Madrigal Pharmaceuticals Announces Presentation of Positive Clinical Data of Resmetirom from Open-Label Portion of Ongoing Phase 3 Clinical Trial MAESTRO-NAFLD-1 at The International Liver Congress™ 2021

June 25, 2021

- *Use of non-invasive measurements demonstrated that resmetirom:*
  - *was safe and well-tolerated at 100 mg per day in non-cirrhotic NASH patients treated for 52 weeks;*
  - *provided rapid and sustained reductions, measured by imaging and/or blood levels, of hepatic fat, fibrosis, liver cell injury and inflammation in non-cirrhotic NASH patients treated for 52 weeks;*
  - *reduced atherogenic lipids in non-cirrhotic NASH patients treated for 52 weeks;*
  - *was safe and well-tolerated, reduced hepatic fat, liver enzymes, fibrosis markers and atherogenic lipids in well-compensated cirrhotic NASH patients treated for up to 24 weeks.*
- *Study highlights the potential use of non-invasive assessments to diagnose NASH and monitor individual patient response to resmetirom treatment.*

CONSHOHOCKEN, Pa., June 25, 2021 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), today announced the presentation of positive clinical data from the open-label portion of its ongoing Phase 3 MAESTRO-NAFLD-1 study of resmetirom at the European Association for the Study of the Liver Annual Meeting, The International Liver Congress™ 2021, being held virtually, June 23-26, 2021. The data continue to position resmetirom as a promising treatment option for nonalcoholic steatohepatitis (NASH) patients.

Resmetirom, a once daily oral, liver-directed, selective thyroid hormone receptor (THR) β agonist, is currently in Phase 3 development for the treatment of patients with NASH. The Phase 3 clinical program comprises (i) MAESTRO NAFLD-1 (non-alcoholic fatty liver disease) a 52-week ~1200 patient safety study in presumed NASH subjects diagnosed non-invasively and (ii) MAESTRO-NASH a 52-week serial liver biopsy study in more than 900 NASH subjects with biopsy-confirmed significant fibrosis.

“Based on Phase 2 results, together with the open-label data from the ongoing MAESTRO-NAFLD-1 Phase 3 clinical trial, we remain confident that resmetirom has the potential to become the best-in-class and first-to-market treatment option for patients with NASH, especially those with significant liver fibrosis,” said Paul Friedman, M.D., Chief Executive Officer of Madrigal.

“In the ongoing MAESTRO-NAFLD-1 Phase 3 clinical study that we characterize as a ‘real-life’ study of NASH, a series of non-invasive markers and imaging are used to diagnose and monitor NASH,” said Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal. “Improvements in non-invasive measurement of hepatic fat, fibrosis, liver injury and inflammatory biomarkers, as well as atherogenic lipids, including LDL, further support the potential of resmetirom to treat patients with NASH.”

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, “Importantly, the MAESTRO-NAFLD-1 study is providing us with a growing body of evidence that non-invasive tests may allow us to accurately diagnose NASH and help us find effective and much needed treatments for NASH patients.”

ILC 2021 Oral Plenary Presentation: GS-2563: Reduction in Fibrosis and Steatohepatitis Imaging and Biomarkers in a Phase 3 52 Week Resmetirom NASH Trial. Presenter: Stephen Harrison [click here to view oral presentation]

At the time of this presentation, in this Phase 3 open label arm of MAESTRO-NAFLD-1, 52 week data was available on 115 non-cirrhotic presumed NASH patients, including safety analyses, various blood chemistry measurements, magnetic resonance imaging proton density fat-fraction (MRI-PDFF), magnetic resonance elastography (MRE), and FibroScan (VCTE and CAP). All patients received 100 mg of resmetirom, once-a-day. The study demonstrated rapid and sustained reduction in hepatic fat (as assessed by MRI-PDFF and CAP) and fibrosis (as assessed by ELF, MRE and VCTE). Key imaging findings are summarized in the table below. Reductions were also observed in multiple liver enzymes, inflammatory biomarkers, LDL cholesterol, and other atherogenic lipids. Resmetirom was safe and well-tolerated with the only adverse event observed at more than 5% frequency being a transient increase in stool frequency in the first two weeks of therapy (~10% over historical placebo rates) and COVID infection (6.8%). As seen throughout the resmetirom clinical trial program, no central thyroid axis changes or adverse effects on vital signs were observed.

