Metacrine Reports Positive Results from Phase 1 Trial of MET642

December 17, 2020

MET642 Demonstrated Sustained Pharmacokinetic Profile and Robust FXR Target Engagement with Once-Daily Oral Dosing, without Pruritis or LDL-Cholesterol Increase

Doses Selected for Phase 2a Trial in Patients with NASH; On-Track to Initiate in 1H21

SAN DIEGO, Dec. 17, 2020 (GLOBE NEWSWIRE) -- Metacrine, Inc. (Nasdaq: MTCR), a clinical-stage biopharmaceutical company focused on discovering and developing differentiated therapies for patients with liver and gastrointestinal diseases, today reported preliminary results from its Phase 1 trial of MET642, a farnesoid X receptor (FXR) agonist being developed for the treatment of non-alcoholic steatohepatitis (NASH) and inflammatory bowel disease. Findings show that treatment with MET642 was safe and generally well-tolerated and demonstrated a sustained pharmacokinetic (PK) profile and robust FXR target engagement after 14 days of daily oral dosing in healthy volunteers.

"There are no treatments currently available for NASH patients, and given FXR agonism works through multiple mechanisms to improve NASH and fibrosis, I believe that an optimized FXR agonist could become both a first-line monotherapy and foundation for combination therapies in the future," said Stephen A. Harrison, M.D., Visiting Professor of Hepatology at University of Oxford's Radcliffe Department of Medicine, Medical Director of Pinnacle Clinical Research and President of Summit Clinical Research. "I am encouraged by the sustained activity and safety demonstrated with MET642, in particular the lack of pruritis and LDL-cholesterol increases, which support its continued evaluation in patients with NASH."

Metacrine has developed a proprietary FXR platform utilizing a unique chemical scaffold, which has demonstrated a clinically differentiated and improved therapeutic profile. The company's lead FXR clinical candidate, MET409, has successfully completed a 12-week trial in patients with NASH. MET642, Metacrine's second clinical candidate, is derived from the same chemical scaffold as MET409 and has shown comparable FXR target engagement and pharmacology in preclinical studies, as well as increased potency and differentiated pharmaceutical properties.

The MET642 Phase 1 trial was a first-in-human, randomized, placebo-controlled, double-blind single-ascending dose (SAD) and multiple-ascending dose (MAD) trial, in which healthy volunteers received once-daily MET642 doses ranging from 10 mg to 300 mg in the SAD cohorts and 2.5 mg to 10 mg in the MAD cohorts for 14 days. The primary objective of the trial was to evaluate safety and tolerability, and the secondary objectives were to assess PK parameters and FXR target engagement, the latter through the measurement of 7α-hydroxy-4-cholesten-3-one (C4), a blood biomarker of bile acid synthesis that decreases with FXR activation.

Safety Findings
MET642 was safe and generally well-tolerated, with no serious adverse events reported, and all adverse events were mild to moderate in severity. Importantly, pruritus and LDL-cholesterol increases were not seen at any dose level.

PK and Target Engagement Findings
MET642 exhibited a sustained PK profile as well as robust FXR target engagement throughout 24 hours after once-daily oral dosing, with notable C4 repression – up to an approximately 95% decrease in area-under-the-curve (AUC) relative to placebo – observed after the last dose in all MAD cohorts of the trial. The magnitude of C4 decrease can be used to project potential levels of liver fat reduction in NASH patients, with ≥30% relative liver fat reduction being associated with increased likelihood of histological benefits upon liver biopsy.

"We are encouraged by the overall safety profile of MET642, and with meaningful target engagement seen at as low as the 2.5 mg dose level, we intend to evaluate the 3 mg and 6 mg dose levels in our upcoming Phase 2a trial in NASH patients," said Hubert C. Chen, M.D., chief medical officer of Metacrine. "With the benefit of greater potency and improved pharmaceutical properties, we believe MET642 has the potential to be another best-in-class FXR agonist in our proprietary portfolio."

Summary of MET642 Phase 1 Trial Results

Number of subjects	32 total in SAD cohorts 32 total in MAD cohorts
Serious adverse events	None
Severity of treatment-related adverse events	Mild to moderate only
Pruritus	None[1]
LDL-cholesterol	Mean change from baseline to Day 14: -0.12 to -0.57 mmol/L for MET642 subjects -0.10 mmol/L for pooled placebo subjects
Liver function tests	Sporadic, isolated ALT/AST increases in MAD cohorts; resolved with continued MET642 dosing/exposure
Pharmacokinetics	Mean elimination half-life: ~40-68 hours after 14 days of dosing
FXR target engagement	Mean repression of C4 AUC after last multiple-dose administration: ~55% (2.5 mg) to ~95% (10 mg) relative to placebo

[1]One case of localized, overnight itch was reported on Day 7 by one MET642 subject in the 5 mg cohort, a finding that is atypical of FXR-associated pruritus; dosing was continued without subsequent events.

Based on the Phase 1 findings, Metacrine plans to advance two dose levels of MET642 – 3 mg and 6 mg – in a 16-week, randomized, placebo-controlled Phase 2a monotherapy trial enrolling up to 180 patients with NASH. The two doses are projected to repress C4 to levels that are likely to result in meaningful reductions in liver fat content. The trial is scheduled to start in the first half of 2021, with an interim analysis planned in the second half of 2021, after approximately 60 patients have completed 16 weeks of treatment.

About Metacrine
Metacrine, Inc. (Nasdaq: MTCR) is a clinical-stage biopharmaceutical company building a differentiated pipeline of therapies to treat liver and gastrointestinal (GI) diseases. The company's most advanced programs, MET409 and MET642, target the farnesoid X receptor (FXR), which is central to modulating liver and GI diseases. Both MET409 and MET642 are currently being investigated in clinical trials as potential new treatments for non-alcoholic steatohepatitis (NASH).

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Statements in this press release that are not purely historical are forward-looking statements. Forward-looking statements contained in this press release include statements regarding the therapeutic potential of MET409 and MET642; Metacrine's timelines; the differentiated nature of Metacrine's FXR program; plans underlying Metacrine's clinical trials; plans underlying Metacrine's clinical trials in NASH; plans for advancing the clinical development of Metacrine's FXR program; and the potential best-in-class nature of Metacrine's FXR program; and the potential for its FXR product candidates to be long-term therapies for NASH. Words such as "may," "will," "expect," "likely," "plan," "aim," "anticipate," "estimate," "intend," "potential," "preliminary," "prepare," "projected," "scheduled," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. These forward-looking statements are based on Metacrine's expectations and assumptions that may never materialize or prove to be incorrect. Each of these forward-looking statements involves risks and uncertainties. Actual results may differ materially from those projected in any forward-looking statements due to numerous risks and uncertainties, including but not limited to: the risk that the preliminary analysis may change upon further evaluation or may not be able to be replicated in a larger patient sample and other risks and uncertainties inherent in early-stage clinical trials; risks and uncertainties regarding regulatory approvals for MET409 or MET642; potential delays in initiating, enrolling or completing any clinical trials; unexpected safety or efficacy data observed during preclinical or clinical studies, potential adverse side effects or other safety risks associated with Metacrine's product candidates; competition from third parties that are developing products for similar uses; and Metacrine's ability to obtain, maintain and protect its intellectual property. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in Metacrine's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on November 12, 2020, and in Metacrine's other filings with the SEC. All forward-looking statements contained in this press release speak only as of the date on which they were made. Except as required by law, Metacrine assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

Contact:
Chelcie Lister
THRUST Strategic Communications
910.777.3049
investors@metacrine.com