Madrigal Pharmaceuticals Announces Publication in The Lancet of Positive Phase 2 Results for Resmetirom (MGL-3196) for the Treatment of Non-alcoholic Steatohepatitis (NASH)

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Data from this 36-week, multicenter, randomized, double-blind, placebo-controlled Phase 2 clinical trial in patients with NASH:

- *demonstrated that resmetirom treatment resulted in statistically significant reduction in hepatic fat measured non-invasively (magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at week 12, the primary endpoint of the study, and sustained fat reduction at Week 36*
- *achieved secondary endpoints include statistically significant reduction and resolution of NASH on liver biopsy and statistically significant improvement in multiple noninvasive parameters of NASH and liver fibrosis including fibrosis biomarkers and liver enzymes*
- *achieved secondary endpoints include statistically significant reduction in multiple atherogenic lipids and lipoproteins including LDL cholesterol, triglycerides, apolipoprotein B, apolipoprotein CIII and lipoprotein (a)*

First study to demonstrate a strong association between liver fat reduction by a pharmaceutical agent and improvement and resolution of NASH on liver biopsy

CONSHOHOCKEN, Pa., Nov. 11, 2019 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL) announced today the online publication in *The Lancet* of the resmetirom (MGL-3196) Phase 2 multi-center, randomized, double-blind, placebo-controlled clinical trial in patients with non-alcoholic steatohepatitis (NASH). See The Lancet publication - Madrigal Phase 2 NASH Study

The 36-week Phase 2 NASH study in 125 patients, and a 36-week extension study in 31 of those patients (described below), are highly supportive of MAESTRO-NASH, an ongoing international Phase 3 registrational clinical trial of resmetirom in patients with NASH and liver fibrosis, that is powered at >90% to achieve the primary endpoint of NASH resolution and key secondary endpoints of LDL cholesterol lowering and reduction in liver fibrosis. Additional information about Madrigal's Phase 3 study in patients with NASH can be obtained at Madrigal Pharmaceuticals Initiates Phase 3 MAESTRO-NASH Study and www.clinicaltrials.gov [NCT03900429]

Stephen Harrison, M.D., Principal Investigator of the resmetirom Phase 2 study, and Medical Director for Pinnacle Clinical Research, San Antonio, Texas, and Visiting Professor of Hepatology, Oxford University, and primary author of *The Lancet* paper stated, "In this trial, resmetirom as compared with placebo demonstrated statistically significant and meaningful reduction of hepatic fat at 12 weeks, the primary endpoint of the study, and this reduction was sustained over 36 weeks. Statistically significant reduction and resolution of NASH on liver biopsy, lowering and normalizing elevated liver enzymes, and reductions of markers of fibrosis were also observed. A strong association was observed between reduction in hepatic fat by resmetirom and improvement in the inflammatory components of NASH, ballooning and inflammation."

"MRI-PDFF is a noninvasive imaging biomarker that provides an accurate and reproducible assessment of hepatic fat content. It has been shown to correlate with the liver biopsy steatosis score and can be used to assess the change in hepatic fat content over time. This study shows the potential value of MRI-PDFF for assessing early treatment response in patients with NASH," stated Mustafa R. Bashir M.D., Associate Professor of Radiology and Associate Professor in the Department of Medicine Duke University, Gastroenterology, Director MRI, Director, Center for Advanced Magnetic Resonance Imaging, Bashir Lab for Liver Imaging Research, and a coauthor of *The Lancet* paper.

"Liver biopsy is an invasive technique with associated morbidity. A goal of the NASH field is to find noninvasive tests that predict outcome of NASH treatments to avoid use of serial liver biopsies. In addition to improving the understanding of the pharmacology and safety of resmetirom in patients with NASH, this study provides results of serial non-invasive imaging of liver fat content, serial biomarkers of liver injury and fibrosis, and serial liver biopsies at baseline and after 36 weeks of treatment, providing the potential to demonstrate associations between changes in non-invasive measures and liver histology," stated Rebecca Taub, M.D., Chief Medical Officer and President of Research & Development at Madrigal.

