Positive Topline Phase 3 MAESTRO-NAFLD-1 Data Demonstrate Resmetirom was Safe, Well-Tolerated and Provided Statistically Significant Improvements in Key Measures of Liver and Cardiovascular Health

January 31, 2022

Primary and key secondary endpoints from the double-blind placebo-controlled 969-patient MAESTRO-NAFLD-1 safety study were achieved and demonstrate that resmetirom:

- *Was safe and well-tolerated at 80 and 100 mg in patients treated for 52 weeks*
- *Provided significant and clinically relevant reductions in liver fat as measured by magnetic resonance imaging proton density fat-fraction (MRI-PDFF)*
- *Significantly reduced atherogenic lipids, including LDLc, apolipoprotein B and triglycerides*

The increased enrollment of patients into the safety database is consistent with meeting regulatory guidance for chronic disease therapies

Madrigal to host conference call at 8:00 am EST to review the data

CONSHOHOCKEN, Pa., Jan. 31, 2022 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), today announced positive topline clinical data from the placebo-controlled, double-blind portion of its Phase 3 MAESTRO-NAFLD-1 (non-alcoholic fatty liver disease) safety study of resmetirom. The 52-week study demonstrated that resmetirom was safe and well-tolerated at 80 and 100 mg once a day dosing. Additionally, resmetirom helped patients with presumed non-alcoholic steatohepatitis (NASH) achieve significant, clinically relevant reductions in liver fat and atherogenic lipids.

“These positive results from the first of our two Phase 3 MAESTRO trials support our conviction that resmetirom has the potential to be the first medication approved for the treatment of patients with NASH and liver fibrosis. The blinded, placebo-controlled data from MAESTRO-NAFLD-1 reinforce previous positive Phase 2 and open-label Phase 3 safety findings in a much larger population of patients followed for 56 weeks. Rigorous safety evaluation is critical in NASH drug development because of the large numbers of patients with NASH that could be treated with a new medication once FDA approved. The large safety database we are generating through the MAESTRO trials supports our regulatory strategy under Subpart H and reflects our commitment to providing the data necessary for overall benefit-risk assessment,” 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, “These positive topline MAESTRO-NAFLD-1 placebo-controlled data are highly encouraging and increase our confidence in the pivotal serial liver biopsy Phase 3 trial, MAESTRO-NASH, that will deliver safety and efficacy data later this year. MAESTRO-NAFLD-1 was conducted during the height of the COVID-19 pandemic. COVID-related visits and blister pack manufacturing interruptions were observed in the study. Despite this, MRI-PDFF reductions were robust, with nearly half of patients in the resmetirom 100 mg arm achieving a 50% PDFF reduction. Importantly, COVID-related issues or patient withdrawals have not had a significant impact in the MAESTRO-NASH serial liver biopsy study.”

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, “This positive readout from MAESTRO-NAFLD-1 is a significant milestone for the field. As the first Phase 3 study in NASH that does not rely on liver biopsy to identify patients and measure treatment response, MAESTRO-NAFLD-1 will help accelerate the role of non-invasive imaging and biomarkers in NASH drug development. We see a safety and tolerability profile for resmetirom in this study of nearly one thousand patients treated for 52 weeks that, similar to earlier studies, leads to very low adverse event discontinuation rates. We look forward to presenting additional analyses of safety and efficacy data from MAESTRO-NAFLD-1 at future scientific congresses.”

Study Population
A total of 972 patients were randomized in the double-blind arms of the MAESTRO-NAFLD-1 study: 969 patients were included in the safety population and 943 patients in a modified intent-to-treat population for evaluation of key secondary and other endpoints. Important inclusion criteria included the presence of three risk factors of Metabolic Syndrome, a level of liver fibrosis (measured by FibroScan) consistent with a range of stages of liver fibrosis, and >=8% liver fat (measured by MRI-PDFF). The study remains blinded to study personnel at the individual patient level. Any occurrence of <25 events of an individual safety measurement was also blinded by treatment group.

Primary Endpoint
Resmetirom was safe and well-tolerated at the 80 mg dose and also importantly at the top dose of 100 mg in MAESTRO-NAFLD-1. Adverse events observed in the MAESTRO-NAFLD-1 trial were generally mild to moderate in severity. The frequency of serious adverse events was similar across treatment arms (Table 1) and discontinuation for adverse events was low. Serious adverse events occurred at expected rates based on the patient population.

Consistent with published data, the most common adverse event reported with greater frequency in the resmetirom groups vs placebo was generally mild diarrhea or increased stool frequency at the beginning of therapy, which occurred in 9% and ~17% over the placebo rate in the 80 and 100 mg dose groups, respectively.

