

SAT-347

MRI-PDFF response in MGL-3196 and placebo treated patients predicts reduction in ballooning and inflammation components of NAS and NASH resolution in a 36-week serial liver biopsy study

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Background and aims: MGL-3196 is a liver-directed, orally active, highly selective THR- β agonist which may reduce NASH by increasing hepatic fat metabolism and normalizing liver function. In a 12-week interim and 36 week final analysis, MGL-3196 treated patients had reduced liver fat on MRI-PDFF compared with Placebo (pbo) patients and more MGL-3196 (60%) treated than pbo (18%) patients showed at least 30% reduction in hepatic fat (PDFF response) ($p < 0.0001$). NASH resolution was 39% in MGL-3196 patients who were MRI-PDFF responders at Week 12 ($p < 0.001$). We assessed whether response and magnitude of response on MRI-PDFF at week 12 in pbo or MGL-3196 patients predicted ALT improvement and histologic response on liver biopsy at Week 36.

Method: MGL-3196-05 (NCT02912260) was a 36-week multicenter, randomized, double-blind, pbo-controlled serial MRI-PDFF, paired liver biopsy study in adults with biopsy-confirmed NASH (NAS ≥ 4 , F1-F3) and hepatic fat fraction $\geq 10\%$, assessed by MRI-PDFF. At 36 weeks 107 paired liver biopsies, 73 drug-treated, 34 pbo were assessed. NAS component, correlation and responder analyses were conducted to examine the predictive power of MRI-PDFF response on histologic response of NAS components and ALT reduction in pbo and MGL-3196 patients.

Results: In MGL-3196 patients, week 12 MRI-PDFF response versus non-response predicted NASH resolution at Week 36 ($p = 0.001$). MGL-3196 PDFF or steatosis responders compared with MGL-3196 non-responders were more likely to show a reduction in other components of NAS (ballooning, inflammation) (OR 8.86, $p = 0.0036$). In MGL-3196 patients, Week 12 PDFF response correlated with improvement in steatosis (direct relationship), improvement in inflammation and ballooning components of NAS (0.42) and reduction in ALT (0.34). Pbo patients with $\geq 5\%$ weight loss were likely PDFF responders (71%, $p = 0.007$). In pbo patients PDFF response correlated with weight loss (0.58), which predicted inflammation and ballooning responses (0.58). In pbo patients with $< 3\%$ weight loss, ballooning reduction was not correlated with any improvement in steatosis, inflammation, fibrosis or ALT. In MGL-3196 patients, a ballooning reduction without a reduction in steatosis and/or MRI-PDFF response was not associated with improvement in inflammation, fibrosis or ALT.

Conclusion: In both MGL-3196 and placebo treated patients, MRI-PDFF response correlated with reduction in ballooning and inflammation scores on liver biopsy and was associated with NASH resolution. In pbo, but not MGL-3196, patients most of the response was driven by weight loss. These data suggest that reduction of hepatic fat is a critical component of NASH improvement and resolution.