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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

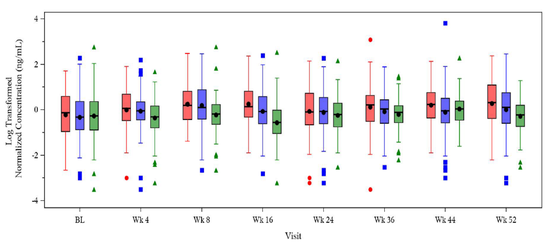
- Drug interaction studies of resmetirom with commonly prescribed statins were performed in Phase 1 healthy volunteers
- Statin levels were measured in MAESTRO-NAFLD-1, a non-invasively diagnosed NASH population
- In MAESTRO-NASH:
  - Liver enzymes were assessed in patients on statins and not on statins
  - 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)

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/m²) 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

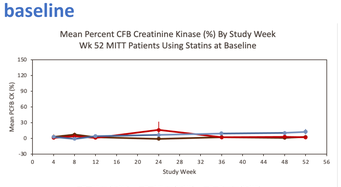


Figure 3. Changes in Liver Enzymes (ALT). A= all patients (baseline >=30 U/L). B= patients on statins (baseline >=30 U/L). C= patients not on statins (baseline >=30 U/L)

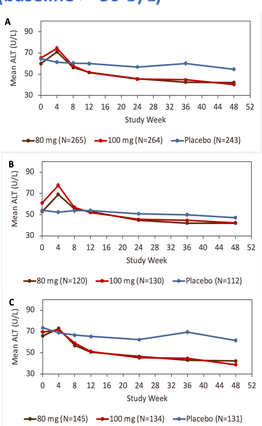


Table 3A. MAESTRO-NASH Statin Safety (AEs and SAEs)

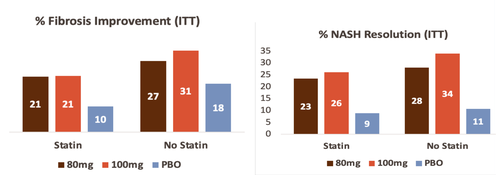
Event	Resmetirom 80 mg (N = 322)		Resmetirom 100 mg (N = 323)		Placebo (N=321)	
	Statin at BL (N = 149) n (%)	No statin at BL (N=173) n (%)	Statin at BL (N=166) n (%)	No statin at BL (N=157) n (%)	Statin at BL (N=158) n (%)	No statin at BL (N=163) n (%)
≥ 1 adverse event	141 (94.6)	155 (89.6)	149 (89.8)	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)

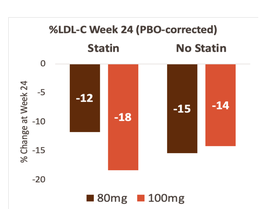
Table 3B. MAESTRO-NASH Statin Safety (muscle-related events)

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





Safety of Statins in MAESTRO-NASH

- No increase in AEs was observed with resmetirom alone or in combination with statins (**Table 3A**)
- No change in muscle AEs or no DILI AEs occurred (**Table 3B**)

Conclusions

- **The resmetirom US label recommends resmetirom use with 98% of statin doses used by NASH patients; in addition, statin drug levels (PK) in Phase 3 patients on resmetirom were within the range of statin PK variability**
- **NASH patients on statins had lower baseline liver enzymes than patients not on statins. Transient increase to approximately 1.3 times baseline at week 4, not generally above the level in patients not on statins, was observed in patients on resmetirom and statins; no significant week 4 elevations were observed in patients on resmetirom not on statins (Figure 3)**
- **Liver enzymes improved relative to baseline over time in resmetirom-treated patients compared with placebo, independent of statin use (Figure 3)**
- **No statin-related safety findings were noted in MAESTRO-NASH patients who took statins**
- **Efficacy measures, including lipid lowering and NASH and fibrosis biopsy endpoints, were similar and statistically significantly improved in resmetirom-treated patients whether on statins or not on statins (Figure 4)**

Disclosures

- **Baum reports: Altimmune, Amgen, Axcella, Beren Therapeutics, Boehringer Ingelheim, Eli Lilly, Esperion, Ionis Pharmaceuticals, Madrigal Pharmaceuticals, Merck, Novartis, Regeneron**
- **Alkhouri reports: Echosens, Fibronostics, Gilead Sciences, Inc.,89Bio, Inc., Boehringer Ingelheim, Intercept Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., Madrigal Pharmaceuticals, Novo Nordisk, Viking Therapeutics, Zydus Pharmaceuticals, Inc. Novo Nordisk**
- **Taub and Labriola are employees of Madrigal**
- **Noureddin reports: Altimmune, Aligos Therapeutics, AstraZeneca, Boehringer Ingelheim, Boston Pharmaceuticals, CytoDyn Inc., GSK plc., Lilly, Madrigal Pharmaceuticals, Merck & Co., Inc., Novo Nordisk, Takeda Pharmaceutical Company Limited, Terns Pharmaceuticals, Inc., ChronWell, Rivus Pharmaceuticals, Allergan Pharmaceuticals, Akero Therapeutics, Inc., Bristol Myers Squibb, Conatus Pharma, Corcept Therapeutics, Inc., Enanta Pharmaceuticals, Inc., Gilead Sciences, Inc., Galectin Therapeutics, Genfit, Novartis, Viking Therapeutics, Zydus Pharmaceuticals, Inc.**