy
- As part of the resmetirom clinical development program, four Phase 1 pharmacokinetic studies assessing potential drug interactions of resmetirom with commonly prescribed statins were carried out

Methods

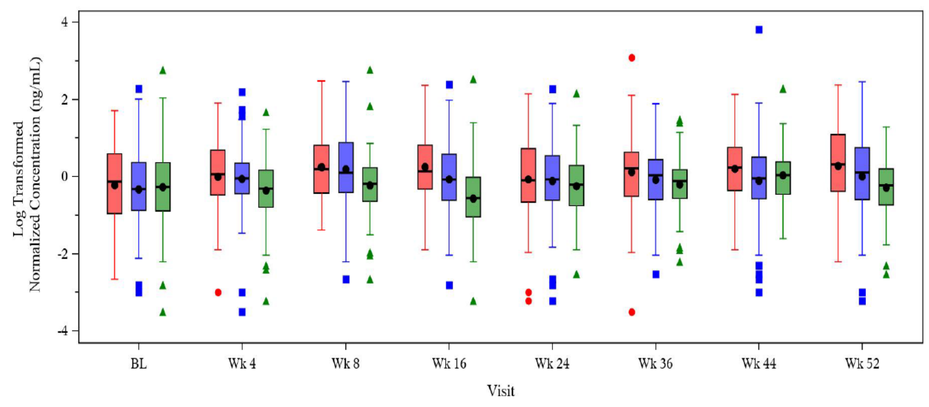
- Drug interaction studies of resmetirom with commonly prescribed statins were performed in Phase 1 healthy volunteers
- Statin levels were measured in MAESTRO-NAFLD-1, a non-invasively diagnosed NASH population
- In MAESTRO-NASH:
  - Liver enzymes were assessed in patients on statins and not on statins
  - Assessments of common statin AEs were assessed in MAESTRO-NASH
  - Safety was assessed in patients in MAESTRO-NASH according to statin therapy at baseline
- Safety and responses were assessed as a function of statin therapy in MAESTRO-NASH
- We analyzed data from the Phase 1 pharmacokinetic studies and the Phase 3 study to evaluate the potential impact of co-administration of resmetirom and statins on statin pharmacokinetics in healthy subjects and patients with NASH and fibrosis
- Safety and efficacy by statin dose in Phase 3 were also evaluated

Results

Drug Interaction Studies—Phase 1 and 3

- Phase 1 studies showed generally weak interactions between resmetirom and statins
- In Phase 3 patients, the PK of atorvastatin with resmetirom were within the range of normal PK variability (**Figure 1; red= 80 mg dose, blue= 100 mg dose, green= placebo**)

Figure 1. Pharmacokinetics of Atorvastatin with Concomitant Resmetirom



Results (continued from above right)

Table 1. Patients on Statins in MAESTRO-NASH

Baseline Characteristic	Statin (N=472)	No Statin (N=494)
Age (years) – Mean (SD)	59.3 (9.4)	54.1 (11.7)
Sex, Male – n (%)	223 (47.2)	201 (40.7)
Race, White – n (%)	414 (87.7)	449 (90.9)
Ethnicity, Hispanic or Latino – n (%)	94 (19.9)	110 (22.3)
Body Mass Index (kg/m^2) Mean (SD)	35.9 (6.8)	35.4 (6.7)
Type 2 Diabetes – n (%)	376 (79.7)	271 (54.9)
Hypertension – n (%)	407 (86.2)	347 (70.2)
Dyslipidemia – n (%)	472 (100)	217 (43.9)
Hypothyroidism – n (%)	70 (14.8)	59 (11.9)
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)
FibroScan CAP (dB/m) Mean (SD)	350.5 (36.7)	344.8 (38.4)
(%)MRI-PDFF– Mean (SD)	16.8 (6.5)	18.6 (6.9)
Stiffness by MRE (kPa)– Mean (SD)	3.6 (1.0)	3.5 (0.98)
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)
On GLP-1 Therapy – n (%)	84 (17.8)	53 (10.7)
Statin Intensity		
High	127 (26.9)	N/A
Moderate	288 (61.0)	N/A
Low	56 (11.9)	N/A
Baseline Livery Biopsy – n (%)		
NAS ≥5 at Screening	393 (83.3)	414 (83.8)
Fibrosis 1B	32 (6.8)	17 (3.4)
Fibrosis 2	128 (27.1)	191 (38.7)
Fibrosis 3	303 (64.2)	280 (56.7)

Table 2. Statins and Doses

Statin Dose (N=966)	%
% Patients taking a statin	49.0
Atorvastatin	23.1
≤40 mg	22.7
>40 mg	0.4
Lovastatin	0.7
Pitavastatin	0.3
Pravastatin	6.5
≤40 mg	6.4
>40 mg	0.1
Rosuvastatin	11.8
≤20 mg	11.6
>20 mg	0.2
Simvastatin	6.6
≤20 mg	6.5
>20 mg	0.1

