In a 36-Week Placebo-Controlled Phase 2 Trial in Patients with Non-alcoholic Steatohepatitis (NASH), Treatment with MGL-3196 (resmetirom) Significantly Reduces Atherogenic Lipoprotein Particles

Poster No 1521

R. Taub[1], JP. Frias[2], SJ. Baum[3], S. Hsia[2], S. Harrison[4] - (1) Madrigal Pharmaceuticals, Conshohocken, United States of America (2) University of California San Diego, San Diego, United States of America (3) DelRay Medical Center, Boca Raton, United States of America (4) John Radcliffe Hospital, Oxford, United Kingdom

PURPOSE

Resmetirom (MGL-3196) is a liver-directed, orally active, highly selective THR-β agonist (Fig 1) in Phase 3 development for the treatment of NASH with advanced stage 2-3 fibrosis. In a 36-week serial liver biopsy study, compared with placebo, resmetirom treated patients showed statistically significant reductions in liver fat, liver enzymes and atherogenic lipids including low-density lipoprotein cholesterol (LDL-C) and triglycerides. NASH was reduced and resolved in resmetirom treated compared with placebo.

Most NASH patients die of cardiovascular disease (CVD) rather than liver disease, and, in NASH patients, CV risk correlates better with LDL particle than LDL-C levels. The impact of NASH therapeutics on CV disease is of key importance.

METHODS

MGL-3196-05 (NCT02912260) was a 36-week multicenter, double-blind, randomized, placebo-controlled trial in 125 adults with biopsy-confirmed NASH (NAS≥4, F1-F3) and hepatic fat fraction ≥10% (Table 1). The study incorporated an adaptive dosing design with all resmetirom patients starting on 80 mg (Fig 2). Patients with higher exposure had their dose reduced to 60 mg at week 4; a few had their dose increased to 100 mg at week 4 and were included in the 80 mg group. Lipids were assessed throughout the 36 week treatment period. At 36 weeks lipoprotein particle concentrations were assessed in fasting blood samples and compared to baseline.

RESULTS

The Phase 2 NASH study included a high percentage of diabetics on multiple therapies, including statins and other lipid lowering agents (Table 1). Resmetirom statistically significantly lowered LDL-C, ApoB, TGs, ApoCIII, Lp(a), and remnant cholesterol, particularly in patients with higher LDL cholesterol at baseline (Figure 4). Patients on higher doses showed greater reductions (Figure 5). As shown (Table 2), resmetirom significantly reduced the level of lipoprotein particles, with greater reductions in patients with baseline (BL) LDL-C >=100 mg/dL and the patient group with higher resmetirom exposures (Exposure grp high). Reductions in small LDL particles, up to 39.4% and large VLDL and chylomicron particles up to 71.3% were observed.

Figure 1.

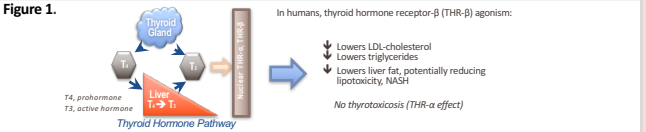


Figure 2. Phase 2 Study Design

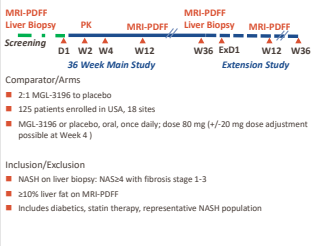


Table 1. Patient Baseline Characteristics

	Placebo (41)	Remetirom (84)
Mean age, years (SD)	47.3 (11.7)	51.8 (10.4)
Male, n (%)	24 (58.5)	38 (45.2)
White	37 (90.2)	79 (94.0)
Hispanic/Latino	22 (53.7)	37 (44.0)
Diabetic, n (%)	13 (31.7)	35 (41.7)
Mean BMI (SD)	33.6 (5.8)	35.8 (6.2)
Mean ALT	60.1 (32.8)	50.0 (29.2)
PRO-C3	16.2 (8.3)	17.8 (10.3)
ELF	9.2 (1.0)	9.2 (0.88)
Mean LDL-C	116.9 (30.0)	111.3 (30.4)
Mean Triglycerides (TG)	161.1 (75.2)	178.5 (82.4)
Mean MRI-PDFF*	19.8 (6.7)	20.7 (7.0)
Mean NAS	4.8 (1.1)	4.9 (1.0)
Fibrosis stage** 1, n (%)	19 (46.3)	47 (55.9)
2-3, n (%)	20 (48.8)	36 (42.8)

* Patients with both baseline and week 12 assessments; **FO placebo=2 (4.9); MGL-3196=1 (1.2) were included in all analyses

