Madrigal Pharmaceuticals Presents New Data from the Phase 3 MAESTRO-NASH Trial Demonstrating Broad Treatment Effects of Resmetirom on Noninvasive Measures of Liver Health

November 10, 2023

- *Data to be featured in an oral presentation at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting®*
- *Analyses from comprehensive set of noninvasive tests used in MAESTRO-NASH provide new insights on strategies to identify patients and measure response to resmetirom*
- *A significant majority (>70%) of patients treated with resmetirom 100 mg experienced a ≥30% reduction in MRI-PDFF, which predicted treatment response on biopsy, including both the NASH resolution and fibrosis improvement endpoints*
- *Multiple additional abstracts examine resmetirom safety and efficacy in NASH with significant fibrosis and NASH with compensated cirrhosis*

CONSHOHOCKEN, Pa., Nov. 10, 2023 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced new data from the Phase 3 MAESTRO-NASH trial demonstrating broad treatment effects of resmetirom on noninvasive tests that may be used to monitor NASH with liver fibrosis. The noninvasive testing data and multiple additional abstracts from the MAESTRO program are being presented at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting, taking place in Boston from November 10-14, 2023.

Resmetirom is a liver-directed thyroid hormone receptor (THR)-β agonist oral therapy that is designed to target key underlying causes of NASH. It is the only investigational therapy for NASH that has achieved both fibrosis improvement and NASH resolution primary endpoints in a Phase 3 trial.

In MAESTRO-NASH, resmetirom treatment helped patients with NASH with significant fibrosis (F2/F3) as diagnosed on liver biopsy achieve improvements in liver enzymes, magnetic resonance imaging-proton density fat fraction (MRI-PDFF), magnetic resonance elastography (MRE), FibroScan Vibration Controlled Transient Elastography (VCTE), FibroScan Controlled Attenuation Parameter (CAP), and the Enhanced Liver Fibrosis (ELF) test. Resmetirom also reduced levels of LDL cholesterol and other lipids that are associated with heart disease.

Rohit Loomba, M.D., Chief of the Division of Gastroenterology and Hepatology at University of California San Diego School of Medicine and lead author of the new MAESTRO-NASH analysis, stated, “These new data from MAESTRO-NASH highlight the importance of noninvasive tests in the care pathway for NASH with significant liver fibrosis and further improves our understanding of resmetirom’s liver-directed efficacy as a THR-β agonist. In our analyses, resmetirom-mediated reduction in liver fat as measured by MRI-PDFF, a noninvasive imaging test, was the strongest predictor of both NASH resolution and fibrosis improvement on biopsy. This suggests that reducing liver fat with a THR-β agonist may resolve the underlying hepatitis that drives the disease and reverse or halt the fibrosis progression that leads to negative patient outcomes.”

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, “It is encouraging to see such a broad and consistent treatment response with resmetirom across multiple noninvasive tests, from simple blood-based tests that are widely used in clinical practice today to advanced imaging tests that will play a larger role in future care pathways for NASH. If resmetirom receives accelerated approval, clinicians will have many opportunities to highlight treatment response for their patients over time; even something as readily measurable as an improvement in ALT or LDL can be highly motivating for patients and support treatment adherence.”

A significant majority (>70%) of patients treated with resmetirom 100 mg had a ≥30% MRI-PDFF response. A ≥30% MRI-PDFF reduction was strongly associated with NASH resolution (96% of patients) and fibrosis improvement (88% of patients). Median reduction in MRI-PDFF was 52% overall in this group.

Resmetirom is an investigational therapy and has not been approved by the FDA or any other regulatory authority. In September 2023, the FDA granted Priority Review for the new drug application (NDA) seeking accelerated approval of resmetirom for the treatment of NASH with liver fibrosis and assigned a Prescription Drug User Fee Act date for resmetirom of March 14, 2024.

Artificial Intelligence-Based Analyses of MAESTRO-NASH Biopsy Results

A second oral presentation from the MAESTRO program examined the use of an artificial intelligence (AI) biopsy reading method (HistoIndex Second Harmonic Generation “qFibrosis” score) to measure the effect of resmetirom on fibrosis on serial liver biopsy using both continuous and quantitative scoring. In this analysis, AI-based reading of the biopsies reinforced the primary results from the central pathologists: measurements of fibrosis change using qFibrosis on either a continuous or categorical scale demonstrated a clear improvement and less worsening in fibrosis among resmetirom-treated patients as compared with placebo-treated patients after 52 weeks. A late-breaking poster examining another AI-based biopsy reading method (PathAI “AIM-NASH”)

also recapitulated the MAESTRO-NASH primary endpoint results and showed a high degree of alignment with pathologists on NASH component scoring.

Full Listing of Resmetirom Data Presentations at AASLD

Multiple resmetirom and Madrigal health economics outcomes research abstracts will be presented at the AASLD Liver Meeting:

- Oral presentation: “Relationship of Non-Invasive Measures with Histological Response in Patients with Nonalcoholic Steatohepatitis and Fibrosis: 52-Week Data from the Phase 3 MAESTRO-NASH Trial” [Monday, November 13 at 8:30 AM. Presenter: Rohit Loomba]
- Oral presentation: “Artificial Intelligence to Measure Fibrosis Change on Liver Biopsy in MAESTRO-NASH: A Phase 3 Serial Liver Biopsy Study in 966 Patients with NASH Treated with Resmetirom or Placebo” [Sunday, November 12 at 11:00 AM. Presenter: Stephen Harrison]
- Late-Breaking poster: “Artificial Intelligence-Based Measurement of NASH Histology (AIM-NASH) Recapitulates Primary Results from Phase 3 Study of Resmetirom for Treatment of NASH/MASH” [Presenter: Janani Iyer]
- Poster of Distinction: “Resmetirom Treatment Helps Restore Thyroid Hormone Levels in Patients with Nonalcoholic Steatohepatitis: 52-Week Data from the Phase 3 MAESTRO-NASH Trial” [Presenter: Stephen Harrison]
- Poster: “Resmetirom Improves the Atherogenic Lipid/Lipoprotein Profile in Patients with Nonalcoholic Steatohepatitis: 52-Week Data from the Phase 3 MAESTRO-NASH Trial” [Presenter: Naim Alkhouri]
- Poster: “The Next Generation of HepQuant Tests Measure Reduction in Risk for Clinical Events in Compensated NASH Cirrhosis Subjects Treated with Resmetirom” [Presenter: Michael McRae]
- Poster: “Understanding the Incremental Costs of Nonalcoholic Steatohepatitis and Diabetes Using Electronic Health Records and Closed Claims Data” [Presenter: Jesse Fishman]
- Poster: “Characterizing the Management of Patients with NASH (With Versus Without Cirrhosis) in Real-World Clinical Practice: Rare Assessment by Hepatologists and Low Frequency of Imaging” [Presenter: Christina Qian]

About the Resmetirom Phase 3 Program

Resmetirom is a liver-directed THR-β agonist oral therapy that is 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 study were reported in December 2022.
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 (F2/F3), 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.

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 liver-directed THR-β agonist oral therapy that is 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; 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; 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; 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 sections 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 Part II, Item 1A of its Quarterly Reports on Form 10-Q for the quarters ended June 30, 2023 and September 30, 2023, and as updated from time to time by Madrigal's other filings with the SEC.

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