MET409, a Sustained FXR Agonist, Decreased Hepatic Fat and Improved Liver Function without Raising LDL-C after 28 Days in NASH Patients

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BACKGROUND

Activating farnesoid X receptor (FXR) has been clinically validated to improve non-alcoholic steatohepatitis (NASH), although common drawbacks include increased low-density lipoprotein cholesterol (LDL-C) levels and moderate-severe pruritus within the therapeutic dose range.

Recently, non-bile acid agonists have shown limited efficacy with once-daily dosing, likely due to transient target engagement. Sustained FXR engagement appears key to efficacy based on preclinical and clinical studies.

MET409, an optimized FXR agonist with a novel non-bile acid structure and enhanced potency, has demonstrated sustained FXR engagement and an encouraging safety profile – including a lack of adverse impact on LDL-C – in healthy subjects.

OBJECTIVE

We conducted an open-label, single-center study to determine the safety and pharmaco-dynamics of low-dose MET409 (50 mg) administered for 28 days in patients with NASH.

METHODS

Men and women (18 to 75 years-old) with (1) biopsy-confirmed NASH or (2) transient elastography findings of kPa ≥8.5 and controlled attenuation parameter >300 dB/m were eligible for participation. All subjects had ≥ 10% liver fat content (LFC) by magnetic resonance imaging–proton density fat fraction at baseline.

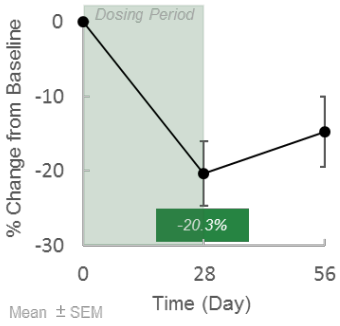
Ten subjects received oral MET409 daily for 28 days at 50 mg, which was shown to reduce plasma levels of 7α -hydroxy-4-cholesten-3-one (C4) by ~80% after 14 days in healthy subjects. The primary study objective was to assess the safety and tolerability of MET409. Secondary study objectives included liver function and LFC assessment.

RESULTS

Key baseline parameters were comparable to those in recent NASH trials: Mean body weight 106.0 kg, LFC 23.4%, alanine aminotransferase (ALT) 71 U/L, aspartate aminotransferase (AST) 52 U/L, total bilirubin 0.76 mg/dL, and gamma-glutamyl transferase (GGT) 57 U/L.

MET409 at 50 mg was safe and well-tolerated. There were no serious adverse events or early terminations due to adverse events (AE). All treatment-related AEs were mild, and no pruritus was reported by any of the subjects. There was no change in mean body weight (0.0 ± 0.3 kg).

Liver Fat Reduction after 28 Days of Dosing: Superior Potential Relative to Other FXR Agonists



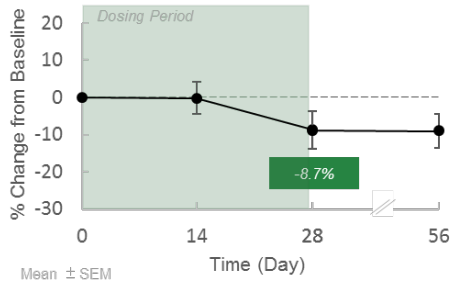
Candidate	Profile/ Structure	Treatment Duration *(wks)*	Relative Liver Fat Reduction *(low→high dose)*
MET409 (Metacrine)	Sustained/ Non-bile acid	4	20%→TBD
Obeticholic Acid (Intercept)	Sustained/ Bile acid	72	17%*
Cilofexor (Gilead)	Transient, Non-bile acid	12	8→16%
Tropifexor (Novartis)	Transient, Non-bile acid	12	7→17%

*Placebo-corrected; only 1 dose level reported

MET409 reduced mean relative LFC by -20.3%. Reduction was observed in all subjects, with ≥30% reduction seen in 30% of subjects.

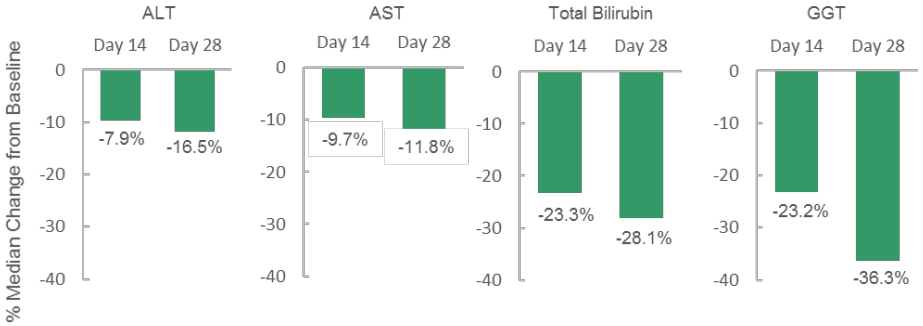
The magnitude appears comparable or superior to those observed with longer-term dosing of other FXR agonists.

No Adverse Impact on LDL-C



MET409 lowered mean LDL-C by -8.7%, a differentiating attribute relative to other FXR agonists and FGF19 analogs.

Improved Liver Function in NASH Patients



CONCLUSIONS

MET409, an optimized sustained non-bile acid FXR agonist, reduced hepatic fat, improved liver function, did not raise LDL-C or cause pruritus, and was safe and well-tolerated at 50 mg after 28 days of dosing in patients with NASH.

These results demonstrate the potential of sustained FXR agonism to deliver a differentiated, best-in-class profile. Higher dose levels of MET409 – those that suppress C4 levels by >99% – are being assessed in a longer-term, placebo-controlled study.