Dose-Dependent Changes in the Pharmacokinetic and Pharmacodynamic Profiles of MET409, a Sustained FXR Agonist, in Patients with NASH

Eric J. Lawitz[1,2], Kyoung-Jin Lee[3], Jennifer Shim-Lopez[3], Jonathan Lee[3], Hubert C. Chen[3]
[1]Texas Liver Institute, San Antonio, Texas, USA; [2]University of Texas Health San Antonio, Texas, USA; [3]Metacrine, Inc., San Diego, California, USA

3985 Sorrento Valley Blvd., Suite C
San Diego, CA 92121 USA
www.metacrine.com

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 12 weeks of daily oral dosing in patients with NASH, including significant reductions in liver fat content (LFC) and improved liver chemistries.

We now report the pharmacokinetic (PK) and pharmacodynamic (PD) findings from the randomized, double-blind, placebo (PBO)-controlled study.

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. All study participants were required to have ≥10% liver fat content (LFC) by magnetic resonance imaging-proton density fat fraction 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.

Blood samples were obtained at baseline, Day 14, Day 28, Day 56, and Day 84 for measurements of MET409, 7α-hydroxy-4-cholesten-3-one (C4; an intermediate in the synthesis of bile acids from cholesterol and a biomarker of hepatic CYP7A1 activity), and fibroblast growth factor 19 (FGF19; a biomarker of intestinal FXR activation)

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).

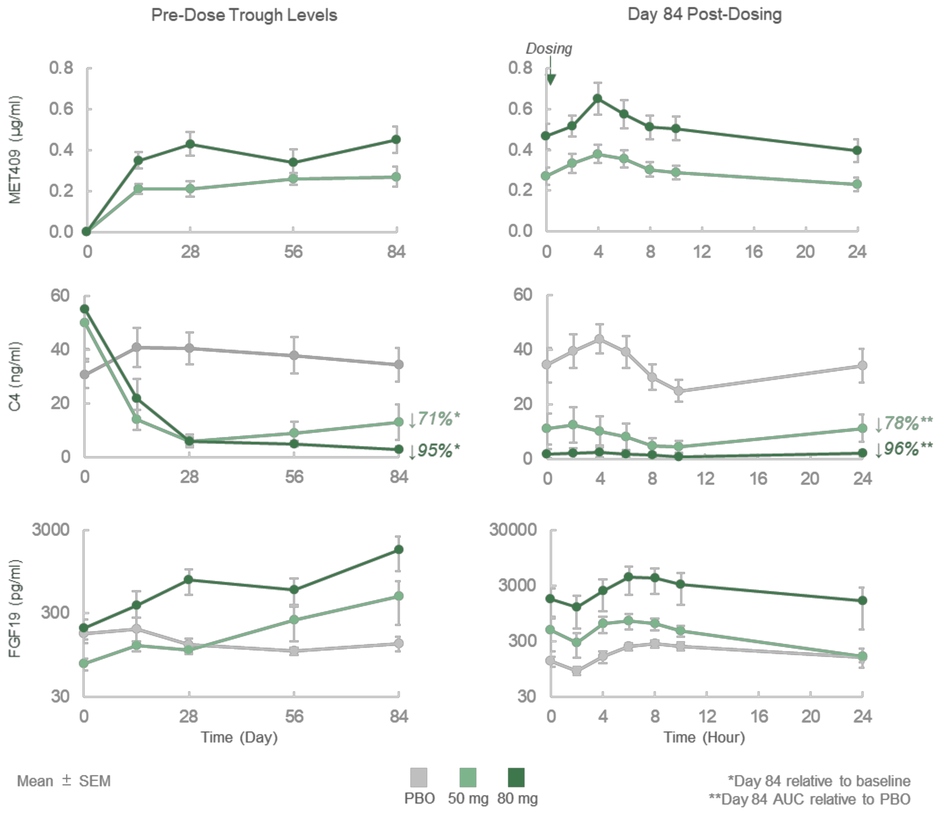
RESULTS

As previously reported, MET409 lowered LFC at Week 12 (Day 84), with mean relative reductions of 55% (80 mg) and 38% (50 mg) vs 6% in PBO, and ≥30% relative LFC reduction in 93% (80 mg) and 75% (50 mg) of patients vs 11% in PBO.

Increase in low-density lipoprotein cholesterol (LDL-C) was observed with MET409, with mean relative changes of 24% (80 mg) and 7% (50 mg) vs -1% in PBO. No subject required statin initiation, and no pre-existing statin therapy required dose titration.

Treatment-related generalized pruritus (mild-moderate grade only) was reported by 40% (80 mg) and 16% (50 mg) of MET409-treated patients. Pruritus-related treatment discontinuation occurred in 10% of patients in the 80 mg cohort.

		MET409 50 mg	MET409 80 mg
Pharmacological Activity	Relative liver fat reduction (PBO-corrected)	32%	49%
	% Patients with ≥30% relative liver fat reduction	75%	93%
Safety & Tolerability	LDL-C increase (PBO-corrected)	8%	25%
	Overall pruritus rate	16%	40%
	Pruritus-related treatment discontinuation	0%	10%



Dose-dependent increases in trough levels and Day 84 area-under-the-curve (AUC) of MET409 were observed. Additionally, there were dose-dependent decreases in levels of C4 (↓71-95% at Day 84 relative to baseline and ↓78-96% in Day 84 AUC relative to PBO; P<0.05 for both comparisons) – findings that are consistent with sustained FXR target engagement. Although increases in FGF19 were observed in MET409-treated subjects, the results were not statistically significant due to large inter-subject variability.

SUMMARY & CONCLUSIONS

Dose-dependent increases in MET409 levels were seen after 12 weeks of treatment in patients with NASH. MET409 also decreased circulating levels of C4 and was associated with increasing trends of FGF19. These results demonstrate robust, sustained FXR activation by MET409 and correlate with previously-reported benefits of LFC reduction and improvement in liver chemistries.

Combined with a differentiated, favorable pruritus and LDL-C profile at 50 mg, these MET409 findings 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 are being conducted.