Madrigal Pharmaceuticals Announces Publication of the Phase 3 MAESTRO-NASH Trial of Resmetirom in the New England Journal of Medicine

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- *Resmetirom is the first investigational medicine for NASH to achieve fibrosis improvement and NASH resolution primary endpoints in a Phase 3 trial*
- *Detailed analyses reinforce the safety profile of resmetirom*
- *Resmetirom has the potential to become the first and only medicine approved for NASH; PDUFA date is March 14, 2024*

CONSHOHOCKEN, Pa., Feb. 08, 2024 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced the publication of the pivotal Phase 3 MAESTRO-NASH trial of resmetirom in the *New England Journal of Medicine*.

NASH is a leading cause of liver-related mortality and an increasing burden on healthcare systems globally. Resmetirom received Breakthrough Therapy designation from the FDA and is under review to become the first medicine approved to treat patients with NASH with liver fibrosis. The FDA granted resmetirom Priority Review and assigned a Prescription Drug User Fee Act (PDUFA) date of March 14, 2024, the target date by which FDA intends to complete its review.

Stephen Harrison, M.D., Chairman for both Pinnacle Clinical Research and Summit Clinical Research, San Antonio, Texas, Visiting Professor of Hepatology, Oxford University, and lead Principal Investigator of the MAESTRO studies, commented, “MAESTRO- NASH is a landmark study in a disease that has historically been very challenging for drug development. The publication of detailed efficacy and safety data in the *New England Journal of Medicine* will provide clinicians with valuable information about the medication that may soon become the first approved therapy for patients with NASH.”

The MAESTRO-NASH trial evaluates resmetirom treatment vs. placebo in patients with NASH with significant fibrosis (consistent with fibrosis stages 2 and 3), a population at elevated risk of progressing to cirrhosis and other adverse liver outcomes. The study includes a 52-week biopsy assessment to support accelerated approval and an ongoing 54-month outcomes study designed to generate confirmatory data that, if positive, will help verify resmetirom’s clinical benefit and support full approval.

Based on the results of the 52-week biopsy portion of the trial, MAESTRO-NASH is the only Phase 3 study in NASH to achieve both primary endpoints that FDA proposed as reasonably likely to predict clinical benefit: NASH resolution with no worsening of fibrosis and fibrosis reduction with no worsening of NAFLD activity score (NAS). Approximately 50% of patients treated with resmetirom 100 mg with biopsies at Week 52 showed either NASH resolution or fibrosis improvement. More than 80% of patients with biopsies at Week 52 had either fibrosis reversal or no progression of fibrosis.

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, “Patients with NASH with significant fibrosis are at increased risk of progressing to cirrhosis, liver failure, liver cancer and premature death. Additionally, NASH is the leading cause of liver transplant among women in the U.S. and may soon be the leading cause overall. Despite its serious impact on patients and the health system, there are no approved treatments for the disease. As a liver-directed therapy that has demonstrated efficacy in both reversing fibrosis and resolving NASH in a pivotal Phase 3 clinical trial, we believe resmetirom will change the treatment paradigm for patients with NASH with significant fibrosis if it receives accelerated approval from the FDA.”

In addition to the two primary endpoints, multiple secondary endpoints were achieved in the MAESTRO-NASH study, including statistically significant reduction from baseline in liver enzymes (ALT, AST and GGT). Reductions in atherogenic lipids and lipoproteins, fibrosis biomarkers and imaging tests (MRI-PDFF, CAP and liver stiffness measures) were observed in resmetirom treatment arms as compared with placebo. MAESTRO-NASH also included many biomarker and imaging assessments that may be used in real world clinical practice to identify appropriate patients for treatment and monitor response to resmetirom, if approved.

The incidence of serious adverse events was similar across the treatment groups, 10.9%, 12.7%, and 11.5% in 80 mg, 100 mg and placebo groups respectively. Transient diarrhea and nausea were more frequent with resmetirom at the beginning of therapy. No increase in the incidence of diarrhea and nausea was noted among resmetirom-treated patients relative to placebo-treated patients after the first few weeks of treatment. There was no incidence of drug-induced liver injury. There were no increases in bone fractures, or fracture risk score with resmetirom or increase in adverse events related to thyroid hormone effects outside the liver such as heart rate changes or sex hormone abnormalities.

Bill Sibold, Chief Executive Officer of Madrigal, stated, “The unprecedented efficacy and safety results from the pivotal MAESTRO- NASH Phase 3 trial provide Madrigal with a unique opportunity to establish resmetirom as the foundational therapy for NASH with significant fibrosis and transform care for patients who currently have no approved treatment options. Resmetirom is the only investigational medication to achieve both fibrosis improvement and NASH resolution endpoints in Phase 3, and we intend to build on our leadership position in NASH drug development with two ongoing outcomes trials that carry the potential to confirm clinical benefit and expand the eligible patient population for resmetirom to include patients with more advanced disease.”

About the Resmetirom Phase 3 Program

Resmetirom is a once-daily, oral, liver-directed THR-β agonist designed to target key underlying causes of NASH.

