Positive Resmetirom Data from Completed Open-Label Portion of Phase 3 MAESTRO-NAFLD-1 Clinical Study Presented at American Association for the Study of Liver Diseases (AASLD) The Liver Meeting® Digital Experience 2021

November 12, 2021

- *This final read-out of the 52-week open-label resmetirom 100 mg treatment study of 171 patients with presumed non-alcoholic steatohepatitis (NASH) and fibrosis, identified using non-invasive tests, demonstrate that resmetirom:*
  - *provided rapid and sustained reduction in liver fat and liver volume;*
  - *provided rapid and sustained reductions in liver fibrosis, as measured by biomarkers, magnetic resonance elastography (MRE) and FibroScan;*
  - *reduced atherogenic lipids, including LDLc and triglycerides, liver enzymes and inflammatory biomarkers;*
  - *was safe and well-tolerated at 100 mg per day in patients treated for 52 weeks.*
- *This "real-life" study supports the potential use of non-invasive assessments to diagnose and manage NASH with fibrosis, including assessment of individual patient response to resmetirom treatment.*

CONSHOHOCKEN, Pa., Nov. 12, 2021 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), today announced the presentation of positive clinical data from the open-label portion of its ongoing MAESTRO-NAFLD-1 (non-alcoholic fatty liver disease) study of resmetirom at the AASLD The Liver Meeting®, being held virtually November 12th – 15th, 2021. Madrigal will host a webcast and conference call after the meeting on Tuesday, November 16th at 8:00 AM EST to summarize and discuss the data.

"These new data from MAESTRO-NAFLD-1, our ongoing Phase 3 non-invasive study of resmetirom in patients with presumed NASH, reinforce and deepen our understanding of the therapeutic potential of resmetirom. The positive safety and efficacy findings from the open-label portion of MAESTRO-NAFLD-1 are particularly encouraging as we prepare to report initial topline data from the placebo-controlled double-blind portion of the study by year-end," stated Paul Friedman, M.D., Chief Executive Officer of Madrigal.

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal added, "The completed 52-week open-label MAESTRO-NAFLD-1 results being presented at The Liver Meeting 2021 demonstrate resmetirom's ability to potently reduce hepatic fat and liver volume in all subgroups of patients with NASH, including patients stably treated with diabetes medications such as GLP-1 agonists and SGLT2 inhibitors. Liver volume reduction may be explained in part by reduction in liver fat, but is also likely driven by other factors related to resmetirom's mechanism of action, potentially including effects on inflammation. Consistent with previous studies, there was a low discontinuation rate from adverse effects with no changes in central thyroid hormone axis or bone mineral density."

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, "Patients treated with 100 mg per day of resmetirom for up to 52 weeks achieved rapid and sustained improvements in multiple clinically relevant NASH endpoints and resmetirom continues to be well-tolerated. The MAESTRO-NAFLD-1 study has shown a potential for using non-invasive imaging and biomarkers to diagnose and monitor NASH patients treated with resmetirom without the use of liver biopsies."

Late-Breaking Poster Presentation (abstract #LP19): Friday, November 12th
Biomarkers, imaging and safety in resmetirom 52-week non-cirrhotic NASH Phase 3 clinical trial, completed open-label arm of MAESTRO-NAFLD-1. Presenter: Stephen Harrison [click here to view poster]

MAESTRO-NAFLD-1 is a Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom being conducted in 1,200 patients with NAFLD and presumed NASH. A 171-patient 100 mg open-label arm of the study was completed in July 2021. Patients in the open-label arm demonstrated rapid and sustained reduction in hepatic fat on MRI-PDFF >50% and liver volume >20%, and fibrosis as assessed by biomarkers, magnetic resonance elastography (MRE), and vibration-controlled transient elastography (VCTE) and controlled attenuation parameter (CAP), LDLc and atherogenic lipids, liver enzymes and inflammatory biomarkers. No safety flags were identified; blood pressure (systolic, diastolic) was reduced by ~2mmHg, (p=0.02); bone mineral density was unchanged at 52 weeks.

Poster Presentation: (abstract #1922): Friday, November 12th
Liver volume reduction in resmetirom treated non-cirrhotic and cirrhotic NASH patients. Presenter: Stephen Harrison [click here to view poster]

Liver enlargement, or hepatomegaly, is a potential cause of pain in patients with NASH and is thought to be driven primarily by high liver fat content. In a 36-week Phase 2 serial MRI-PDFF and liver biopsy study in adults with biopsy-confirmed NASH (NAS≥4, F1-F3) and hepatic fat fraction ≥10%, resmetirom-treated patients showed statistically significant liver fat reduction

associated with NASH resolution as assessed by liver biopsy compared to placebo. In a secondary analysis, statistically significant ($p<0.0001$) reduction in liver volume of ~21% in resmetirom-treated non-cirrhotic NASH patients as compared with placebo was observed. Liver volume reduction was also observed in an open-label resmetirom-treated cohort of well-compensated NASH cirrhotic patients who also had greatly elevated liver volume at baseline. Liver volume reduction was much greater than expected in these patients based on the small reduction in MRI-PDFF; for example, a cohort of NASH cirrhotic patients with normal baseline liver fat (≤5%) experienced an average 15% reduction in liver volume independent of any effect on liver fat. NASH cirrhotics with elevated baseline liver fat >=8% had 30% reduction in liver fat fraction and 18% reduction in liver volume. Liver volume reduction is likely driven by other factors related to resmetirom's mechanism of action in addition to liver fat reduction, potentially including reduced inflammation.