Figure 2. Creatine kinase change from baseline

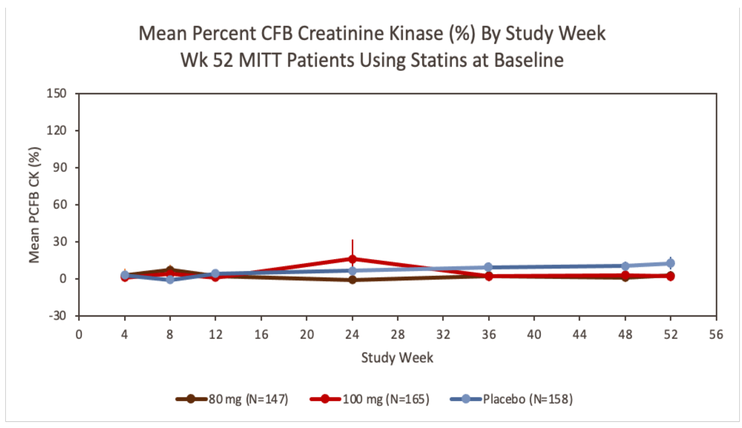


Figure 3. Changes in Liver Enzymes (ALT)
A= all patients (baseline >=30 U/L). B= patients on statins (baseline >=30 U/L). C= patients not on statins (baseline >=30 U/L)

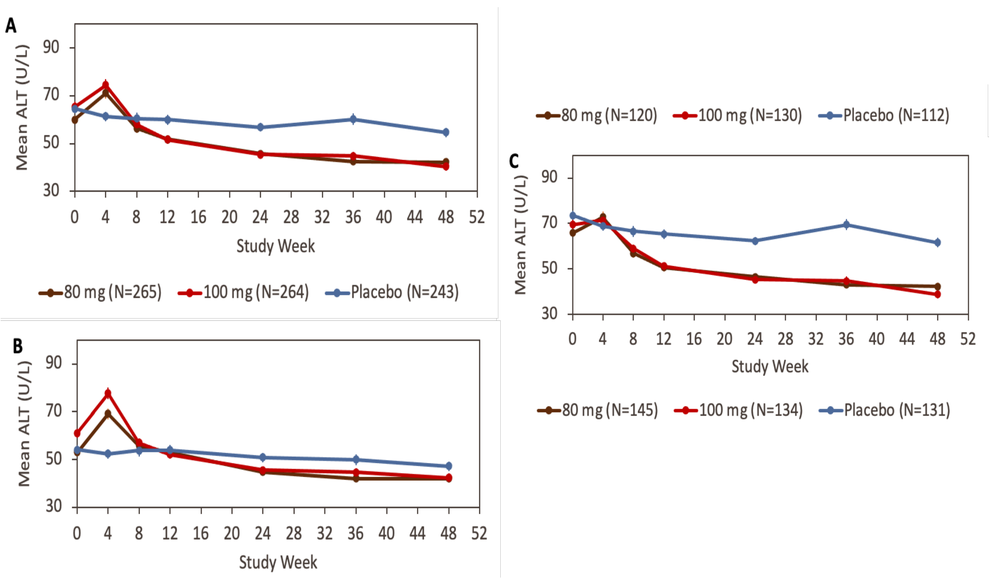


Table 3A. MAESTRO-NASH Statin Safety (AEs and SAEs)