Table 1

	Resmetirom 80 mg	Resmetirom 100 mg	Placebo
Safety population	(N=327)	(N=324)	(N=318)
At least one TEAE	289 (88.4)	279 (86.1)	260 (81.8)
At least one Serious TEAE	20 (6.1)	24 (7.4)	20 (6.3)
TEAE ≥ Grade 3 Severity	26 (8.0)	29 (9.0)	29 (9.1)
AE discontinuations from study	All treatments combined, n=21; (2.17%)		
Maximum NCI CTCAE Severity Grade			
Grade 1	99 (30.3)	99 (30.6)	92 (28.9)
Grade 2	164 (50.2)	151 (46.6)	139 (43.7)
AEs over 10%			
Diarrhea	76 (23.2)	101 (31.2)	44 (13.8)
Nausea	38 (11.6)	59 (18.2)	25 (7.9)

AE (adverse event); TEAE (treatment emergent adverse event); NCI (National Cancer Institute); CTCAE (Common Terminology Criteria for Adverse Events)

Key Secondary Endpoints
Hierarchically-controlled key secondary endpoints were achieved for both the 80 and 100 mg resmetirom dose groups (Table 2). Resmetirom provided significant reductions in liver fat as measured by MRI-PDFF and reduced atherogenic lipids, including LDLc, apolipoprotein B and triglycerides. Although both arms were randomized in MAESTRO-NAFLD-1, lipid reductions were numerically greater in the 100 mg open label treatment arm compared to the 100 mg double-blind arm. Patients in the open-label active 100 mg treatment arm were less impacted by COVID-related dose interruptions than double-blind patients.

Table 2

	Resmetirom 100 mg OL	Resmetirom 80 mg	p-value	Resmetirom 100 mg	p-value	Placebo
LDLc %CFB (SE) (Week 24)	-21 (1.9)	-12.7 (2.1)	<.0001	-14.4 (2.1)	<.0001	-1.7 (2.0)
ApoB %CFB (SE) (Week 24)	-22 (1.5)	-14.6 (1.5)	<.0001	-16.6 (1.6)	<.0001	-0.1 (1.5)
MRI-PDFF %CFB (Week 16)	-49%	-41%	<.0001	-48%	<.0001	-6%
Liver volume PDFF correction %CFB	-60%					
MRI-PDFF %CFB (Week 52)	-53%	-43%	<.0001	-48%	<.0001	8%
Liver volume PDFF correction %CFB	-61%					
Triglycerides baseline >150 mg/dL, CFB (SE)	-65 (8.3)	-55.6 (8.6)	NA	-59 (6.5)	NA	-6.9 (16.1)
Triglycerides baseline >150 mg/dL (geomean) %CFB (95% CI)	-25 (3.1)	-19.5 (-27.0 to -11.1)	=.0005	-21.5 (-28.0 to -14.3)	<.0001	-2.1 (-10.6 to 7.4)

CFB (change from baseline); SE (standard error); APOB (Apolipoprotein B); MRI-PDFF (magnetic resonance imaging proton density fat-fraction); CI (confidence interval); OL, open label non-cirrhotic arm randomized concurrently with double-blind arms

Madrigal will continue to generate data from the MAESTRO-NAFLD-1 study, with future readouts of safety, additional biomarkers and non-invasive measures of liver fibrosis. The company intends to provide at least one additional public disclosure prior to publication/presentation at a major medical meeting.

Resmetirom Safety Database
The Phase 3 clinical program for resmetirom is comprised of (i) MAESTRO-NAFLD-1 a 52-week >1,200 patient safety study in patients with presumed non-alcoholic steatohepatitis (NASH) diagnosed non-invasively and (ii) MAESTRO-NASH, a histology-based outcome study which incorporates a 52-week serial liver biopsy in more than 900 patients with biopsy-confirmed NASH with significant liver fibrosis. The 52-week data from MAESTRO-NASH and the MAESTRO-NAFLD-1 safety study, together comprising well over 2,000 patients, are designed to support accelerated approval of resmetirom for the treatment of patients with NASH with significant fibrosis. An additional ongoing study, MAESTRO-NAFLD-OLE (open label extension) enrolls consenting patients completing MAESTRO-NAFLD-1 and additional F2-F3 stage patients who screen fail MAESTRO-NASH (NAS<4) for 52 weeks of active resmetirom treatment.

Based on patients dosed with at least 80 and/or 100 mg per day in completed and ongoing studies, exposure to resmetirom has now reached a number of patients that Madrigal believes is consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for long-term treatment therapies (at least 1,500 patients dosed for specified lengths at the approved dose).