Figure 3. Patient Disposition

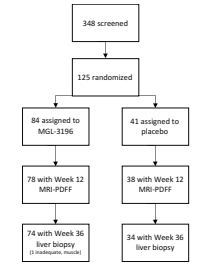


Figure 4. Resmetirom Effects on Lipids and Lipoproteins

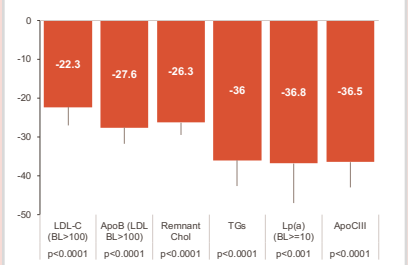
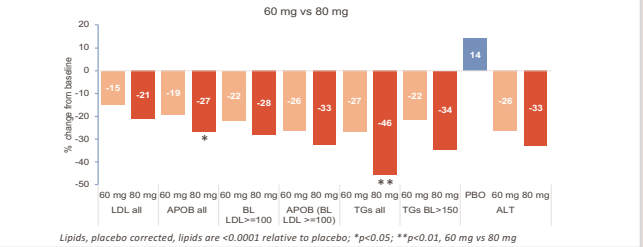


Figure 5. Reductions in LDL-C, ApoB and Triglycerides Dose Response



*Lipids, placebo corrected, lipids are <0.0001 relative to placebo; *p<0.05; **p<0.01, 60 mg vs 80 mg*

Table 2. Resmetirom Effects on Lipoprotein Particles

Particle concentrations by NMR	Time	Placebo	Resmetirom	LS mean % change from baseline vs placebo (SE)	p-value
Total LDL particles (nmol/L), mean (SD)					
All, Pbo, n=34; Res, n=73	BL	1234 (276)	1275 (328)		
	W36	1251 (323)	1045 (264)	-19·6 (-27·9, -11·3)	p< 0·0001
BL LDL-C≥100mg/dL, , Pbo, n=24; Res, n=44	BL	1360 (227)	1443 (290)		
	W36	1354 (314)	1155 (248)	-19·8 (-31·0, -8·5)	p= 0·0008
Exposure Grp-High, BL LDL-C≥100mg/dL, n=25	BL		1407 (266)		
	W36		1090 (216)	-22·8 (-35·4,-10·1)	p= 0·0006
Small LDL particles (nmol/L), mean (SD)					
All, Pbo, n=34; Res, n=73	BL	746 (295)	835 (294)		
	W36	749 (343)	641 (207)	-27·7 (-45·4,-10·1)	p = 0·002
BL LDL-C≥100mg/dL Pbo, n=24; Res, n=44	BL	783 (311)	887 (329)		
	W36	784 (375)	641 (234)	-34·3 (-60·3,-8·2)	p = 0·01
Exposure Grp-High, BL LDL-C≥100 mg/dL, n=25	BL		916 (314)		
	W36		618 (149)	-39·4 (-68·7,-10)	p = 0·009
IDL particles (nmol/L)					
All, Pbo, n=34; Res, n=73	BL	159 (146)	157 (100)		
	W36	197 (144)	158 (100)	-200 (-369,-29·7)	p=0·02
Total VLDL and chylomicron particles (nmol/L), mean (SD)					
All, Pbo, n=34; Res, n=73	BL	56·8 (23·9)	55·9 (22·9)		
	W36	58·8 (24·4)	46·0 (21·1)	-22·7 (-36·3,-9·0)	p= 0·001
BL LDL-C≥100mg/dL Pbo, n=24; Res, n=44	BL	59·0 (26·1)	61·4 (24·5)		
	W36	60·5 (27·5)	47·6 (22·9)	-27·2 (-42·3,-12·2)	p= 0·0006
Exposure Grp-High, BL LDL-C≥100 mg/dL, n=25	BL		66·0 (24·8)		
	W36		47·4 (23·1)	-34·7 (-51·2,-18·2)	p<0·0001
Large VLDL and chylomicron Particles (nmol/L), mean (SD)					
All, Pbo, n=34; Res, n=73	BL	6·3 (4·3)	8·7 (5·8)		
	W36	7·2 (4·5)	6·6 (3·9)	-52·5 (-76·0,-29·1)	p < 0·0001
BL LDL-C≥100mg/dL Pbo, n=24; Res, n=44	BL	6·6 (3·7)	8·9 (6·1)		
	W36	8·1 (4·9)	6·7 (4·1)	-65·6 (-96·5,-34·7)	p < 0·0001
Exposure Grp-High, BL LDL-C≥100 mg/dL, n=25	BL		10·2 (6·8)		
	W36		7·2 (4·7)	-71·3 (-106,-36·5)	p = 0·0001

CONCLUSIONS

- Resmetirom statistically significantly lowered LDL-C in NASH patients, greater at the higher dose of 80 (and 100 mg) currently used in MAESTRO-NASH an ongoing Phase 3 study in patients with NASH fibrosis
- Resmetirom decreased other atherogenic lipids and lipoproteins including ApoB, triglycerides, ApoCIII and Lp(a) and remnant cholesterol
- LDL, small LDL, IDL , VLDL and chylomycron lipoprotein particles were statistically significantly reduced
- The % ApoB reduction is similar to the reduction in LDL-C, an unusual property of this mechanism
- Apo B reduction is positively correlated with CV benefit
- These findings are consistent with a potential for a beneficial effect of resmetirom on the CV risk profile in NAFLD/NASH patients

Contact information

Rebecca Taub, M.D., President R&D.
Madrigal Pharmaceuticals.
becky@madrigalpharma.com

Declarations of Interest

- Taub, management position: Madrigal Pharmaceuticals
- Harrison, Received remuneration from Madrigal for consulting services
- Frias, no conflicts
- Baum, research grant
- Hsia, no conflicts