LDL cholesterol, apolipoprotein B, lipoprotein(a), apolipoprotein CIII and triglyceride lowering by MGL-3196, a thyroid hormone receptor beta selective agonist, in a 12 week study in HeFH patients

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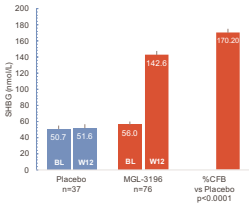
PURPOSE

The hepatic THR-β receptor mediates the beneficial effects of thyroid hormone on LDL-cholesterol and triglycerides, fatty liver and insulin sensitivity. MGL-3196 is a liver-directed, highly β-selective orally active, THR-β agonist being studied in both NASH and dyslipidemia. Here, a Phase 2 clinical trial was conducted in 116 patients with proven heterozygous familial hypercholesterolemia (HeFH). The primary endpoint was reduction in LDL-C compared with placebo and secondary endpoints included effects on additional lipids and lipoproteins.

METHODS

MGL-3196-06 (NCT03038022) is a 12 week multicenter, randomized, double blind, placebo controlled trial in HeFH patients not at LDL-C target on maximally tolerated statins. Patients received MGL-3196 100 mg or placebo once daily for 12 weeks (in a 2:1 ratio) in addition to their LDL-C lowering regimen. Based on blinded Week 2 PK, MGL-3196 patients continued on 100 mg or a dose of 60 mg from Week 4-12. (Figure 1)

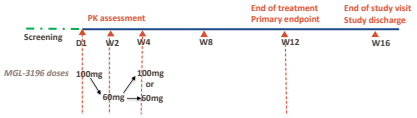
Figure 3. SHBG, a Highly Specific Biomarker for MGL-3196 Levels



RESULTS

Approximately 75% of patients were on high intensity statins (atorvastatin 80 mg; rosuvastatin 20/40 mg); 25.9% were on no or moderate statin doses (up to 40 mg atorva) (Table 1). MGL-3196 treated patients (ITT) achieved highly significant (p< 0.0001) LDL-C lowering compared with placebo (Fig. 2,4). LDL-C lowering reached 28.5% compared to placebo in a prespecified group of MGL-3196-treated patients intolerant of high intensity statin doses. Apolipoprotein B (ApoB) (-18-29%), Triglyceride (TG) (-25-31%) , apolipoprotein CIII (Apo CIII) (-22%) and lipoprotein (a) (Lp(a))(-26-33%) lowering were also observed (p<0.0001). MGL-3196 was well-tolerated. Seven patients did not complete the study, 6 withdrew for mild to moderate AEs (placebo, 2; MGL-3196, 4). No effect on vital signs, including HR and BP. AEs, mild to moderate, were balanced (Table 3); 3 severe AEs, placebo, 3; mild nausea and diarrhea occurred in some MGL-treated patients which lasted 1-2 days at the beginning of therapy. One SAE occurred in a placebo patient.

Figure 1. MGL-3196 HeFH Study Design



Comparator/Arms

- 2:1 MGL-3196 to placebo
- 116 patients enrolled at 13 centers in Europe
- MGL-3196 or placebo, once daily; starting dose 100 mg per day, to 60mg between weeks 2 and 4, dose adjustment back to 100 mg at Week 4 based on Week 2 PK

Inclusion

- Genetically confirmed HeFH not at target on maximally tolerated statins

Table 1. HeFH Patient Demographics

Baseline Characteristics	Placebo	MGL-3196
	N=38	N=78
Mean age, years (SD)	59.1 (11.3)	56.4 (12.4)
Male, n (%)	22 (57.9)	39 (50.0)
White (%)	37 (97.4)	78 (100.0)
Mean BMI (SD)	27.7 (3.6)	28.5 (4.5)
Cardiovascular Disease (%)	11 (28.9)	19 (24.4)
Mean LDL-C direct (SD)	137.0 (57.5)	131.4 (47.2)
Mean Apo B (SD)	111.1 (36.1)	106.9 (28.0)
Mean TGs (SD)	127.9 (89.3)	106.4 (57.9)
Mean Lp(a) (SD)	67.6 (110.1)	84.3 (142.0)
Statin use category (%)		
Atorvastatin 80 mg	11 (28.9)	32 (41.0)
Rosuvastatin 20 / 40 mg	14 (36.8)	29 (37.2)
No/Moderate Dose Statin	13 (34.2)	17 (21.8)
Ezetimibe use (%)	26 (68.4)	57 (73.1)
PCSK9 use (%)	1 (2.6)	1 (2.6)

