MET409, a Sustained FXR Agonist, Decreased Liver Fat and Improved Liver Chemistries in 12 Weeks in Patients with Nonalcoholic Steatohepatitis

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BACKGROUND & AIM

Farnesoid X receptor (FXR) agonists have been validated to benefit patients with nonalcoholic steatohepatitis (NASH), although improvements in efficacy and/or tolerability for the class remain elusive.

MET409, a sustained FXR agonist with a novel non-bile acid structure, has demonstrated an encouraging profile after 14 days of dosing in healthy subjects.

In this 12-week, randomized, double-blind, placebo (PBO)-controlled study, we investigated the effects of MET409 in patients with biopsy-confirmed or phenotypic NASH based on non-invasive assessment.

PATIENTS & METHODS

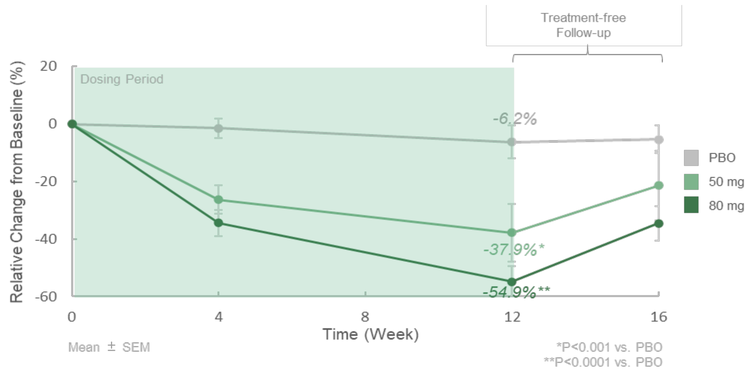
Men and women with (1) biopsy-proven NASH, (2) corrected T1 ≥830 ms on multiparametric magnetic resonance imaging, or (3) transient elastography-measured liver stiffness ≥8.5 kPa were eligible for participation. All study participants were required to have ≥10% liver fat content (LFC) and serum alanine aminotransferase (ALT) ≥30 IU/L at baseline.

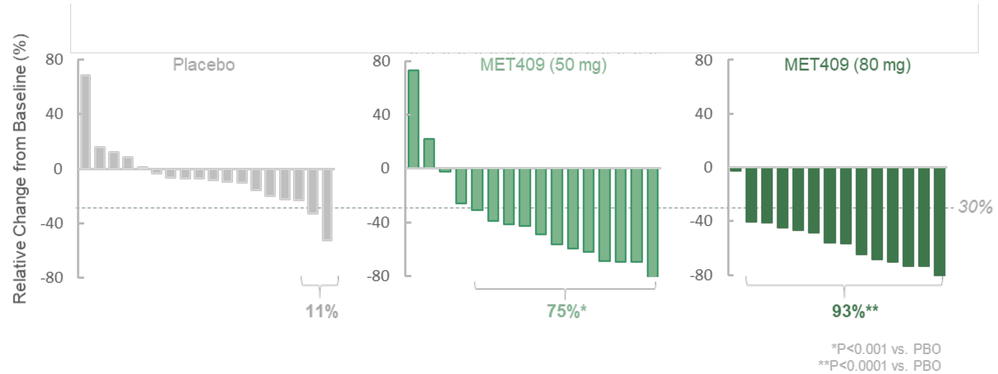
Most participants were female (67%), with a mean (±SD) baseline LFC of 19.7% (±7.4%) and body weight of 100.9 (±22.1) kg. Approximately 36% had type 2 diabetes, and 16% were receiving statin therapy at baseline.

A total of 58 patients were randomized to receive once-daily oral MET409 or matching PBO for 12 weeks: 80 mg (n=20), 50 mg (n=19), PBO (n=19), with 48 patients completing 12 weeks of treatment: 80 mg (n=14), 50 mg (n=16), PBO (n=18).