Madrigal is currently conducting multiple Phase 3 clinical trials to evaluate the safety and efficacy of resmetirom for the treatment of NASH:

1. The pivotal **MAESTRO-NASH (Significant Fibrosis)** study includes a 52-week biopsy assessment to support accelerated approval and an ongoing 54-month outcomes study designed to generate confirmatory data that, if positive, will help verify resmetirom's clinical benefit and support full approval. Positive topline results from the 52-week biopsy portion of the trial were reported in December 2022 and the primary results were published in the *New England Journal of Medicine*.
2. **MAESTRO-NASH Outcomes (Compensated Cirrhosis)** evaluates progression to liver decompensation events in patients with well-compensated NASH cirrhosis treated with resmetirom versus placebo. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH and expand the eligible patient population for resmetirom with an additional indication in patients with compensated NASH cirrhosis.
3. The **MAESTRO-NAFLD-1 (Safety)** study was designed to noninvasively evaluate the safety and tolerability of resmetirom and provide a larger safety database to support regulatory benefit-risk assessment. Positive topline results from the study were reported in January 2022 and the primary publication appeared in *Nature Medicine*. MAESTRO-NAFLD-OLE, an open-label active treatment extension of MAESTRO-NAFLD-1, is ongoing to collect additional safety data in patients with noncirrhotic NASH and patients with well-compensated NASH cirrhosis.

Data from the 52-week first 1,000 patient portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, Phase 2 and Phase 1 data, including safety parameters, form the basis for Madrigal's subpart H submission to FDA for accelerated approval of resmetirom for treatment of NASH with liver fibrosis.

About NASH

Nonalcoholic steatohepatitis (NASH) is a more advanced form of nonalcoholic fatty liver disease (NAFLD). NASH is a leading cause of liver-related mortality and an increasing burden on healthcare systems globally. Additionally, patients with NASH, especially those with more advanced metabolic risk factors (hypertension, concomitant type 2 diabetes), are at increased risk for adverse cardiovascular events and increased morbidity and mortality.

Once patients progress to NASH with significant fibrosis (consistent with fibrosis stages 2 and 3), the risk of adverse liver outcomes increases dramatically. NASH is rapidly becoming the leading cause of liver transplantation in the U.S.

Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with significant fibrosis. Madrigal plans to focus on approximately 315,000 diagnosed patients with NASH with significant fibrosis under the care of the liver specialist physicians during the launch of resmetirom.

There are currently no FDA-approved therapies available for the treatment of NASH.

NASH is also known as "metabolic dysfunction-associated steatohepatitis (MASH)" following a change in disease nomenclature introduced by hepatology medical societies in 2023.

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, liver-directed THR-β agonist designed to target key underlying causes of 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 Madrigal's beliefs and assumptions and on information currently available to it, but are subject to factors beyond its control. Forward-looking statements reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events. Forward-looking statements include: all statements that are not historical facts; statements referenced by forward-looking statement identifiers, including the examples in the paragraph below; the relationship between NASH progression and adverse patient outcomes; the estimated clinical burden of uncontrolled NASH; analyses for patients with NASH with significant fibrosis concerning potential progression to cirrhosis, decompensated cirrhosis, liver transplant or death, and cardiovascular risks, comorbidities and outcomes; health economics assessments or projections; resmetirom's potential to be the first specialty therapy for NASH patients with significant liver fibrosis; projections or objectives for obtaining accelerated or full approval for resmetirom, including all statements concerning potential clinical benefit to support accelerated approval and/or potential approval; and statements or references concerning - the potential efficacy and safety of resmetirom for noncirrhotic NASH patients and cirrhotic NASH patients, possible or assumed future results of operations and expenses, business strategies and plans (including ex-US. Launch/partnering plans), research and development activities, and the timing and results associated with the future development of resmetirom, the timing and completion of projected future clinical milestone events, including enrollment, additional studies, top-line data and open label projections, plans, Madrigal's primary and key secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections, the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis, optimal dosing levels for resmetirom, 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, and strategies, objectives and commercial opportunities, including potential prospects or results..

Forward-looking statements can be identified by terms such as "accelerate," "achieve," "allow," "anticipates," "appear," "be," "believes," "can," "confidence," "continue," "could," "demonstrates," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "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: the assumptions underlying the forward-looking statements; risks of obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections; risks

associated with meeting the objectives of Madrigal's clinical studies, including, but not limited to Madrigal's ability to achieve enrollment objectives concerning patient numbers (including an adequate safety database), outcomes objectives and/or timing objectives for Madrigal's studies; any delays or failures in enrollment, and the occurrence of adverse safety events; risks related to the effects of resmetirom's mechanism of action; the achievement of enrollment objectives concerning patient number, safety database and/or timing for Madrigal's studies; enrollment and trial conclusion uncertainties; market demand for and acceptance of our products; the potential inability to raise sufficient capital to fund ongoing operations as currently planned or to obtain financings on terms similar to those arranged in the past; the ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitive studies; future topline data timing or results; our ability to prevent and/or mitigate cyber-attacks, unauthorized exfiltration of data or other security incidents; the risks of achieving potential benefits in studies that includes substantially more patients, and patients with different disease states, than prior studies; the timing and outcomes of clinical studies of resmetirom; the uncertainties inherent in clinical testing; and uncertainties concerning analyses or assessments outside of a controlled clinical trial. 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 with the U.S. Securities and Exchange Commission, or SEC, 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. Madrigal specifically discusses these risks and uncertainties in greater detail in the section appearing in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2022, filed with the SEC on February 23, 2023, as amended by our Form 10-K/A filed with the SEC on March 3, 2023, and as updated from time to time by Madrigal's other filings with the SEC.

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