Figure 2. Effect of Dose

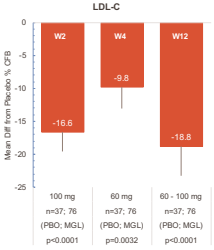
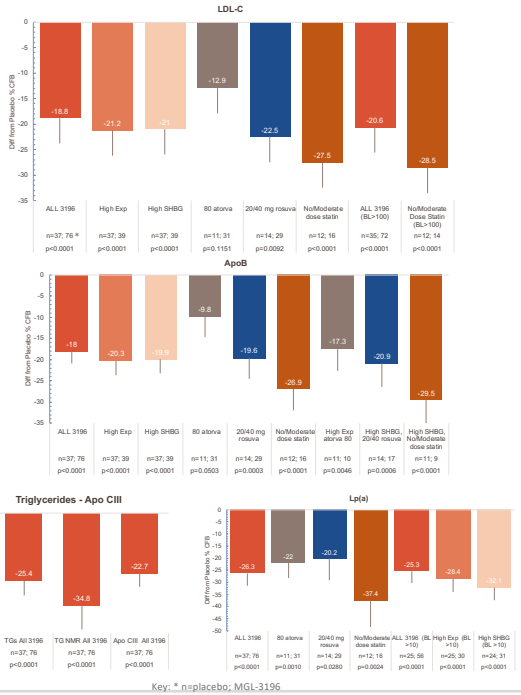


Figure 4. MGL-3196 Effects on Lipids



Key: * n=placebo; MGL-3196

Figure 5. LDL, VLDL Particles

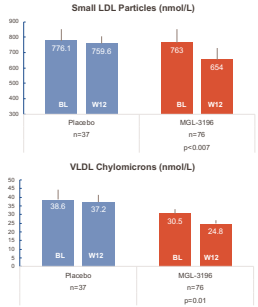
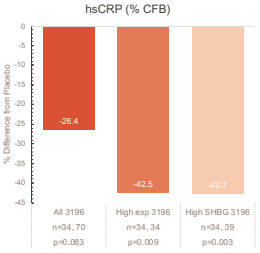


Figure 6. hsCRP Lowering



Based on log normalization

Table 2.

		TSH µIU/mL	FT4 ng/dL	FT3 pg/mL	rT3 ng/dL
MGL-3196 Mean (SD) n=76	Baseline	1.9 (0.9)	1.1 (0.2)	3.1 (0.4)	14.6 (3.9)
	Week 12	1.9 (0.8)	0.9 (0.2)	3.0 (0.4)	10.4 (3.5)
Placebo Mean (SD) n=37	Baseline	2.2 (1.0)	1.1 (0.1)	3.0 (0.3)	14.9 (4.6)
	Week 12	2.2 (1.2)	1.1 (0.2)	3.2 (0.4)	13.9 (4.9)

- No effect on vital signs including HR or BP
- No thyroid hormone related symptoms
- No effects on central thyroid axis, active hormone T3, minimal effect on prohormone FT4
- Anti-inflammatory action to reduce RT3

Table 3. Summary of Adverse Events

	Placebo	MGL-3196
	N = 38	N = 78
Patients with Adverse Events	28 (73.7)	65 (83.3)
Severe	3 (7.9)	0
Moderate	7 (18.4)	16 (20.5)
Mild	18 (47.4)	49 (62.8)
Patients with SAEs	1 (2.6)	0
Patients with Drug-Related SAEs	0	0
Most Common Adverse Events > 10%		
Diarrhea	4 (10.5)	15 (19.2)
Nausea	2 (5.3)	16 (20.5)
Nasopharyngitis	6 (15.8)	10 (12.8)
Headache	6 (15.8)	10 (12.8)
Myalgia/Muscle Spasm	5 (13.2)	9 (11.5)
Dizziness	4 (10.5)	4 (5.1)

CONCLUSIONS

- MGL-3196 statistically significantly lowers LDL-C and other atherogenic lipids in patients with HeFH, a difficult to treat genetic dyslipidemia
- MGL-3196 is most effective in patients intolerant to high intensity statins
- MGL-3196 robustly decreases ApoB, triglycerides, ApoCIII and Lp(a)
- The % ApoB reduction is similar to the reduction in LDL-C an unusual property of this mechanism suggesting that MGL-3196 directly lowers ApoB particles
- ApoCIII reduction is likely an important mechanism by which MGL-3196 lowers TGs
- The effect to reduce multiple atherogenic lipids makes MGL-3196 an excellent candidate to lower CHD risk in NAFLD/NASH and mild to severely statin intolerant patients

Contact information

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Declarations of Interest

- Rebecca Taub - Management Position: Madrigal Pharmaceuticals
- JJP. Kastelein: Has been a consultant for CSL Behring, Regeneron, Staten Biotech, Madrigal, The Medicines Company, Kowa, Lilly, Esperion, Gemphire, Ionis Pharmaceuticals, and Akcea Pharmaceuticals.