Based in part on the results of this study, a multi-center, double-blind, randomized, placebo-controlled Phase 3 registration study, MAESTRO-NASH, is currently enrolling patients with biopsy-proven NASH (fibrosis stage 2 or 3), randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo.

Summary of key results featured in *The Lancet* and the 36-week extension study presented today by Dr. Stephen Harrison as an oral presentation at AASLD

The Phase 2 clinical trial was designed to determine the effect of resmetirom compared to placebo on hepatic fat at week 12 (the

primary endpoint) and week 36 in patients with liver biopsy confirmed NASH and stage 1-3 fibrosis. Steatosis was assessed by MRI-PDFF, a sensitive measure of hepatic fat. Secondary objectives were to assess safety and tolerability and to assess the impact of resmetirom on liver histology, serum lipids, liver enzymes and biomarkers of fibrosis after 36 weeks of treatment. 348 patients were screened and 84 were randomized to resmetirom and 41 to placebo at 18 sites in the US. Resmetirom-treated patients (n=78) demonstrated a relative reduction (%) of hepatic fat compared with placebo (n=38) at week 12 (–32.9% resmetirom vs –10.4% placebo; least squares mean difference –22.5%, 95% CI –32.9 to –12.2; p<0·0001) and week 36 (–37.3% resmetirom [n=74] vs –8.5 placebo [n=34]; –28.8%, –42.0 to –15.7; p<0·0001). NASH resolution without worsening of fibrosis occurred in 24.7% of resmetirom treated as compared with 6.5% of placebo treated patients (p=0.024) and in resmetirom treated patients who had at least 30% reduction in liver fat at week 12, NASH resolution at 36 weeks occurred in 37% (p=0.0026).

A 36-week extension study was conducted in patients completing the 36-week main Phase 2 study who had at least some remaining elevation of liver enzymes. The treatment code was unknown at the time of entry of 31 patients into the 36-week non-invasive extension study in which all patients received active treatment with 80 or 100 mg of resmetirom. Twenty-nine patients completed all 36 weeks. Endpoints of the extension study were non-invasive. Statistically significant reductions were observed in hepatic fat (64% at the 100 mg dose), atherogenic lipids, fibrosis markers, serial fibroscan liver stiffness, and liver enzymes, suggesting that non-invasive biomarkers and imaging indicative of improvement in NASH with fibrosis could ultimately be used to monitor response to treatment.

Safety in the Phase 2 NASH clinical trial and overall resmetirom development program
Resmetirom was well tolerated and appeared safe in more than 400 treated patients and healthy volunteers. There was a low incidence of severe and serious adverse events in the NASH Phase 2 clinical trial, none related to resmetirom. There was no imbalance in severe or moderate AEs with resmetirom treatment compared to placebo. There was an increase in the incidence of mild transient gastrointestinal side effects including loose stools and mild nausea, typically a single instance at the initiation of dosing; these were not observed in the NASH Phase 2 extension study. More than 50 healthy volunteers have received 1-2 weeks of 100 mg doses of resmetirom without increase in incidence of diarrhea or nausea (<2%).

Safety data in more than 150 patients treated at the top dose being used in Phase 3, 100 mg, for up to 1.5 years demonstrate that there is no effect of resmetirom on thyroid axis hormones, and no symptoms, clinical signs or incidence of either hyperthyroidism or hypothyroidism.

About NASH
Non-alcoholic Steatohepatitis (NASH) is a common liver disease in the United States and worldwide, unrelated to alcohol use, that is characterized by a build-up of fat in the liver, inflammation, damage (ballooning) of hepatocytes and increasing fibrosis. Although people with NASH may feel well and often do not know they have the disease, NASH can lead to permanent damage, including cirrhosis and impaired liver function in a high percentage of patients.