	WEEK 52
MRI-PDFF	
Relative %change	-53.4

p- value	<0.0001
FibroScan[1] CAP	
Change (db/M)	-45.2
p-value	<0.0001
FibroScan[1] VCTE (Baseline>=7.4)	
Change (kPa)	-2.8
p-value	0.0006
MRE (Baseline>=2.9)	
Change (kPa)	-0.43
p-value	0.01

[1]FibroScan: VCTE (vibration-controlled transient elastography), and CAP (controlled attenuation parameter). VCTE and MRE are measures of liver stiffness equated with liver fibrosis.

ILC 2021 Madrigal Hosted Symposium: Phase 3 development of resmetirom, a liver-directed thyroid hormone receptor (THR)-β agonist for the treatment of patients with NASH and significant liver fibrosis. Presenters: Vlad Ratziu, Jörn Schattenberg and Stephen Harrison [click here to view slides, click here to view webcast]

The symposium provides a review of the resmetirom MAESTRO studies including: insights on the utilization of non-invasive technologies to identify patients and monitor treatment; evidence of fibrosis stage reduction as assessed by ELF, MRE and FibroScan; and a comprehensive assessment of NASH non-cirrhotic and cirrhotic patients utilizing non-invasive measures.

Poster abstract number: PO-849: Treatment of a non-alcoholic steatohepatitis cirrhotic patients with resmetirom: baseline characteristics and effects on safety, biomarkers and imaging. Presenter: Stephen Harrison [click here to view poster]

In the 105 well-compensated NASH cirrhotic patients enrolled in MAESTRO-NAFLD-1, the data demonstrated that NASH cirrhotics have significantly higher MRE and lower MRI-PDFF measures than non-cirrhotic NASH patients. NASH cirrhotics with lower baseline PDFF values may represent a more advanced subtype of cirrhosis relative to those patients with higher baseline MRI-PDFF. Key findings include: Resmetirom appeared to be safe in well-compensated NASH cirrhotic patients; Resmetirom reduced MRI-PDFF, liver enzymes, some fibrosis markers and LDL cholesterol and other atherogenic lipids in NASH cirrhotic patients. Limitations of the study include early stage of the study and lack of a placebo control group.

About the Phase 3 Registration Program for the Treatment of NASH (Non-alcoholic steatohepatitis)

Analyses from the resmetirom Phase 2 NASH study demonstrate that the magnitude of liver fat reduction accurately predicts NASH resolution and liver fibrosis reduction and, specifically, that the resmetirom doses being used in Madrigal's Phase 3 MAESTRO-NASH trial could achieve the level of fat reduction predictive of NASH resolution and fibrosis reduction [Madrigal COVID and ABSTRACT Press Release_20200414].

The Phase 3 MAESTRO-NASH trial is initially 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 are liver fibrosis improvement of at least one stage, with no worsening of NASH, and lowering of LDL-cholesterol [ClinicalTrials.gov/NCT03900429].

A second 52-week Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom, MAESTRO-NAFLD-1, was initiated in December 2019 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. MAESTRO-NAFLD-1 also includes a 100 mg resmetirom open label arm. The trial was expanded to include more than 1,200 patients, in order to significantly enhance resmetirom's safety database and provide further opportunity to study selected patient subgroups. Unlike MAESTRO- NASH, MAESTRO-NAFLD-1 is a non-biopsy study and represents a "real-life" NASH study. NASH or presumed NASH is documented using historical liver biopsy or non-invasive techniques including FibroScan and MRI-PDFF. 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; 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 a 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 that is in currently in two Phase 3 clinical studies, MAESTRO-NASH and MAESTRO- NAFLD-1, designed to demonstrate multiple benefits across a broad spectrum of NASH (non-alcoholic steatohepatitis) and NAFLD (non-alcoholic fatty liver disease) 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; research and development activities; 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; 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; the predictive power of liver fat reduction measured by non-invasive tests on NASH resolution with fibrosis reduction or improvement; 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 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," "plans," "potential," "predicts," "predictive," "projects," "seeks," "should," "will," "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 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 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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