Madrigal Pharmaceuticals Completes Submission of New Drug Application Seeking Accelerated Approval of Resmetirom for the Treatment of NASH with Liver Fibrosis

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CONSHOHOCKEN, Pa., July 17, 2023 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), announced the completion of the rolling submission of its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for resmetirom for the treatment of adults with NASH with liver fibrosis, a disease with no approved therapy. Madrigal has requested a priority review of the resmetirom NDA.

Resmetirom is a once daily, oral, thyroid hormone receptor (THR)-β selective agonist designed to target key underlying causes of NASH in the liver. The clinical development program for resmetirom is comprised of 18 clinical studies supporting the NDA: twelve Phase 1 studies, two Phase 2 studies, and four Phase 3 studies. In the pivotal Phase 3 MAESTRO-NASH serial liver biopsy trial, resmetirom achieved both liver histological improvement endpoints – resolution of NASH and reduction of liver fibrosis – proposed by FDA as reasonably likely to predict clinical benefit to support accelerated approval for the treatment of NASH with liver fibrosis. Throughout the development program resmetirom appeared generally safe and well-tolerated. In both MAESTRO-NASH and the phase 3 safety study MAESTRO-NAFLD-1, atherogenic lipids and lipoproteins, including LDL cholesterol and triglycerides, were reduced by resmetirom and patients achieved potentially meaningful improvements in noninvasive measures of liver health. In April 2023, resmetirom was granted Breakthrough Therapy designation by FDA for the treatment of adults with NASH with liver fibrosis.

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, “Based on the positive efficacy results observed in MAESTRO-NASH and the large safety database we have established across the MAESTRO trials, we believe resmetirom has the potential to become the first approved treatment for patients with NASH with liver fibrosis, a disease that is rapidly becoming the leading cause of liver transplantation in the U.S. Madrigal has generated a robust evidence package to support the FDA’s benefit-risk evaluation and our two ongoing Phase 3 outcomes studies, one of which is already fully enrolled, reflect our commitment to verifying clinical benefit following a potential accelerated approval.”

Paul Friedman, M.D., Chief Executive Officer of Madrigal, stated, “The NDA filing represents an important step forward on Madrigal’s path to delivering resmetirom to patients who currently have no approved medications to treat NASH with liver fibrosis. We’d like to thank the many patients and investigators who have contributed to the clinical research supporting the resmetirom NDA.”

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. The portion of the study designed to support a subpart H approval enrolled more than 1,000 patients with biopsy-proven NASH with fibrosis, randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. The dual primary surrogate endpoints on biopsy were 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 NAS after 52 weeks of treatment. Achievement of either primary endpoint was considered a successful trial outcome.

In December 2022, Madrigal announced that both daily oral doses of resmetirom achieved both MAESTRO-NASH primary liver biopsy endpoints. Multiple secondary endpoints were also achieved, including statistically significant reductions by resmetirom as compared with placebo in atherogenic lipids and lipoproteins, liver enzymes, fibrosis biomarkers, and imaging tests.

Resmetirom was generally safe and well-tolerated at both the 80 mg and 100 mg doses. Consistent with previous Phase 2 and Phase 3 data, the most common adverse event reported with greater frequency in the resmetirom groups versus placebo was an excess of generally mild and transient diarrhea and nausea at the beginning of therapy.

Patients enrolled in MAESTRO-NASH (approximately 1,750 total enrollment) 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, as well as all-cause mortality. This portion of the study is designed to generate confirmatory data that, if positive, will help verify resmetirom’s clinical benefit and support full approval.

MAESTRO-NAFLD-1 was a 52-week multicenter, randomized, placebo-controlled, double-blind Phase 3 study of resmetirom in ~1,200 patients with NAFLD, presumed NASH. MAESTRO-NAFLD-1 might be considered a “real-world” NASH study in that diagnosis was based on noninvasive measures rather than liver biopsy. The primary endpoint was to evaluate the safety and

tolerability of resmetirom.

Patients in the MAESTRO-NAFLD-1 study were randomized 1:1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo in double-blind arms or resmetirom 100 mg in an open-label arm. 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 of MAESTRO-NAFLD-1 and key secondary endpoints were achieved: resmetirom was safe, well-tolerated and provided statistically significant improvements in LDL-C, apolipoprotein B, triglycerides, and liver fat as measured by MRI-PDFF.

An additional open-label active treatment arm in 180 patients with early (well-compensated) NASH cirrhosis was conducted. Resmetirom was safe and well tolerated in the MAESTRO-NAFLD-1 open-label cohort of patients with well-compensated NASH cirrhosis. As observed in patients with noncirrhotic NASH, mild GI adverse events were seen at the beginning of therapy. Resmetirom reduced LDL-C, other atherogenic lipids and lipoproteins, and MRI-PDFF in patients with NASH cirrhosis and also reduced liver and spleen volume.

A separate 52 week Phase 3 clinical trial, an open-label active treatment extension study of MAESTRO-NAFLD-1 (MAESTRO-NAFLD-OLE), in about 700 patients is ongoing.

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.

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 NASH

Nonalcoholic steatohepatitis (NASH) is a more advanced form of nonalcoholic fatty liver disease (NAFLD). In the United States, NAFLD is estimated to affect approximately 25% of the population, and approximately 25% of those will progress from NAFLD to NASH.

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 NASH progresses to significant liver fibrosis the risk of adverse liver outcomes increases dramatically. NASH is rapidly becoming the leading cause of liver transplantation in the U.S. There are currently no FDA-approved therapies available for the treatment of NASH.

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. 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; resmetirom's potential to be the first specialty therapy for NASH patients with significant liver fibrosis; statements concerning potential accelerated 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, objectives, timing and support for making 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, Madrigal's primary and key secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections, demonstrating clinical benefit to support accelerated approval, the potential to support an additional indication for resmetirom in patients with well-compensated NASH

cirrhosis, 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.

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," 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; 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; 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 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.

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

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

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