About Resmetirom
Thyroid hormone, through activation of its β-receptor in hepatocytes, plays a central role in liver function impacting a range of health parameters from levels of serum cholesterol and triglycerides to the pathological buildup of fat in the liver. Thyroid hormone receptor (THR)-β action in the liver is key to proper function of the liver, including regulation of mitochondrial activity such as breakdown of liver fat and control of the level of normal, healthy mitochondria. Patients with NASH have reduced levels of thyroid hormone activity in the liver with resultant impaired hepatic function, in part due to the inflamed state of the liver that causes degradation of thyroid hormone.

To exploit the thyroid hormone receptor (THR)-β pathway for therapeutic purposes in liver and cardio-metabolic diseases, it is important to avoid

activity at the THR-α receptor, the predominant systemic receptor for thyroid hormone that is responsible for activity outside the liver including in heart and bone. The lack of selectivity of older thyromimetic compounds, chemically-related toxicities and undesirable distribution in the body led to safety concerns. Madrigal recognized that greater selectivity for thyroid hormone receptor (THR)-β and liver targeting might overcome these challenges and deliver the full therapeutic potential of THR-β agonism. Resmetirom has been shown to be highly selective based on 1) THR-β receptor functional selectivity based on both in vitro and in vivo assays and 2) specific uptake into the liver, its site of action, virtually avoiding any uptake into tissues outside the liver. In short and long- term human and animal studies, resmetirom has been confirmed to be safe and devoid of activity at the THR-α receptor and without impact on bone or cardiac parameters. Resmetirom does not impact the thyroid axis hormones, including the central thyroid axis. Madrigal believes that resmetirom is the first orally administered, small-molecule, liver-directed, truly β-selective THR agonist.

About the Phase 3 Registration Program for the Treatment of NASH (Non-alcoholic steatohepatitis)
Madrigal is currently conducting two Phase 3 Clinical trials, MAESTRO-NASH and MAESTRO-NAFLD-1, to demonstrate the safety and efficacy of resmetirom for the treatment of NASH.

MAESTRO-NASH is a Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom in patients with liver biopsy confirmed NASH and was initiated in March 2019. The study targets enrollment of 900 patients with biopsy-proven NASH (fibrosis stage 2 or 3, at least 450 fibrosis stage 3), randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo. After 52 weeks of treatment a second biopsy is performed. The primary surrogate endpoint on biopsy will be NASH resolution, with at least a 2-point reduction in NAS (NASH Activity Score), and with no worsening of fibrosis. Two key secondary endpoints are liver fibrosis reduction of at least one stage, with no worsening of NASH on liver biopsy, and lowering of LDL-cholesterol [ClinicalTrials.gov/NCT03900429]. Madrigal announced achievement of the planned target enrollment on June 30, 2021.

The first 900 patients in the MAESTRO-NASH study will continue on therapy after the initial 52-week treatment period; and up to another 1,100 patients are to be added using the same randomization plan. The study is expected to continue 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.

MAESTRO-NAFLD-1 is a 52-week Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom, and was initiated in December 2019 in patients with non-alcoholic fatty liver disease (NAFLD), presumed NASH. The primary endpoint for this study is to evaluate the safety and tolerability of resmetirom. Completion of enrollment of over 1,200 patients into the study was announced in October 2020.

Patients in MAESTRO-NAFLD-1 are randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo. MAESTRO-NAFLD-1 also includes a 100 mg resmetirom open label arm. MAESTRO-NAFLD-1 (unlike MAESTRO-NASH), does not include a liver biopsy and represents a "real-life" NASH study. NASH or presumed NASH is documented using historical liver biopsy or non-invasive techniques including FibroScan and magnetic resonance imaging, proton density fat fraction (MRI-PDFF) respectively. Using non-invasive measures, MAESTRO-NAFLD-1 is 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. These key secondary endpoints include LDL-cholesterol, apolipoprotein B and triglyceride (TG) lowering; and reduction of liver fat as determined by MRI-PDFF [ClinicalTrials.gov/NCT04197479]. Additional secondary and exploratory endpoints will be assessed including reduction in liver enzymes, FibroScan scores and other fibrosis and inflammatory biomarkers.

Data from the 52-week portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1 and other data, including safety parameters, will form the basis for a potential subpart H submission to FDA for accelerated approval for the treatment of NASH.

Conference Call at 8:00 am EST
Madrigal will hold a conference call and webcast to discuss the topline results of the Phase 3 MAESTRO-NAFLD-1 study at 8:00 am EST. To access the conference call, please dial (833) 660-2754 for domestic callers or (409) 350-3497 for international callers and reference conference ID: 9170277. 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 and patient treatment 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 liver fibrosis; 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," "demonstrate," "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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