Madrigal Pharmaceuticals Initiates the MAESTRO-NASH Outcomes Study Evaluating Resmetirom for the Treatment of Patients with Compensated NASH Cirrhosis

August 31, 2022

CONSHOHOCKEN, Pa., Aug. 31, 2022 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced initiation of the "MAESTRO- NASH Outcomes" study of resmetirom (recruiting, first patient screened). MAESTRO- NASH Outcomes is a Phase 3, double-blind, randomized, placebo-controlled study that will noninvasively measure progression to liver decompensation events in approximately 700 patients with compensated NASH cirrhosis. It is the fourth Phase 3 MAESTRO study of resmetirom, joining the MAESTRO-NAFLD-1 safety study, which reported positive data in January 2022, the ongoing MAESTRO-NAFLD Open-Label Extension study, and the pivotal MAESTRO-NASH biopsy study, which is on track for a topline data readout in Q4 2022.

The primary endpoint of MAESTRO-NASH Outcomes is the incidence of composite liver-related outcome events, including all-cause mortality, liver transplant, hepatic decompensation (ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage), and confirmed increase of Model for End-Stage Liver Disease (MELD) score from <12 to ≥15 due to progression of NASH cirrhosis. Key inclusion criteria are well-compensated NASH cirrhosis (Child-Pugh A) and presence of three metabolic risk factors (metabolic syndrome). Patients will be randomized 3:1 in a blinded manner to receive 80 mg resmetirom or matching placebo, given orally once daily. The study duration is expected to be two to three years for accrual of the required number of composite clinical outcome events.

Paul Friedman, M.D., Chief Executive Officer of Madrigal, stated, "The MAESTRO- NASH Outcomes study is designed to address an urgent unmet need for patients and expand the long-term commercial opportunity for resmetirom. Positive results from this study could support full approval in the noncirrhotic population and potential for approval in an additional indication in patients with well-compensated NASH cirrhosis. Importantly, MAESTRO-NASH Outcomes does not impact the timeline for our MAESTRO-NASH biopsy study readout or initial new drug application filing in the noncirrhotic NASH population."

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, "Our decision to conduct MAESTRO- NASH Outcomes is supported by promising 52-week data from 180 patients with well-compensated NASH cirrhosis studied in a resmetirom active treatment arm of our Phase 3 study, MAESTRO-NAFLD-1; initial findings from this cohort were featured in an oral presentation at EASL's International Liver Congress in June and we plan to share additional analyses at the AASLD Liver Meeting in November."

Stephen Harrison, M.D., Medical Director for Pinnacle Clinical Research, San Antonio, Texas, Visiting Professor of Hepatology, Oxford University, and Principal Investigator of the MAESTRO studies, commented, "As the first noninvasive Phase 3 study in well-compensated NASH cirrhosis, the initiation of MAESTRO-NASH Outcomes is an important milestone for the field. This study avoids the variability and invasiveness of liver biopsy and instead focuses on the treatment goals that are most important to liver specialists and patients: halting progression of NASH cirrhosis and improving long-term outcomes."

More than 100 sites in the United States and Europe are expected to participate in the MAESTRO-NASH Outcomes study. Further information is available at ClinicalTrials.gov (NCT05500222).

About the Resmetirom Phase 3 Registration Program for the Treatment of NASH

Madrigal is currently conducting four Phase 3 clinical trials to demonstrate the safety and efficacy of resmetirom for the treatment of NASH: MAESTRO-NASH, MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, and MAESTRO-NASH Outcomes.

MAESTRO-NASH is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study of resmetirom in patients with liver biopsy-confirmed NASH and was initiated in March 2019. The study enrolled more than 1,000 patients with biopsy-proven NASH (at least half with F3 (advanced) fibrosis, the remainder F2 or F1B (moderate fibrosis, with a few earlier F1 patients), randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second biopsy is performed. The dual primary surrogate endpoints on biopsy are NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score), and with no worsening of fibrosis OR a 1-point decrease in fibrosis with no worsening of NASH. Achievement of either primary endpoint is considered a successful trial outcome. A key secondary endpoint is lowering of LDL-C. The planned target enrollment was announced as completed on June 30, 2021.

