Madrigal Pharmaceuticals Presents Late-Breaking Phase 3 NASH Data and Multiple Oral Abstracts at EASL's International Liver Congress™

June 25, 2022

- *Late-breaking data from the double-blind portion of the noninvasive Phase 3 MAESTRO NAFLD-1 study show resmetirom to be safe and well-tolerated and to reduce liver fat, fibrosis measures on FibroScan and MRE, and liver enzymes, as well as multiple atherogenic lipids*
- *In NASH patients with well-compensated cirrhosis, resmetirom:*
  - *was safe and well tolerated*
  - *reduced liver fat, LDL-C, and other atherogenic lipids*
  - *reduced noninvasive measures of liver fibrosis and liver enzymes*
  - *reduced liver volume by an average of ~20% and also reduced spleen volume*
- *Company to host an investor event and webcast to review the new resmetirom data at 8:00 PM BST / 3:00 PM ET*

CONSHOHOCKEN, Pa., June 25, 2022 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced data from multiple resmetirom abstracts presented at the European Association for the Study of the Liver's International Liver Congress (EASL 2022), including a late-breaking presentation of data from the Phase 3 MAESTRO-NAFLD-1 study and three additional oral presentations from the resmetirom clinical development program.

Paul Friedman, M.D., Chief Executive Officer of Madrigal, stated, "Today's late-breaking presentation at EASL is our first opportunity to share the double-blind results from the MAESTRO-NAFLD-1 safety study in a major scientific meeting. The data from this study will play an important role in the planned new drug application submission for resmetirom and help shape the noninvasive testing strategies that guide patient care in 'real world' clinical practice."

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, added, "In addition to the late-breaker, we are sharing new safety and efficacy data from patients with compensated NASH cirrhosis who participated in an open-label portion of MAESTRO NAFLD-1; these data informed our decision to initiate a new Phase 3 outcomes study in this more advanced NASH patient population."

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, "The MAESTRO-NAFLD-1 data we are presenting at EASL continue to reinforce confidence in the favorable safety profile of resmetirom and provide a deeper view of efficacy in patients with both early-to-moderate fibrosis and compensated NASH cirrhosis. The marked reductions in noninvasive measures of fibrosis, liver fat, and liver volume observed at 52 weeks in the open-label cirrhosis portion of the trial are particularly encouraging; this is a difficult-to-treat population at elevated risk of progressing to negative outcomes."

Late-Breaking Oral Presentation: "Primary data analyses of MAESTRO-NAFLD-1, a 52 week double-blind placebo-controlled phase 3 clinical trial of resmetirom in patients with NAFLD" (LB005)

Primary and key secondary endpoints from the double-blind, placebo-controlled, 969-patient MAESTRO-NAFLD-1 safety study were achieved; resmetirom was safe and well tolerated and provided significant reductions in liver fat (measured using magnetic resonance imaging proton density fraction (MRI-PDFF) and FibroScan controlled attenuation parameter (CAP)), LDL-C, and other atherogenic lipids vs placebo.

Patients treated with resmetirom also achieved significant reductions relative to placebo in ALT, AST, and GGT.

For those patients with sufficient baseline liver stiffness, as measured by FibroScan vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE), responder analyses showed statistically significant VCTE and MRE responses in the resmetirom groups compared to placebo.

Adverse event-related withdrawals were uncommon in the MAESTRO-NAFLD-1 study. The most common adverse event reported with greater frequency in the resmetirom groups vs placebo was generally mild diarrhea or increased stool frequency at the beginning of therapy.

Oral Presentation: "Biomarkers, imaging and safety in a well-compensated NASH cirrhotic cohort treated with resmetirom, a thyroid hormone receptor beta agonist, for 52 weeks" (OS121)

105 patients with well-compensated NASH cirrhosis were enrolled in the open-label arm of the MAESTRO-NAFLD-1 study. Baseline FibroScan VCTE (kPa 24.6) and MRE (5.7) scores were consistent with F4 fibrosis. Patients with lower MRI-PDFF (≤5%) at baseline had more progressed cirrhosis and greater spleen volumes. Similar to patients with non-cirrhotic NASH, liver volume was greatly elevated compared to normal at baseline.

Resmetirom reduced MRI-PDFF and LDL-C and other atherogenic lipids in patients with NASH cirrhosis and reduced FibroScan controlled attenuation parameter (CAP), VCTE, and MRE in a significant fraction of patients. The largest reduction in FibroScan VCTE (mean reduction of 9 kPa) occurred in the more advanced group (baseline PDFF ≤5%). Similar improvements were observed in MRE.

73% of patients, independent of baseline cirrhosis severity, had at least 15% reduction in liver volume at Week 52. Spleen volume was also reduced

and was strongly correlated with liver volume change and exposure to resmetirom.

