Madrigal Pharmaceuticals Announces First Patient Dosed in MAESTRO-NAFLD-1, a Second Phase 3 Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of Resmetirom (MGL-3196) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Presumed NASH (NASH/NAFLD (non-alcoholic fatty liver disease))

-- MAESTRO-NAFLD-1 is the second resmetirom Phase 3 clinical trial in patients with NASH and presumed NASH and follows MAESTRO-NASH, a Phase 3 multi-center, double-blind, randomized, placebo-controlled study in patients with non-alcoholic steatohepatitis (NASH) and fibrosis, that was initiated in March 2019 --

-- The primary goals of MAESTRO-NAFLD-1 are to:

- *collect additional safety data in resmetirom treated patients with biopsy-confirmed or presumed NASH;*
- *further support the broad potential therapeutic benefits of resmetirom on liver and cardiovascular endpoints that were demonstrated in Phase 2 clinical studies; and,*
- *assess noninvasive lipid, fibrosis and imaging biomarkers to monitor clinical improvement in NASH patients.*

CONSHOHOCKEN, Pa., December 18, 2019 -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL) announced today that it has dosed the first patient in its second Phase 3 clinical trial, MAESTRO-NAFLD-1 with its first-in-class, once daily, oral thyroid hormone receptor-beta selective agonist, resmetirom (MGL-3196). Madrigal initiated its first Phase 3 clinical program, MAESTRO-NASH, in NASH patients with advanced liver fibrosis (stages F2 and F3) in March 2019. The primary endpoint for that trial, after one year of treatment, is resolution of NASH; key secondary endpoints include LDL-cholesterol lowering and reduction in liver fibrosis. Additionally, clinical benefit in reducing progression to more advanced liver disease, including cirrhosis, is a long-term goal of MAESTRO-NASH. [clinicaltrials.gov/NCT03900429]

MAESTRO-NAFLD-1 is a 52-week Phase 3 double-blind, placebo-controlled clinical study in 700 patients designed to evaluate the safety and biomarkers in resmetirom as compared with placebo treated patients in a broad segment of patients with NASH and to support registration for the treatment of NASH. The primary endpoint of the study is safety. MAESTRO-NAFLD-1 is also expected to provide additional data regarding clinically relevant efficacy endpoints including lowering of atherogenic lipids and lipoproteins. Key secondary endpoints include LDL-cholesterol, apolipoprotein B and triglyceride (TG) lowering; reduction of liver fat as determined by magnetic resonance imaging, proton density fat fraction (MRI-PDFF); and reduction of PRO-C3, a NASH fibrosis biomarker. Reduction of liver enzymes, fibroscan scores, and other NASH and lipid biomarkers will be assessed.

MAESTRO-NAFLD-1 is expected to enroll 700 patients with biopsy-proven or presumed NASH, many of whom screened for MAESTRO-NASH, all with documented metabolic risk factors and fatty liver disease on MRI-PDFF and fibroscan, but who screen failed MAESTRO-NASH because fibroscan or biopsy prerequisites were not met. Unlike MAESTRO- NASH, only non-invasive serial evaluations are included. Patients will be randomized 1:1:1 to receive a single oral daily dose of placebo, resmetirom 80 mg or resmetirom 100 mg. Up to 100 patients will be randomized to an open label arm and receive resmetirom 100 mg. Treatment duration in MAESTRO-NAFLD-1 is 52 weeks. [clinicaltrials.gov/NCT04197479]

"The initiation of this second Phase 3 NASH safety and biomarker study is an important next step in establishing the broad therapeutic benefits of resmetirom and its unique potential among NASH drugs in development to decrease cardiovascular risk through the reduction of hepatic fat and multiple atherogenic lipids including LDL-cholesterol," stated Dr. Rebecca Taub, M.D., Chief Medical Officer and President of R & D of Madrigal. "It is well-established that NAFLD/NASH patients are at significantly increased risk of cardiovascular morbidity and mortality. Based on treatment effects on NASH and the cardiovascular risk reducing profile of resmetirom to date, we believe results from our Phase 3 program have the potential to support a highly favorable therapeutic benefits for resmetirom in patients with biopsy confirmed advanced NASH and, ultimately, in patients diagnosed with NASH based on noninvasive tests."

Dr. Stephen Harrison, M.D., Principal Investigator of the study, and Medical Director for Pinnacle Clinical Research, San Antonio, Texas, and Visiting Professor of Hepatology, Oxford University, commented, "The NASH community is in great need of establishing clinically relevant, noninvasive biomarkers capable of providing accurate and reproducible assessments of hepatic fat content and the formation of fibrotic tissue in the liver. I believe results from MAESTRO-NAFLD-1, along with results from MAESTRO-NASH, have the potential to add important insights about the predictive value of noninvasive tests."

"Because the leading cause of death for patients with NASH and NAFLD is cardiovascular disease (CVD), I believe our most effective approach to the treatment of these patients is to aggressively assess and manage their CVD risk factors. Resemetirom has the potential to offer patients and the physicians who treat them a potentially safe and effective way to reduce the broad array of atherogenic lipids and lipoproteins in addition to reducing fatty liver, a potentially independent cardiovascular risk factor," stated Seth Baum, MD, FACC, FAHA, FASPC Immediate Past President American Society for Preventive Cardiology, Excel Medical Clinical Trials, LLC Founder, FNLA (Fellow National Lipid Association), Chief Medical Officer Clinical Affiliate Professor of Biomedical Science Charles E. Schmidt College of Medicine. [see: Seth Baum AASLD 2019 Presentation]

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 [see: Madrigal Pharmaceuticals Announces Lancet Publication of Positive Phase 2 Results for resmetirom], in March 2019, 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 clinicaltrials.gov/NCT03900429]].

About the Phase 3 Registration Program for the Treatment of NASH
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 (NASH Activity Score), 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.

In 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.

A second 52-week Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom, MAESTRO-NAFLD-1, in 700 patients with non-alcoholic fatty liver disease (NAFLD), presumed NASH, randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo was initiated in December 2019. MAESTRO-NAFLD-1 also includes a 100 mg resmetirom open label arm in up to 100 patients. Unlike MAESTRO-NASH, MAESTRO-NAFLD-1 is a non-biopsy study. NASH or presumed NASH is documented using non-invasive techniques or historical liver biopsy. 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 using noninvasive measures. These key secondary endpoints include LDL-cholesterol, apolipoprotein B and triglyceride (TG) lowering; reduction of liver fat as determined by magnetic resonance imaging, proton density fat fraction (MRI-PDFF); and reduction of PRO-C3, a NASH fibrosis biomarker. [clinicaltrials.gov/NCT04197479] Additional secondary and exploratory endpoints will be assessed including reduction in liver enzymes, fibroscan scores and other fibrosis and inflammatory biomarkers.

These and other data, including safety parameters, form the basis for potential subpart H submission to FDA for accelerated approval for the treatment of NASH. The original 900 patients in the MAESTRO-NASH study will continue on therapy after the initial 52-week treatment period; up to another 1,100 patients are to be added using the same randomization plan and the study is expected to continue 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.

Investor Contact:
Marc Schneebaum, Madrigal Pharmaceuticals, Inc. IR@madrigalpharma.com

Media Contact:
Mike Beyer, Sam Brown Inc. mikebeyer@sambrown.com 312 961 2502