Madrigal Pharmaceuticals Presents Phase 3 MAESTRO-NASH Data During the Opening General Session of the EASL Congress™

June 22, 2023

- *First scientific presentation of detailed MAESTRO-NASH results confirms achievement of primary endpoints across multiple patient subgroups*
- *Noninvasive imaging and biomarker data support findings on liver biopsy and demonstrate broad treatment response to resmetirom*
- *Further analyses of results reinforce resmetirom safety and tolerability profile*
- *Company to host an investor event and webcast on Saturday, June 24 at 6:30 PM CEST / 12:30 PM ET*

CONSHOHOCKEN, Pa., June 22, 2023 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today presents resmetirom Phase 3 MAESTRO-NASH data at the opening general session of the European Association for the Study of the Liver Congress (EASL 2023).

In December 2022, Madrigal announced that MAESTRO-NASH achieved both liver histological improvement endpoints that FDA proposed as reasonably likely to predict clinical benefit to support accelerated approval for the treatment NASH with liver fibrosis including: 1- NASH resolution (ballooning 0, inflammation 0,1 with ≥2 point improvement in NAFLD activity score (NAS) and no worsening of fibrosis) 2- ≥1-stage reduction in fibrosis with no worsening of NAS.

Primary Endpoint (mITT*)	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning 0, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	26%	<0.0001	30%	<0.0001	10%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	0.0002	26%	<0.0001	14%

** In the modified intent-to-treat (mITT) population, patients without a Week 52 biopsy are deemed nonresponders*

New MAESTRO-NASH data being presented at EASL 2023 demonstrate that resmetirom helped patients with NASH achieve significant improvements vs placebo in liver fat, liver stiffness, liver enzymes, liver volume, spleen volume, and multiple atherogenic lipids/lipoproteins.

Stephen Harrison, M.D., Chairman for both Pinnacle Clinical Research and Summit Clinical Research, San Antonio, Texas, Visiting Professor of Hepatology, Oxford University, and lead Principal Investigator of the MAESTRO studies, commented, “The selection of the MAESTRO-NASH primary results as the first abstract at this year’s EASL Congress reflects the hepatology community’s strong interest in resmetirom as the potential first approved medication for the treatment of NASH with fibrosis. The new data being presented at EASL build on the impressive topline efficacy findings for both NASH and fibrosis reported last December, reinforce the safety and tolerability profile of resmetirom, and provide important insights for community clinicians seeking to understand the effects of resmetirom on the noninvasive tests that are used to manage patients in real world clinical practice.”

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, “It is encouraging to see such a broad and consistent treatment response with resmetirom across both histologic and noninvasive measures of efficacy, and across multiple patient subgroups. These data reinforce our conviction in the potential of resmetirom to become the first foundational treatment for patients with at-risk NASH.”

MAESTRO-NASH Results Being Presented at EASL 2023

In addition to achieving the two primary endpoints, resmetirom met multiple secondary biopsy endpoints in the MAESTRO-NASH trial, including:

- 2-stage fibrosis improvement in the mITT population (resmetirom 80 mg, 8%; resmetirom 100 mg, 10%; placebo, 3%, p<0.0001);
- NASH resolution AND ≥1-stage improvement in fibrosis in the mITT population (resmetirom 80 mg, 14%; resmetirom 100 mg, 16%; placebo, 5%, p<0.0001);
- NASH resolution with ≥2-point reduction in NAS and no worsening of fibrosis in patients with both a baseline and Week 52 biopsy (resmetirom 80 mg, 32%; resmetirom 100 mg, 39%; placebo, 11%, p<0.0001);
- ≥1-stage fibrosis improvement with no worsening of NAS in patients with both a baseline and Week 52 biopsy (resmetirom 80 mg, 30%; resmetirom 100 mg, 34%; placebo, 16%, p<0.0001); and
- NASH resolution OR ≥1-stage fibrosis improvement in patients with both a baseline and Week 52 biopsy (resmetirom 80

mg, 42%; resmetirom 100 mg, 50%; placebo, 19%, p<0.0001).

Improvements in fibrosis and NASH resolution were observed across all key subgroups, including:

- Baseline fibrosis stage (F2 or F3)
- NAS (<6, ≥6)
- type 2 diabetes status
- Age (<65, ≥65)
- Sex

No meaningful differences in fibrosis or NASH resolution responses were observed based on treatment with common concomitant medications (GLP-1 therapy, 14%; thyroxine, 13%; and statins, 50% of patients in each arm) or in patients with ≥5% weight loss.