Reductions in liver enzymes and atherogenic lipids were similar across patient subgroups.

Resmetirom was safe and well tolerated. As observed in patients with noncirrhotic NASH, mild GI adverse events were seen at the beginning of therapy. No differences in safety parameters between patients with cirrhosis compared to noncirrhotic NASH patients were noted. No thyroid axis changes or hyper- or hypothyroid symptoms were observed.

Additional Oral Presentations and Posters at the International Liver Congress

Abstracts from the resmetirom development program provide new insights to inform noninvasive testing strategies, improve artificial intelligence-based evaluation of treatment response, and better characterize the cost burden of NASH.

- Oral presentation: “Utility of FIB-4 thresholds to identify patients with at-risk F2-F3 NASH based on screening data from a 2,000 patient biopsy confirmed cohort of resmetirom Phase 3 clinical trial, MAESTRO-NASH” (OS101)
- Oral presentation: “Impact of resmetirom-mediated reductions in liver volume and steatosis compared with placebo on the quantification of fibrosis using second harmonic generation in a serial liver biopsy study” (OS030)
- Poster: “Retrospective AI-based measurement of NASH histology (AIM-NASH) analysis of biopsies from Phase 2 study of Resmetirom confirms significant treatment-induced changes in histologic features of nonalcoholic steatohepatitis” (SAT094)
- Poster: “A higher FIB-4 score is associated with higher healthcare costs and hospitalizations in patients with nonalcoholic steatohepatitis” (THU094)

Investor Event and Webcast

Madrigal will host an investor event in London with webcast on Saturday, June 25 at 8:00 PM BST / 3:00 PM ET. Investors and analysts can click here to register for the live event in London. 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 two Phase 3 clinical trials, MAESTRO-NASH and MAESTRO-NAFLD-1, to demonstrate the safety and efficacy of resmetirom for the treatment of NASH.

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 study targeted enrollment of 900 patients with biopsy-proven NASH (fibrosis stage 2 or 3, at least 450 fibrosis stage 3), randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second biopsy is performed. The dual primary surrogate endpoints on biopsy are 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 NASH. Either primary endpoint can be achieved for a successful trial outcome. A key secondary endpoint is lowering of LDL-C. The planned target enrollment was announced as completed on June 30, 2021.

The first 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. The study is expected to continue 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.

MAESTRO-NAFLD-1 was initiated in December 2019 and the 52-week multicenter, randomized, double-blind, 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 is to evaluate the safety and tolerability of resmetirom. An open-label extension study (MAESTRO-NAFLD-OLE) is ongoing.

Patients in the 52-week blinded phase of MAESTRO-NAFLD-1 were randomized 1:1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, placebo or a 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. These key secondary endpoints included 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 portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1 and other data, including safety parameters, will form the basis for a potential subpart H submission to FDA for accelerated approval of resmetirom for treatment of NASH.

In May 2022, Madrigal announced plans to expand the resmetirom development program by initiating MAESTRO-NASH Outcomes, a randomized double-blind placebo-controlled study in approximately 700 patients with early NASH cirrhosis to allow for non-invasive 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 broaden the label for resmetirom to include NASH patients with compensated cirrhosis.

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. Resmetirom is currently being evaluated in two Phase 3 clinical studies (MAESTRO-NASH and MAESTRO-NAFLD-1) designed to demonstrate multiple benefits in patients with NASH. 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, including the anticipated timing of disclosure, presentations of data from, or outcomes from our trials; research and development activities; market size and patient treatment estimates for NASH and NAFLD patients; 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; plans, objectives and timing 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 resemtirom for non-cirrhotic NASH patients and NASH patients with compensated cirrhosis; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment and/or biomarker effects with resmetirom; the potential efficacy and safety of resmetirom for non-cirrhotic NASH patients and cirrhotic NASH patients; ex-U.S. launch/partnering plans; the predictive power of liver fat reduction, as measured by non-invasive tests, on NASH resolution with fibrosis reduction or improvement; the predictive power of liver fat, liver volume changes or MAST scores for NASH and/or NAFLD patients; the effects of resmetirom' s mechanism of action; 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 or improvement with resmetirom using non-invasive tests, including the use of ELF, FibroScan, MRE and/or MRI-PDFF; the ability to develop clinical evidence demonstrating the utility of non-invasive tools and techniques to screen and diagnose NASH and/or NAFLD patients; 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 liver fibrosis; 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 "accelerate," "achieve," "allow," "anticipates," "be," "believes," "can," "continue," "could," "demonstrate," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "hopeful," "inform," "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. 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, and patients with different disease states, than our prior studies; limitations associated with early stage or 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 submissions filed or furnished 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, 2021, our Quarterly Report on form 10-Q for the Quarter ended March 31, 2022, and in our other filings with the SEC.

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