Effects of Resmetirom (MGL-3196) 60 and 80 mg in a 36-Week Study of NASH Patients

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INTRODUCTION

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, MGL-3196 treated patients showed statistically significant reduction in liver fat and NASH resolution. A per protocol post-hoc dose evaluation was conducted in patients completing 36-weeks of treatment with resmetirom 60 or 80 mg to analyze dose response.

METHODS

MGL-3196-05 (NCT029212260) was a 36-week multicenter, double-blind, randomized, placebo-controlled trial in 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 MGL-3196 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. At 36 weeks 107 paired liver biopsies, 73 drug-treated, 34 placebo were assessed (Fig 3). The overall safety and efficacy of resmetirom in patients on 60 or 80 mg doses in NASH patients was determined.

RESULTS

At 60 mg (n=36) or 80 mg (n=33) relative fat reductions on MRI-PDFF were -39.4 and -50.2% respectively; absolute hepatic fat reductions -8.0 (1.2) and -10.8 (1.2)%, respectively (Fig 4A-C). A 2-potent reduction in NAS was observed in 55.5 and 63.6% on 60 and 80 mg respectively (Table 2) and NASH resolution with at least a 2-potent reduction in NASH and no worsening in fibrosis was achieved in 19% and 33.3% of patients receiving 60 mg and 80 mg resmetirom, respectively. Of patients with baseline LDL-C >100 mg/dl receiving resmetirom 80 mg (n=20) LDL-C and ApoB were reduced -21.5 (3.9)% and -24.9 (2.7)%, respectively (Fig 5, Table 3). Resmetirom was well tolerated, with few minor AE's.

CONCLUSIONS

- The data obtained from this 36-week per protocol complete analysis of patients treated with resmetirom, indicates 80 mg appeared more effective than 60 mg in reducing hepatic fat and resolving NASH.
- Lipid lowering, in particular ApoB and TG lowering, was more pronounced at 80 as compared with 60 mg.
- These results support the efficacy and safety of 80 and 100 mg doses, which are being used in the ongoing NASH Phase 3 study, MAESTRO-NASH (NCT03900429).

REFERENCES

1. Role of gene expression changes in identifying differences between 60 and 80 mg in reducing hepatic fat and resolving NASH. Lipid lowering, in particular ApoB and TG lowering, was more pronounced at 80 as compared with 60 mg.

DISCLOSURES

Stephen A. Harrison, Oxford University, received remuneration from Madrigal for consulting services Rebecca Taub, Management Position, Madrigal Pharmaceuticals

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Table 1. Study Patient Baseline Characteristics

Table 2. Liver Biopsy and Hepatic Fat Responses by Dose

Table 3. Lipid Responses by Dose