Oral Presentation (abstract #118): Sunday, November 14th at 4:00 PM EST
Utilization of the MAST (MRI-PDFF-MRE-AST) score to predict NASH on liver biopsy in MAESTRO-NASH and assess response to resmetirom in MAESTRO-NAFLD-1. Presenter: Mazen Noureddin

The purpose of this analysis was to investigate the utility of the MAST (MRI-PDFF-MRE-AST) scores for non-invasive identification of patients with NASH with significant fibrosis in the MAESTRO-NASH and MAESTRO-NAFLD-1 Phase 3 studies of resmetirom. The analysis included baseline screening data from more than 1,000 patients who had AST, MRE, MRI-PDFF, fibroscan and liver biopsy assessments. The results show that MAST is predictive of fibrosis stage in NASH and of the level of NASH activity (steatosis, inflammation and ballooning) in the NASH liver. The investigators concluded that in the absence of a liver biopsy, elevated MAST score in the setting of metabolic syndrome may predict NASH with significant liver fibrosis.

Virtual Product Theatre: Friday, November 12th at 1:00 PM EST
NASH with Fibrosis: Updates from the Resmetirom Clinical Program

Manal Abdelmalek, M.D. and Mazen Noureddin, M.D. will discuss NASH disease state, provide an update on the resmetirom development program, review the mechanism of action and summarize new data presented at The Liver Meeting 2021 from the Phase 2 and Phase 3 trials.

Conference Call and Webcast Information
Madrigal will hold a conference call and live webcast, Tuesday, November 16, 2021 at 8:00 AM EST to discuss the resmetirom data recently presented at AASLD's The Liver Meeting. To access the conference call, please dial (833) 660-2754 for domestic callers or (409) 350-3497 for international callers and reference conference ID: 2458676. To access the live webcast of the call with slides please visit the Events and Presentations section of Madrigal's website or click here. An archived webcast will be available on the Madrigal website after the event.

About Madrigal Pharmaceuticals
Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a clinical-stage biopharmaceutical company pursuing novel therapeutics that target a specific thyroid hormone receptor pathway in the liver, which is a key regulatory mechanism common to a spectrum of fatty liver and cardio-metabolic diseases with high unmet medical need. Madrigal's lead candidate, resmetirom, is a first-in-class, orally administered, small-molecule, liver-directed, thyroid hormone receptor (THR)-β selective agonist that is currently in two Phase 3 clinical studies, MAESTRO-NASH and MAESTRO- NAFLD-1, designed to demonstrate multiple benefits in NASH (non-alcoholic steatohepatitis) patients. For more information, visit www.madrigalpharma.com.

Forward Looking Statements
This communication contains "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: our clinical trials, including the anticipated timing of disclosure or presentations of data from our trials; research and development activities; market size estimates for NASH and NAFLD patients; the timing and results associated with the future development of our lead product candidate, MGL-3196 (resmetirom); our primary and secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections; plans, objectives and timing for making a Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) submission to FDA; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment or biomarker effects with resmetirom; the efficacy and safety of resmetirom for non-cirrhotic NASH patients and cirrhotic NASH patients; ex-U.S. launch/partnering plans; the predictive power of liver fat reduction measured by non-invasive tests on NASH resolution with fibrosis reduction or improvement; the predictive power of liver fat liver volume changes or MAST scores for NASH and/or NAFLD patients; the effects of resmetirom's mechanism of action; the achievement of enrollment objectives concerning patient number, safety database and/or timing for our studies; the predictive power of NASH resolution and/or liver fibrosis reduction with resmetirom using non-invasive tests, including the use of ELF, FibroScan, MRE and/or MRI-PDFF; the ability to develop clinical evidence demonstrating the utility of non-invasive tools and techniques to screen and diagnose NASH and/or NAFLD patients; the predictive power of non-invasive tests generally, including for purposes of diagnosing NASH, monitoring patient response to resmetirom, or recruiting a NASH clinical trial; potential NASH or NAFLD patient risk profile benefits with resmetirom; the potential for resmetirom to become the best-in-class and/or first-to-market treatment option for patients with NASH; and our possible or assumed future results of operations and expenses, business strategies and plans, capital needs and financing plans, trends, market sizing, competitive position, industry environment and potential growth opportunities, among other things. 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 "allow,"

“anticipates,” “be,” “believes,” “continue,” “could,” “demonstrates,” ”design,” “estimates,” “expects,” “forecasts,” “future,” “goal,” “hopeful,” ”inform,” “intends,” “may,” “might,” “planned”, “plans,” “positions,” “potential,” “powers,” “predicts,” ”predictive,” “projects,” “seeks,” “should,” “will,” “will be,” “would” or similar expressions and the negatives of those terms. Although management presently believes that the expectations reflected in such forward-looking statements are reasonable, it can give no assurance that such expectations will prove to be correct and you should be aware that actual results could differ materially from those contained in the forward- looking statements.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: our clinical development of resmetirom; enrollment uncertainties, generally and in relation to COVID-19-related measures that may be continued for an uncertain period of time or implemented; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that include substantially more patients than our prior studies; limitations associated with early stage, 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 entitled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2020, as well as in our other filings with the SEC.

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