MET642, FXR Agonist with a Unique Chemotype, Demonstrates a Safe, Sustained Profile in a 14-Day Randomized Study in Healthy Subjects

Richard Pencek[1], Kyoung-Jin Lee[1], Jonathan Lee[1], Hubert Chen[1]
[1]Metacrine, Inc. San Diego, CA

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 non-alcoholic steatohepatitis (NASH), although improvements in therapeutic index for the class remain elusive. MET642 is a novel, non-bile acid FXR agonist with enhanced potency and sustained FXR engagement in preclinical studies. We conducted a double-blind, placebo (PBO)-controlled, single-ascending dose (SAD) and 14-day multiple-ascending dose (MAD) phase 1 study in healthy subjects to determine the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of MET642.

PATIENTS & METHODS

Healthy men and women aged 18 to 50 years-old were randomized to either MET642 or PBO (6:2 allocation). The primary objective was to assess the safety and tolerability of MET642. The secondary objectives were to establish the PK and PD profiles of MET642, with PD assessed by plasma levels of 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19).

Single doses ranging from 10 to 300 mg and, in the 14-day multi-dose portion, doses of 5 and 10 mg were evaluated over a dosing period of 14 days. Subsequently, simulated doses of 2.5 and 7.5 mg were evaluated using every other day dosing of 5 mg or alternate daily dosing with 5 mg and 10 mg, respectively, leveraging the long half-life of MET642 observed in the clinic.

Subject Demographics: 32 healthy subjects were enrolled in each study cohort (SAD and MAD). Subjects were predominantly Caucasian, non-Hispanic/Latino males in their mid/late 20s.

Table: Subject Demographics for SAD and MAD cohorts

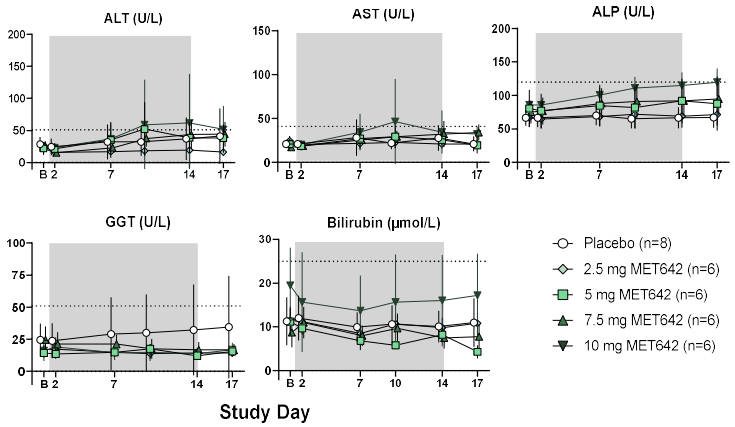
	SAD (N=32)	MAD (N=32)
Female, n (%)	12 (37.5)	8 (25)
Race, n (%)		
Asian	3 (9.4)	4 (12.5)
Black	1 (3.1)	-
White	26 (81.3)	27 (84.4)
Other	2 (6.3)	1 (3.1)
Ethnicity, n (%)		
Hispanic/Latino	3 (9.4)	6 (18.8)
Not Hispanic/Latino	29 (90.6)	25 (78.1)
Unknown	-	1 (3.1)
Age, years	26.8 (7.2)	28.8 (7.5)
Height, cm	173.4 (9.0)	176.7 (7.8)
Weight, kg	74.1 (12.3)	77.9 (11.5)

Data are n (%) or Mean (SD) as applicable

RESULTS

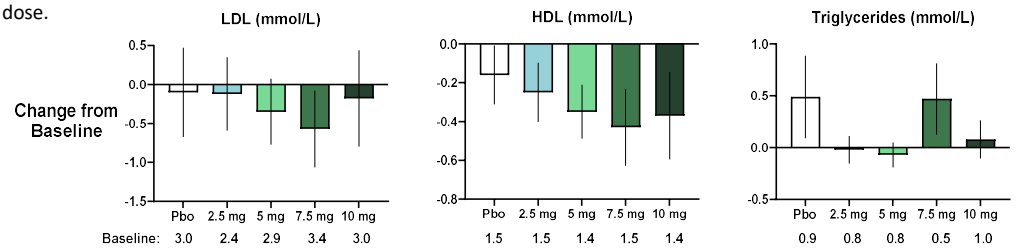
Adverse Events: MET642 was safe and well tolerated at all SAD and MAD dose levels. There were no serious or severe adverse events; dosing was stopped after 10 days in one subject (MET642 10 mg) due to asymptomatic ALT/AST elevations, unaccompanied by other laboratory abnormalities. No generalized pruritus was observed.

Liver Chemistry: Administration of MET642 for 14 days resulted in ALT and AST values which typically remained within the normal range. Individuals with increases above the ULN were otherwise asymptomatic, transient and returned to normal with continued dosing/exposure. Consistent with FXR activation, ALP increased with increasing doses of MET642 but largely remained within the normal range. No changes in GGT or total bilirubin were observed.



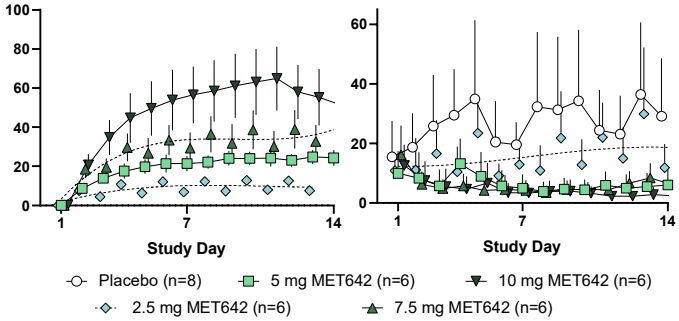
Data are mean±SD. B=Baseline (mean of all data points prior to first dose)
Dotted lines represent the upper limit of normal
Shaded areas represent the dosing window

Cholesterol: No changes in LDL-C or triglycerides were observed. HDL-C tended to decrease with increasing MET642 dose.



Change from baseline data are mean±SD
Baseline is the mean of all data points prior to first dose

PK and FXR activity: MET642 exhibited a sustained PK profile as well as FXR target engagement, with notable C4 repression which has been shown to correlate with potential liver fat reduction. Compared to placebo, C4 area under the curve on the final day of dosing (Day 14 for all doses except 2.5 mg, which was day 13) was suppressed by 55% with 2.5 mg and 89%, 84%, and 95% suppression observed with 5, 7.5 and 10 mg, respectively.



Data are mean ±SD for pre-dose values on the indicated dose day

For 2.5 mg and 7.5 mg, a nonlinear regression curve was fit to the observed data to account for the alternate dosing regimen

Table: Change in C4 area under the curve on final dose day

Dose (mg)	C4 change (relative to PBO)
2.5	-55%
5	-89%
7.5	-84%
10	-95%

CONCLUSIONS

MET642, a novel FXR agonist, demonstrated sustained FXR target engagement and an encouraging safety and tolerability profile – including a lack of adverse LDL-C effects or pruritus – in healthy subjects after 14 days of daily oral dosing.