All patients enrolled in the MAESTRO-NASH study (up to 2,000 in total) continue on therapy after the initial 52-week treatment period for up to 54 months to accrue and measure hepatic clinical outcome events including progression to cirrhosis on biopsy (52 weeks and 54 months) and hepatic decompensation events.

MAESTRO-NAFLD-1 was initiated in December 2019 and the 52-week multicenter, randomized, placebo-controlled Phase 3 study of resmetirom in over 1,200 patients with NAFLD, presumed NASH, has completed the double-blind arms and an open-label 100 mg arm. An additional open-label active treatment arm in patients with early (well-compensated) NASH cirrhosis is ongoing. The primary endpoint was to evaluate the safety and tolerability of resmetirom. A separate 52 week Phase 3 clinical trial, an open-label extension study of MAESTRO-NAFLD-1 (MAESTRO-NAFLD-OLE) is ongoing.

Patients in the 52-week Phase 3 MAESTRO-NAFLD-1 study were randomized 1:1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, placebo in double-blind arms or resmetirom 100 mg in an open-label arm. MAESTRO-NAFLD-1 (unlike MAESTRO-NASH), did not include a liver biopsy and represents a "real-life" NASH study. Patients with 3 metabolic risk factors were documented with NASH or NAFLD by historical liver biopsy

or noninvasive techniques. Using noninvasive measures, MAESTRO-NAFLD-1 was designed to provide incremental safety information to support the NASH indication as well as provide additional data regarding clinically relevant key secondary efficacy endpoints to better characterize the potential clinical benefits of resmetirom on cardiovascular- and liver-related endpoints. The primary safety endpoint and several key secondary endpoints were met, including LDL-C, apolipoprotein B, and triglyceride lowering and reduction of liver fat as determined by MRI-PDFF. Additional secondary and exploratory endpoints were assessed including reduction in liver enzymes, FibroScan, and MRE scores, and other NASH biomarkers.

Data from the 52-week first 1,000 patient portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1 and other data, including safety parameters, will form the basis for a potential subpart H submission to FDA for accelerated approval of resmetirom for treatment of NASH.

In August 2022, Madrigal initiated MAESTRO-NASH Outcomes, a randomized double-blind placebo-controlled study in approximately 700 patients with early NASH cirrhosis to allow for noninvasive monitoring of progression to liver decompensation events. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis.

About Madrigal Pharmaceuticals

Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), a liver disease with high unmet medical need. Madrigal's lead candidate, resmetirom, is a once daily, oral, thyroid hormone receptor (THR)-β selective agonist designed to target key underlying causes of NASH in the liver. Resmetirom is currently being evaluated in two Phase 3 clinical studies (MAESTRO-NASH and MAESTRO-NAFLD-1) designed to demonstrate multiple benefits in patients with NASH. For more information, visit www.madrigalpharma.com.