Patients with NASH are at heightened cardiovascular risk. Patients across the spectrum of non-alcoholic fatty liver disease (NAFLD) die more frequently from cardiovascular events than from their liver disease. Multiple factors may contribute to this risk, including elevated levels of LDL-C and excess liver fat. A significant segment of this large group of patients may also suffer from diabetes and metabolic syndrome, and have lipid levels that are above target despite treatment with established therapies. These patients may benefit from therapy to lower their lipid levels, including excess liver fat.

About Resmetirom (MGL-3196)
Among its many functions in the human body, thyroid hormone, through activation of its beta receptor, plays a central role in controlling lipid metabolism, impacting a range of health parameters from levels of serum cholesterol and triglycerides to the pathological buildup of fat in the liver. Attempts to exploit this pathway for therapeutic purposes in cardio-metabolic and liver diseases have been hampered by the lack of selectivity of older compounds for the thyroid hormone receptor (THR)-β, chemically-related toxicities and undesirable distribution in the body.

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. Madrigal believes that resmetirom is the first orally administered, small-molecule, liver-directed, truly β-selective THR agonist.

Based in part on the positive Phase 2 clinical study results in patients with NASH [Madrigal Pharmaceuticals 36-week Phase 2 NASH Results], Madrigal initiated MAESTRO-NASH, a Phase 3 multinational, double-blind, randomized, placebo-controlled study of resmetirom in patients with non-alcoholic steatohepatitis (NASH) and fibrosis to resolve NASH and reduce progression to cirrhosis and/or hepatic decompensation [Madrigal Pharmaceuticals Initiates Phase 3 MAESTRO-NASH Study and www.clinicaltrials.gov [NCT03900429]].

Additionally, in both the NASH Phase 2 study, and a second positive Phase 2 clinical study in patients with heterozygous familial hypercholesterolemia [Madrigal Pharmaceuticals Phase 2 HeFH Results], significant reductions in multiple atherogenic lipids were observed. Madrigal is planning a non-invasive Phase 3 study in biopsy proven NASH patients and patients with presumed NASH to further assess safety as well as effects on LDL-cholesterol, other atherogenic lipids, MRI-PDFF, liver enzymes, biomarkers of fibrosis and fibroscans to better characterize potential clinical benefits of resmetirom on cardiovascular and liver related endpoints using these noninvasive measures.

The Phase 3 MAESTRO-NASH trial is expected to enroll 900 patients with biopsy-proven NASH (fibrosis stage 2 or 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, and with no worsening of fibrosis. Two key secondary endpoints will be fibrosis improvement of at least one stage, with no worsening of NASH, and lowering of LDL-cholesterol.

These and other data, including safety parameters, would form the basis of a subpart H submission to FDA for accelerated approval. The original 900 patients continue on therapy; up to another 1,100 patients are to be added using the same randomization plan and the study is continued for up to 54 months to accrue and measure clinical events, most relevantly progression to cirrhosis.

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 cardio-metabolic and fatty liver 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. 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. Such statements contain words such as "expect," "could," "may," "might," "will," "be, "predict," "project," "intend," "believe," "estimate," "continue," "future," or the negative thereof or comparable terminology and the use of future dates. Forward-looking statements reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events. Such forward-looking statements include but are not limited to statements or references concerning: our primary and secondary study endpoints and their achievement potential; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, fibrosis treatment, cardiovascular effects and lipid treatment; the achievement of enrollment objectives concerning patient number and/or timing; and potential NASH or NAFLD patient risk profile benefits. Although management believes that the expectations reflected in such statements are reasonable, they 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, the company's clinical development of resmetirom, enrollment uncertainties, outcomes or trends from competitive studies, the risks of achieving potential benefits in a study that includes substantially more patients than our prior study, 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 filings 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 Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2018, as well as in our other filings with the SEC.

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