# Madrigal Pharmaceuticals Initiates Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis a

March 28, 2019

*-- Investigator meeting held March 21/22, 2019 --*

*-- In Phase 2 study resmetirom was statistically significantly superior to placebo in resolving NASH on biopsy, appeared safe and was well-tolerated --*

CONSHOHOCKEN, Pa., March 28, 2019 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL) announced today that it has initiated its Phase 3 trial in NASH with its once daily, oral thyroid hormone receptor beta selective agonist, MGL-3196 (resmetirom). This double-blind, placebo-controlled study will be conducted at more than 150 sites in the United States and the rest of the world. Patients with liver biopsy confirmed NASH with stage 2 or 3 fibrosis will be randomized 1:1:1 to receive a single oral daily dose of placebo, resmetirom 80 mg or resmetirom 100 mg. A second liver biopsy at week 52 in the first 900 patients will be the basis of filing for subpart H-accelerated approval; the primary endpoint will be the percent of patients treated with either dose of resmetirom as compared with placebo who achieve NASH resolution on the week 52 liver biopsy, defined as the absence of hepatocyte ballooning (score=0), and minimal lobular inflammation (score 0-1), associated with at least a 2 point reduction in NAS, and no worsening of fibrosis stage.

Two key secondary endpoints are reduction in LDL-cholesterol and a 1-point or more improvement in fibrosis stage on the week 52 biopsy with no worsening of NASH. Patients will continue in the study for a total of 54 months, and will be evaluated for a composite clinical outcome including cirrhosis on liver biopsy, or a liver related event such a hepatic decompensation. The total anticipated enrollment is approximately 2,000 patients, and will include up to 15% high risk F1 fibrosis stage NASH patients whose efficacy responses will be evaluated as exploratory endpoints.

“We are pleased to announce the start of the Phase 3 NASH study,” said Dr. Paul Friedman, Chief Executive Officer of Madrigal. “In the 36 Week Phase 2 study, NASH resolution was highly correlated with the magnitude of liver fat reduction on MRI-PDFF. In Phase 2, 25% of all resmetirom treated patients, and 37% of treated patients who were on adequate doses of resmetirom, achieved the Phase 3 NASH resolution endpoint (NASH resolution with at least a 2-point reduction in NAS and no fibrosis stage worsening); both results demonstrated statistically significant differences relative to placebo. The resmetirom doses used in Phase 2, in which nearly half of the patients took 60 mg, were lower than the optimal doses of 80 and 100 mg that will be used in Phase 3. Coupling these Phase 2 results with the higher doses in Phase 3 and with longer treatment duration, we believe there is great potential to achieve statistically significant NASH resolution and liver fibrosis reduction relative to placebo at both the 80 and 100 mg doses.”

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, “To date, the results with resmetirom are highly encouraging. In Phase 2, this once a day, oral compound was well tolerated and showed statistically significant superiority to placebo in the 12 week primary endpoint of hepatic fat reduction, as measured by MRI-PDFF, in resolution of NASH on biopsy at 36 weeks, and in lowering elevated liver enzymes, fibrosis markers and atherogenic lipids.” Dr. Harrison continued, “The added requirement of at least a 2 point reduction in NAS to the NASH resolution endpoint, which was used in Phase 2 and will be used in the Phase 3 study, provides the potential to predict ultimate clinical benefit with more certainty.”

Dr. Rebecca Taub, M.D., Chief Medical Officer and Executive Vice President of Madrigal, Research & Development, added, “In our Phase 2 study, half of the resmetirom treated patients with NASH resolution also completely resolved their fibrosis, demonstrating the critical importance of treating the underlying NASH in order to achieve fibrosis benefit. The recent publication by Brunt et al [1], reviewing NASH liver biopsy data from two large Phase 2 studies conducted by the NASH CRN in which several therapeutics and placebo were tested, found that resolution of NASH, a 2-point or more improvement in NAS or a decrease in steatosis, were all strongly predictive of fibrosis improvement. Based on these data and our Phase 2 study results, we believe there is great potential for resmetirom to achieve a key secondary endpoint in our Phase 3 study: at least a 1-point improvement in fibrosis without worsening of NASH.”

Dr. Taub continued, “We are also excited to be working with Summit Clinical Research, LLC and PRA Health Sciences to rapidly enroll our Phase 3 study with a targeted timeline of 15-18 months for enrollment of the first 900 patients. ”

“In addition,” added Dr. Taub, “we believe resmetirom has a unique potential among NASH drugs in development to decrease cardiovascular risk, through reduction of hepatic fat and reduction in the levels of multiple atherogenic lipids including LDL-cholesterol at a magnitude that is consistent with approval for a dyslipidemia indication. As NAFLD/NASH patients are at significantly increased risk of cardiovascular morbidity and mortality, and based on the cardiovascular risk reducing profile of resmetirom, we project a potential for resmetirom to demonstrate a highly favorable benefit to risk profile in patients with advanced

NASH in the Phase 3 NASH study and, ultimately, in early NASH/NAFLD patients treated for LDL-cholesterol and atherogenic lipid lowering."

[1]Hepatology. 2018 Dec 14. doi: 10.1002/hep.30418. [Epub ahead of print]

**Clinical Program Summaries for MGL-3196**

*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.