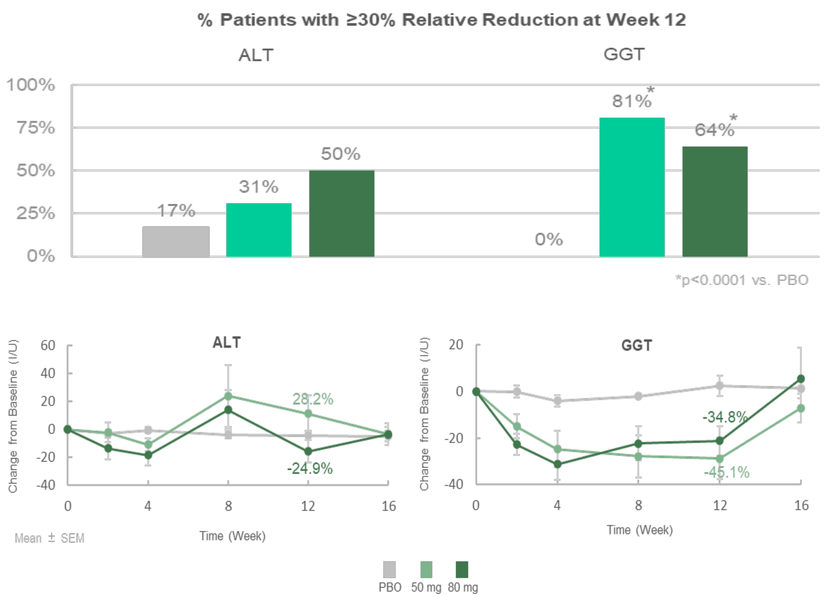
RESULTS

MET409 significantly lowered LFC, as assessed by magnetic resonance imaging-proton density fat fraction, with mean relative reductions of 55% (80 mg) and 38% (50mg) vs 6% in PBO. MET409 normalized Week 12 LFC (≤5%) in 29% (80 mg) and 31% (50 mg) of patients vs 0% in PBO (P<0.05).

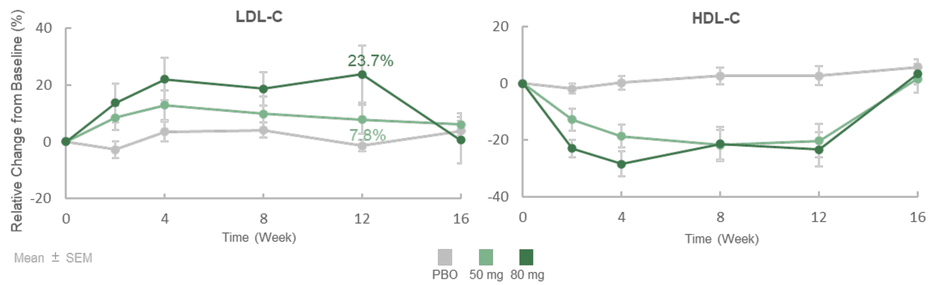




At Week 12, a dose-dependent trend towards ALT reduction, as measured by the percentage of patients with ≥30% relative reduction from baseline, was observed with MET409 (31-50%), as well as ≥30% relative GGT reduction (64-81%). A transient, asymptomatic ALT elevation was observed in a subset of patients at Week 8, without increased GGT or total bilirubin.



MET409 was safe and generally well-tolerated. There were no treatment-related serious adverse events. Treatment-related generalized pruritus was reported by 40% (10% mild, 30% moderate; 80 mg) and 16% (5% mild, 11% moderate; 50 mg) of MET409-treated patients. There were no severe cases of pruritus. Two pruritus-related early terminations occurred, both at 80 mg (10%).



On-target changes in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed with MET409 (for Week 12 LDL-C, P<0.05 for PBO vs 80 mg only). No subject required statin initiation, and no pre-existing statin therapy required dose titration.

CONCLUSION

MET409 significantly lowered LFC in patients with NASH and improved liver chemistries after 12 weeks of dosing, with notable rate and magnitude of reduction relative to other FXR agonists. Additionally, the low dose (50 mg) of MET409 delivered a differentiated pruritus and LDL-C profile.

These results provide the first clinical evidence that the risk-benefit profile of FXR agonists can be enhanced through structural optimization. Further development of MET409 and structurally-related agonists, both as monotherapy and in combination with other agents, are being evaluated.