Forward Looking Statements

This communication includes "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, that are based on our beliefs and assumptions and on information currently available to us, but are subject to factors beyond our control. Forward-looking statements include but are not limited to statements or references concerning: anticipated or estimated future results, including the risks and uncertainties associated with our future operating performance and financial position; our possible or assumed future results of operations and expenses, business strategies and plan (including ex-US. Launch/partnering plans), including incurrence of indebtedness and compliance with debt covenants under the Loan and Security Agreement with Hercules Capital, Inc., as agent and lender, market trends, market sizing, competitive position, industry environment and potential growth opportunities, among other things; our ability to delay certain research activities and related clinical expenses as necessary; our clinical trials, including the anticipated timing of disclosure, presentations of data from, or outcomes from our trials; research and development activities, and the timing and results associated with the future development of our lead product candidate, resmetirom (formerly known as MGL-3196), including projected market size, sector leadership, and patient treatment estimates for NASH and NAFLD patients; the timing and completion of projected future clinical milestone events, including enrollment, additional studies, topline data and open label projections; plans, objectives and timing for making a Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) submission to FDA; projections or objectives for obtaining accelerated or full approval for resmetirom for noncirrhotic NASH patients with compensated cirrhosis; our primary and key secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections, including NASH resolution, safety, fibrosis treatment, cardiovascular effects, and lipid treatment with resmetirom; optimal dosing levels for resmetirom and projections regarding potential NASH or NAFLD and potential patient benefits with resmetirom, including future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment, and/or biomarker effects with resmetirom; the potential efficacy and safety of resmetirom for noncirrhotic NASH patients and cirrhotic NASH patients; the potential for resmetirom to become the best-in-class and/or first-to-market treatment option for patients with NASH and liver fibrosis; anticipated or estimated future results of operations and expenses as we expand our resmetirom clinical development program and our commercial development program; ex-U.S. launch/partnering plans; the ability to develop clinical evidence demonstrating the utility of noninvasive tools and techniques to screen and diagnose NASH and/or NAFLD patients; the predictive power of liver fat reduction with resmetirom, as measured by noninvasive tests, on NASH resolution and/or fibrosis reduction or improvement, and potential NASH or NAFLD patient risk profile benefits with resmetirom; the predictive power of liver fat, liver volume changes or MAST scores for NASH and/or NAFLD patients; the predictive power of NASH resolution and/or liver fibrosis reduction or improvement with resmetirom using noninvasive tests, including the use of ELF, FibroScan, MRE and/or MRI-PDFF; the predictive power of noninvasive tests generally, including for purposes of diagnosing NASH, monitoring patient response to resmetirom, or recruiting and conducting a NASH clinical trial; market demand for and acceptance of our products; research, development and commercialization of new products; obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections; risks associated with meeting the objectives of our clinical studies, including, but not limited to our ability to achieve enrollment objectives concerning patient numbers (including an adequate safety database), outcomes objectives and/or timing objectives for our studies, any delays or failures in enrollment, the occurrence of adverse safety events, and the risks of successfully conducting trials that are substantially larger, and have patients with different disease states, than our past trials; risks related to the effects of resmetirom' s mechanism of action and our ability to accomplish our business and business development objectives and realize the anticipated benefit of any such transactions; the achievement of enrollment objectives concerning patient number, safety database and/or timing for our studies; and assumptions underlying any of the foregoing.

Forward-looking statements reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events; include all statements that are not historical facts; and can be identified by terms such as "accelerate," "achieve," "allow," "anticipates," "appear," "be," "believes," "can," "continue," "could," "demonstrates," "design," "designed to," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "inform," inform," "intended," "intends," "may," "might," "on track," "planned," "planning," "plans," "positions," "potential," "powers," "predicts," "predictive," "projects," "seeks," "should," "will," "will achieve," "will be," "would" or similar expressions and the negatives of those terms.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: our clinical development of resmetirom; enrollment and trial conclusion uncertainties, generally and in relation to COVID-19 related measures and individual precautionary measures that may be implemented or continued for an uncertain period of time; our potential inability to raise sufficient capital to fund our ongoing operations as currently planned or to obtain financings on terms similar to those we have arranged in the past; our ability to service our indebtedness and otherwise comply with our debt covenants; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that includes substantially more patients, and patients with different disease states, than our prior studies; limitations associated with early stage or non-placebo controlled study data; the timing and outcomes of clinical studies of resmetirom; and the uncertainties inherent in clinical testing. Undue reliance should not be placed on forward-looking statements, which speak only as of the date they are made. Madrigal undertakes no obligation to update any forward-looking statements to reflect new information, events or circumstances after the date they are made, or to reflect the

occurrence of unanticipated events. Please refer to Madrigal's submissions filed or furnished with the U.S. Securities and Exchange Commission for more detailed information regarding these risks and uncertainties and other factors that may cause actual results to differ materially from those expressed or implied. We specifically discuss these risks and uncertainties in greater detail in the section appearing in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on February 25, 2022, as updated by the risk factors discussed in Part II, Item 1A of the Quarterly Report on Form 10-Q filed with the SEC on May 9, 2022, as well as in our other filings with the SEC.

Investor Contact
Alex Howarth, Madrigal Pharmaceuticals, Inc., IR@madrigalpharma.com

Media Contact
Christopher Frates, Madrigal Pharmaceuticals, Inc., media@madrigalpharma.com

Source: Madrigal Pharmaceuticals, Inc.