In October 2016, the first patient was treated in the now completed Phase 2 trial of resmetirom for the treatment of NASH. The randomized, double-blind, placebo-controlled, multi-center Phase 2 study enrolled 125 patients 18 years of age and older with liver biopsy-confirmed NASH and included approximately 25 clinical sites in the United States. Patients were randomized to receive either a single daily oral dose of resmetirom or placebo in a 2:1 ratio.

The primary endpoint of the study was the reduction of liver fat at 12 weeks compared with baseline (relative change), assessed by MRI-PDFF. Key secondary endpoints at 36 weeks included: reduction in liver fat compared with baseline (relative change), also assessed by MRI-PDFF; a two-point reduction in NAS on biopsy; resolution of NASH on biopsy associated with at least a 2-point reduction in NAS; and, safety and tolerability based on adverse events and changes in laboratory values.

The primary endpoint of the study at 12 weeks was achieved. Liver fat was reduced from baseline by 36.3% in all resmetirom treated patients (78) and 42.0% in a pre-specified group of high exposure resmetirom treated patients (44/78), as compared with 9.6% median reduction in liver fat in 38 placebo treated patients. These results were statistically significant ($p<0.0001$) for both resmetirom treatment groups. Further, 75% of the high-exposure resmetirom treated patients showed liver fat reductions of ≥30%.

At 36 weeks, multiple key secondary endpoints were achieved in resmetirom treated patients, including a sustained highly significant ($p<0.001$) reduction in liver fat compared to placebo as measured by MRI-PDFF; mean relative fat reduction for resmetirom was 37% versus 8.9% for placebo. Resmetirom treatment was associated with a greater percentage of subjects with a 2-point improvement in NAS (56% of 73 patients vs 32% of 34 placebo subjects, $p=0.02$). NASH resolution (NR) with at least a 2 point reduction in NAS was seen in 27% of resmetirom treated compared with 6% of placebo subjects, $p=0.02$. Resmetirom treated patients with ≥ 30% fat reduction on Week 12 MRI-PDFF demonstrated a higher percentage of 2-point improvement in NAS (70%, $p=0.001$) and NR (39%, $p=0.001$) compared with placebo, demonstrating a strong relationship between early reduction in liver fat as demonstrated by week 12 MRI-PDFF and NASH improvement on liver biopsy at Week 36. In patients with NASH Resolution, 35% of the resmetirom treated patients and no placebo patients had more advanced NASH (baseline NAS ≥5).

At Week 36, resmetirom treated patients showed sustained reduction of fibrosis biomarkers. In resmetirom treated patients with NASH resolution, fibrosis also resolved in 50% of patients and was decreased statistically significantly relative to all placebo patients.

There were statistically significant reductions in liver enzymes in resmetirom treated patients compared to placebo treated patients; reductions of greater magnitude were achieved with longer duration of resmetirom treatment. Statistically significantly more resmetirom treated patients than placebo treated patients had normalization of ALT (alanine transaminase).

Similar to week 12, at week 36 there were sustained, statistically significant reductions in low-density lipoprotein cholesterol (LDL-C), triglycerides, ApoB and lipoprotein(a).

Resmetirom was well tolerated in this trial with mostly mild and a few moderate AEs which were balanced between drug treated and placebo patients. There was an increase in incidence of softer stools in resmetirom-treated patients, often a single episode, only at the start of treatment.

A non-invasive 36 week extension study evaluating 80mg and 100mg resmetirom using MRI-PDFF and biomarker measurements was also successfully completed.

*Dyslipidemia*

Patients with NASH, and its more prevalent precursor, Non-Alcoholic Fatty Liver Disease (NAFLD), are at heightened cardiovascular risk. In fact, patients suffering from these conditions 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. Patients with NASH and NAFLD, however, may not undergo a biopsy to confirm a NASH diagnosis until they reach the more advanced stages of fibrosis (F2 – F4). 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.

Madrigal's studies to date in patients with NASH and patients with heterozygous familial hypercholesterolemia (HeFH), have demonstrated the pleiotropic activity of resmetirom which includes reducing levels of an array of atherogenic lipids; LDL-C, ApoB, triglycerides, ApoCIII, and Lp(a), liver fat and also hs-CRP, all of which are correlated with increased cardiovascular risk. As a result, Madrigal intends to extend its development of resmetirom to address the unmet medical needs of patients across the entire

NASH and NAFLD spectrum. A Phase 3 study is under design to treat the prevalent mixed dyslipidemias, while improving the fatty liver phenotype, in this population.

*HeFH*
Resmetirom has also been studied in heterozygous familial hypercholesterolemia (HeFH). HeFH and a much rarer form called homozygous familial hypercholesterolemia (HoFH) are severe genetic dyslipidemias typically caused by inactivating mutations in the LDL receptor. Both forms of FH lead to early onset cardiovascular disease. The ability of resmetirom to lower LDL-C on top of standard of care was determined in a Phase 2 study in HeFH patients. Resmetirom treated patients (placebo corrected) achieved highly significant ($p< 0.0001$) LDL-C lowering of 18.8% in all treated patients, and 21% in those on an optimal dose of resmetirom. LDL-C lowering was 28.5% in resmetirom treated compared to placebo in a prespecified group of patients who did not tolerate high intensity statin doses. Highly significant reductions ($p<0.0001$) relative to placebo were also observed with ApoB, triglycerides, apolipoprotein CIII and Lp(a). Resmetirom was well tolerated with primarily mild and some moderate AEs, the numbers of which were balanced between placebo and drug-treatment groups.

**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.

**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," "will," "be," "project," "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.*

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