Resmetirom-treated patients showed improvement in all NAS components and fibrosis, with significantly less worsening in fibrosis stage compared with placebo. In patients with F1B or F2 fibrosis at baseline:

- 31% improved, 51% had no change, and 18% worsened in the 80 mg group;
- 33% improved, 48% had no change, and 19% worsened in the resmetirom 100 mg group; and
- 15% improved, 51% had no change, and 34% worsened in the placebo group.

Patients treated with resmetirom achieved significant reductions relative to placebo in key noninvasive tests, including:

- Magnetic resonance imaging-proton density fat fraction (MRI-PDFF), with reductions at week 52 of -42% for resmetirom 80 mg and -51% for resmetirom 100 mg vs -10% for placebo;
- ALT, AST, and GGT in patients with ALT ≥30 IU at baseline; and
- Liver stiffness measured by FibroScan vibration-controlled transient elastography (VCTE), both in mean change from baseline and in responder analyses examining 25% improvement and 25% worsening of kPa.

Safety and tolerability analyses of the MAESTRO-NASH data demonstrate that study discontinuations in the 100 mg arm were increased relative to placebo only during the first few weeks of treatment and were similar in all treatment groups for the remaining period of the first 52 weeks. Most adverse event-related discontinuations in the resmetirom 100 mg arm were GI-related: diarrhea was reported in 34% of patients treated with resmetirom 100 mg and in 16% of patients on placebo. Episodes were mild or moderate, and median duration of diarrhea was approximately two weeks. There were no adjudicated cases of drug-induced liver injury in the MAESTRO-NASH trial.

Separate from the general session presentation, Madrigal is presenting a late-breaker poster at EASL 2023 featuring the first analysis of the MAESTRO-NASH biopsy results using artificial intelligence (AI). Second harmonic generation slide reading technology (HistoIndex) was employed to measure fibrosis change in 768 sets of paired biopsies from MAESTRO-NASH. The results showed highly statistically significant reduction in fibrosis in both resmetirom 80 and 100 mg groups relative to placebo. The authors concluded that AI-based measurements of fibrosis change using either a continuous or categorical scale demonstrated a clear improvement and less worsening in fibrosis in resmetirom-treated patients as compared with placebo after 52 weeks of treatment.

Investor Event and Webcast

Madrigal will host an investor event in Vienna with webcast on Saturday, June 24 at 6:30 PM CEST / 12:30 PM ET. Investors and analysts can click here to register for the live event in Vienna. To access the webcast of the call with slides please visit the Investors section of Madrigal's website or click here. An archived webcast will be available on the Madrigal website after the event.

About the Resmetirom Phase 3 Registration Program for the Treatment of NASH

Madrigal is currently conducting four Phase 3 clinical trials to demonstrate the safety and efficacy of resmetirom for the treatment of NASH: MAESTRO-NASH, MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, and MAESTRO-NASH-OUTCOMES.

MAESTRO-NASH is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study of resmetirom in patients with liver biopsy-confirmed NASH and was initiated in March 2019. The subpart H portion of the study enrolled more than 1,000 patients with biopsy-proven NASH (at least half with F3 (advanced) fibrosis, the remainder F2 or F1B (moderate fibrosis) with a few earlier F1 patients, randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second liver biopsy is performed. The dual primary surrogate endpoints on biopsy were NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score), and with no worsening of fibrosis OR a 1-point decrease in fibrosis with no worsening of NAS. Achievement of either primary endpoint was considered a successful trial outcome. A key secondary endpoint was lowering of LDL-C.

Patients enrolled in the MAESTRO-NASH study (approximately 1,750) continue on therapy after the initial 52-week treatment period 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, as well as all-cause mortality.

MAESTRO-NAFLD-1 was initiated in December 2019 and the 52-week multicenter, randomized, placebo-controlled Phase 3 study

of resmetirom in over 1,200 patients with NAFLD, presumed NASH, has completed the double-blind arms and an open-label 100 mg arm. An additional open-label active treatment arm in patients with early (well-compensated) NASH cirrhosis is ongoing. The primary endpoint was to evaluate the safety and tolerability of resmetirom. A separate 52 week Phase 3 clinical trial, an open-label extension study of MAESTRO-NAFLD-1 (MAESTRO-NAFLD-OLE), is ongoing.

Patients in the 52-week Phase 3 MAESTRO-NAFLD-1 study were randomized 1:1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, placebo in double-blind arms or resmetirom 100 mg in an open-label arm. MAESTRO-NAFLD-1 (unlike MAESTRO-NASH), did not include a liver biopsy and represents a "real-life" NASH study. Patients with 3 metabolic risk factors were documented with NASH or NAFLD by historical liver biopsy or noninvasive techniques. Using noninvasive measures, MAESTRO-NAFLD-1 was 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. The primary safety endpoint and several key secondary endpoints were met, including LDL-C, apolipoprotein B, and triglyceride lowering and reduction of liver fat as determined by MRI-PDFF. Additional secondary and exploratory endpoints were assessed including reduction in liver enzymes, FibroScan, and MRE scores, and other NASH biomarkers.

