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

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)

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 atorv). (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 CII (Apo CII) / (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.

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, ApoCII 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
- ApoCII 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 NASH/NASH and mild to severely statin intolerant patients

Contact information
Rebecca Taub, M.D., Chief Medical Officer, Executive Vice President R&D, Madrigal Pharmaceuticals.
becky@madrigalpharma.com

Declarations of Interest
- Rebecca Taub - Management Position: Madrigal Pharmaceuticals
- JIR Kastelein: Has been a consultant for CSL Behring, Regeneron, Streele Bathe, Madrigal, The Medicines Company, Kowa, Lilly, Esperion, Genmune, Iara Pharmaceuticals, and Alexo Pharmaceuticals.