Madrigal Pharmaceuticals Completes Enrollment of Clinical Outcomes Study of Resmetirom in Patients with Compensated NASH/MASH Cirrhosis

October 21, 2024

- *Positive results from the MAESTRO-NASH OUTCOMES study could make resmetirom the first medication approved for patients with compensated NASH cirrhosis, a population at high risk of progressing to adverse liver-related outcomes*
- *Study may also support full approval of Rezdiffra™ (resmetirom) in noncirrhotic NASH*

CONSHOHOCKEN, Pa., Oct. 21, 2024 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a biopharmaceutical company focused on delivering novel therapeutics for nonalcoholic steatohepatitis (NASH)/metabolic dysfunction-associated steatohepatitis (MASH), today announced the MAESTRO-NASH OUTCOMES trial evaluating resmetirom for the treatment of patients with compensated NASH cirrhosis has completed enrollment.

Bill Sibold, Chief Executive Officer of Madrigal, stated, “The MAESTRO-NASH OUTCOMES trial is important for patients and the NASH field more broadly because there is an urgent unmet need for therapies that can prevent progression to the devastating complications of decompensated cirrhosis and by extension reduce the need for liver transplants due to NASH. NASH is already the leading cause of liver transplantation among women in the U.S. and second-leading cause among men. Today’s enrollment milestone brings us one step closer to our goal of delivering the first effective therapy to patients who currently have no approved treatment options for compensated NASH cirrhosis. A positive outcome for this study is also expected to support the full approval of Rezdiffra for noncirrhotic NASH.”

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, added, “Our confidence in the MAESTRO-NASH OUTCOMES study is grounded in the antifibrotic profile of resmetirom as a liver-directed THR-β agonist and supported by positive 52-week data from 180 patients with compensated NASH cirrhosis studied in the Phase 3 MAESTRO-NAFLD-1 study. Madrigal is committed to long-term leadership in NASH R&D, and we believe our fully enrolled outcomes studies will play a central role in shaping the NASH treatment paradigm over the next decade.”

MAESTRO-NASH OUTCOMES is a Phase 3, double-blind, randomized, placebo-controlled study that noninvasively measures progression to liver decompensation events in 845 patients with compensated NASH cirrhosis, exceeding the initial enrollment target. The primary endpoint of MAESTRO-NASH OUTCOMES is the incidence of composite liver-related outcome events. Key inclusion criteria are well-compensated NASH cirrhosis (Child-Pugh A) and presence of three metabolic risk factors (metabolic syndrome). Patients are 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.

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 moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), the risk of adverse liver outcomes increases dramatically. When a patient with NASH progresses to cirrhosis, their risk of liver-related mortality increases by more than 42 percent. 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 moderate to advanced liver fibrosis. Madrigal is focusing on approximately 315,000 diagnosed patients with NASH with moderate to advanced liver fibrosis under the care of the liver specialist physicians during the launch of Rezdiffra.

NASH is also known as metabolic dysfunction associated steatohepatitis (MASH). In 2023, global liver disease medical societies and patient groups came together to rename the disease, with the goal of establishing an affirmative, non-stigmatizing name and diagnosis. Nonalcoholic fatty liver disease (NAFLD) was renamed metabolic dysfunction-associated steatotic liver disease (MASLD); NASH was renamed MASH; and an overarching term, steatotic liver disease (SLD), was established to capture multiple types of liver diseases associated with fat buildup in the liver. In addition to liver disease, patients with MASH have at least one related comorbid condition (e.g., obesity, hypertension, dyslipidemia, or type 2 diabetes).

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 (Moderate to Advanced Fibrosis)** study included a 52-week biopsy assessment that

supported accelerated approval and an ongoing 54-month outcomes study designed to generate confirmatory data that, if positive, will help verify the clinical benefit of Rezdiffra and support full approval. The primary results of the MAESTRO-NASH trial were published in the *New England Journal of Medicine* in February 2024.

2. **MAESTRO-NASH OUTCOMES (Compensated Cirrhosis)** evaluates progression to liver decompensation events in patients with compensated NASH cirrhosis treated with resmetirom versus placebo. A positive outcome is expected to support the full approval of Rezdiffra for noncirrhotic NASH and expand the eligible patient population for Rezdiffra 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. The primary results from the MAESTRO-NAFLD-1 trial were published in *Nature Medicine* in October 2023. 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 compensated NASH cirrhosis.

Data from the 52-week portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, Phase 2 and Phase 1 data, including safety parameters, formed the basis for accelerated approval of Rezdiffra for treatment of NASH with moderate to advanced liver fibrosis.

About Madrigal Pharmaceuticals
Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), a liver disease with high unmet medical need. Madrigal's medication, Rezdiffra (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 press release 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; and statements regarding: Rezdiffra and its expected use for treating NASH with moderate to advanced fibrosis.

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," "informed," "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; the challenges with the commercial launch of a new product, particularly for a company that does not have commercial experience; 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 mechanism of action of Rezdiffra; enrollment and trial conclusion uncertainties; market demand for and acceptance of our product; 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; the timing and outcomes of clinical studies of Rezdiffra; 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 sections appearing in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2023, filed with the SEC on February 28, 2024, and Part II, Item 1A of its Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, filed with the SEC on August 7, 2024, and as updated from time to time by Madrigal's other filings with the SEC.

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