Data from the 52-week first 1,000 patient portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, Phase 2 and Phase 1 data, including safety parameters, will form the basis of the subpart H submission to FDA for accelerated approval of resmetirom for treatment of NASH.

In August 2022, Madrigal initiated MAESTRO-NASH-OUTCOMES, a randomized double-blind placebo-controlled study in approximately 700 patients with early NASH cirrhosis to allow for noninvasive monitoring of progression to liver decompensation events. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis.

About NASH

Nonalcoholic steatohepatitis (NASH) is a more advanced form of nonalcoholic fatty liver disease (NAFLD). In the United States, NAFLD is estimated to affect approximately 25% of the population, and approximately 25% of those will progress from NAFLD to NASH.

NASH is a leading cause of liver related mortality and an increasing burden on healthcare systems globally. Additionally, patients with NASH, especially those with more advanced metabolic risk factors (hypertension, concomitant type 2 diabetes), are at increased risk for adverse cardiovascular events and increased morbidity and mortality.

Once NASH progresses to significant liver fibrosis (stages F2 and F3) the risk of adverse liver outcomes increases dramatically. NASH is rapidly becoming the leading cause of liver transplantation in the U.S. There are currently no FDA-approved therapies available for the treatment of NASH.

About Madrigal Pharmaceuticals

Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), a liver disease with high unmet medical need. Madrigal's lead candidate, resmetirom, is a once daily, oral, thyroid hormone receptor (THR)-β selective agonist designed to target key underlying causes of NASH in the liver. For more information, visit www.madrigalpharma.com.

Forward Looking Statements

This communication includes "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, that are based on Madrigal's beliefs and assumptions and on information currently available to it, but are subject to factors beyond its control. Forward-looking statements reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events. Forward-looking statements include: all statements that are not historical facts; statements referenced by forward-looking statement identifiers, including the examples in the paragraph below; *resmetirom's potential to be a cost-effective specialty therapy for NASH patients with significant liver fibrosis; and statements or references concerning - the potential efficacy and safety of resmetirom for noncirrhotic NASH patients and cirrhotic NASH patients, possible or assumed future results of operations and expenses, business strategies and plans (including ex-US. Launch/partnering plans), research and development activities, and the timing and results associated with the future development of resmetirom, the timing and completion of projected future clinical milestone events, including enrollment, additional studies, top-line data and open label projections, plans, objectives, timing and support for making for making a Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) submission to FDA, projections or objectives for obtaining accelerated or full approval for resmetirom, Madrigal's primary and key secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections, the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis, optimal dosing levels for resmetirom and projections regarding potential NASH or NAFLD and potential patient benefits with resmetirom, including future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment, and/or biomarker effects with resmetirom.*

Forward-looking statements can be identified by terms such as "accelerate," "achieve," "allow," "anticipates," "appear," "be,"

"believes," "can," "confidence," "continue," "could," "demonstrates," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "inform," inform," "intended," "intends," "may," "might," "on track," "planned," "planning," "plans," "positions," "potential," "powers," "predicts," "predictive," "projects," "seeks," "should," "will," "will achieve," "will be," "would" or similar expressions and the negatives of those terms.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: the assumptions underlying the forward-looking statements; risks of obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections; risks associated with meeting the objectives of Madrigal's clinical studies, including, but not limited to Madrigal's ability to achieve enrollment objectives concerning patient numbers (including an adequate safety database), outcomes objectives and/or timing objectives for Madrigal's studies; any delays or failures in enrollment, and the occurrence of adverse safety events; risks related to the effects of resmetirom's mechanism of action; the achievement of enrollment objectives concerning patient number, safety database and/or timing for Madrigal's studies; enrollment and trial conclusion uncertainties, generally and in relation to COVID-19 related measures and individual precautionary measures that may be implemented or continued for an uncertain period of time; market demand for and acceptance of our products; the potential inability to raise sufficient capital to fund ongoing operations as currently planned or to obtain financings on terms similar to those arranged in the past; the ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that includes substantially more patients, and patients with different disease states, than prior studies; 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 with the U.S. Securities and Exchange Commission, or SEC, 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. Madrigal specifically discusses these risks and uncertainties in greater detail in the section appearing in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2022, filed with the SEC on February 23, 2023, as updated from time to time by Madrigal's other filings with the SEC.

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