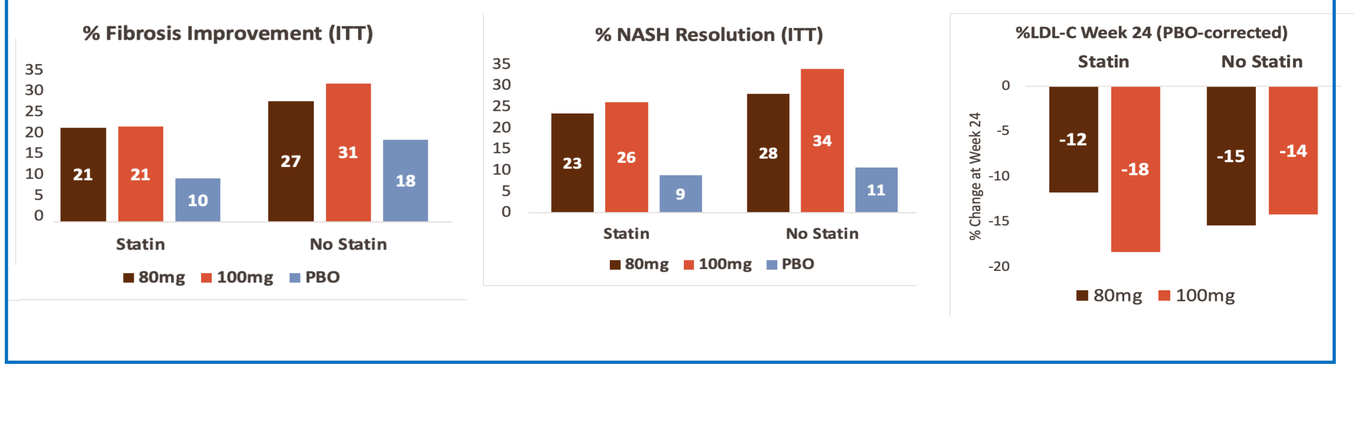
Event	Resmetirom 80 mg (N = 322)		Resmetirom 100 mg (N = 323)		Placebo (N=321)	
	Statin at BL (N = 149) n (%)	No statin at BL (N=173) n (%)	Statin at BL (N=166) n (%)	No statin at BL (N=157) n (%)	Statin at BL (N=158) n (%)	No statin at BL (N=163) n (%)
≥ 1 adverse event	141 (94.6)	155 (89.6)	149 (89.8)	147 (93.6)	146 (92.4)	152 (93.3)
≥ 1 SAE	20 (13.4)	15 (8.7)	23 (13.9)	18 (11.5)	23 (14.6)	14 (8.6)
Adverse events affecting >10% of patients in any group						
Diarrhea	32 (21.5)	55 (31.8)	52 (31.3)	56 (35.7)	19 (12.0)	32 (19.6)
Nausea	29 (19.5)	42 (24.3)	28 (16.9)	33 (21.0)	18 (11.4)	22 (13.5)
COVID-19	31 (20.8)	38 (22.0)	27 (16.3)	27 (17.2)	31 (19.6)	36 (22.1)
Arthralgia	21 (14.1)	27 (15.6)	19 (11.4)	16 (10.2)	16 (10.1)	24 (14.7)
Back pain	21 (14.1)	14 (8.1)	15 (9.0)	12 (7.6)	17 (10.8)	21 (12.9)
Pruritus	16 (10.7)	10 (5.8)	21 (12.7)	16 (10.2)	16 (10.1)	6 (3.7)
Fatigue	16 (10.7)	17 (9.8)	9 (5.4)	17 (10.8)	15 (9.5)	13 (8.0)
Vomiting	14 (9.4)	14 (8.1)	12 (7.2)	23 (14.6)	10 (6.3)	7 (4.3)
Abdominal pain	12 (8.1)	14 (8.1)	13 (7.8)	16 (10.2)	9 (5.7)	9 (5.5)
UTI	12 (8.1)	21 (12.1)	13 (7.8)	14 (8.9)	14 (8.9)	14 (8.6)
Headache	10 (6.7)	20 (11.6)	13 (7.8)	12 (7.6)	12 (7.6)	16 (9.8)

Table 3B. MAESTRO-NASH Statin Safety (muscle-related events)

AE Preferred Term	Resmetirom 80 mg (N = 322) n (%)			Resmetirom 100 mg (N = 323) n (%)			Placebo (N = 321) n (%)		
	Statin	No Statin	Total	Statin	No Statin	Total	Statin	No Statin	Total
Myalgia	2 (1.3)	5 (2.9)	7 (2.2)	3 (1.8)	10 (6.4)	13 (4.0)	5 (3.2)	6 (3.7)	11 (3.4)
Myopathy	1 (0.7)	1 (0.4)	1 (0.3)	0	0	0	0	0	0
Myositis	0	0	0	0	0	0	0	0	0
Rhabdomyolysis	0	0	0	0	0	0	0	0	0

Figure 4. Efficacy of Statins in MAESTRO-NASH

- Lipid lowering similar in statin- and non-statin-treated resmetirom patients
- Liver biopsy endpoints achieved in statin- and non-statin-treated patients on resmetirom



Conclusions

- Pharmacokinetic modeling concluded that higher exposure to resmetirom was associated with higher hepatic target engagement as reflected by higher SHBG responses and higher MRI-PDFF reduction
- The only variable that influenced exposure to resmetirom in the NASH population was body weight
- Resmetirom was well tolerated at both doses with a few more discontinuations in the 100 mg treatment group due to GI AEs. Discontinuations at 100 mg appeared to be slightly higher than 80 mg in patients with baseline body weight <100 kg
- Slightly lower rates of fibrosis improvement and NASH resolution on biopsy were observed in patients who were ≥100 kg or BMI≥ 35 in patients treated with 80 mg versus 100 mg
- Other biomarkers such as ALT, FibroScan, CAP and VCTE showed similar improvements relative to placebo at 80 mg and 100 mg. Responses on FibroScan in resmetirom treated patients were durable out to 3 years of treatment and showed improvement and less worsening than placebo