Madrigal Announces Additional Positive Results from the Pivotal Phase 3 MAESTRO-NASH Clinical Trial of Resmetirom for the Treatment of NASH with Liver Fibrosis

January 6, 2023

- *As previously reported, resmetirom demonstrated improvements in NASH and liver fibrosis on liver biopsies, the primary endpoints of the MAESTRO-NASH trial*
- *A supportive analysis using consensus reads of digitized biopsy images by the central pathologists replicated the positive primary endpoint results*
- *These data will be presented at the NASH-TAG Conference on Friday January 6th, 2023*

CONSHOHOCKEN, Pa., Jan. 06, 2023 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced additional results from the pivotal Phase 3 MAESTRO-NASH biopsy clinical trial of resmetirom, a liver-directed selective thyroid hormone receptor agonist. The new MAESTRO-NASH data are being presented at the NASH-TAG Conference, taking place from January 5-7, 2023 in Park City, Utah.

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. New data to be presented at NASH-TAG using a supportive analysis, a "consensus read" by the central pathologists of digitized biopsy images, supplement the positive topline findings and reinforce the strength of results observed in the primary analysis.

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 magnitude and significance of effect observed for both of the dual primary endpoints was almost identical in the primary analysis and supportive consensus read analysis; this finding reinforces the resmetirom efficacy results. In addition, it is greatly encouraging to see the report of consistent treatment effects across a range of histological measures, including reduction by resmetirom of all components of the NAFLD Activity Score, steatosis, inflammation and ballooning, that measure the severity of NASH. The data demonstrate resmetirom’s potential impact on both the underlying steatohepatitis driving the disease and the fibrosis that is strongly associated with progression to negative clinical outcomes.”

Rohit Loomba MD, MHSc, Director of the NAFLD Research Center, University of California San Diego, and a Principal Investigator of the MAESTRO-NASH study, added, “The MAESTRO- NASH trial recruited patients with three metabolic risk factors who had a prescreening FibroScan to enrich for a high degree of liver fibrosis. An MRI-PDFF conducted during screening confirmed that patients had NAFLD prior to obtaining a liver biopsy. This strategy supported the enrollment of a highly enriched NASH population with serious liver disease.”

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, “In addition to supporting our regulatory filings in the U.S. and Europe, we believe MAESTRO-NASH and the broader MAESTRO Phase 3 program will provide important learnings to advance NASH drug development and gain insight into the NASH patient population. Importantly, the wealth of biomarker and imaging data from the MAESTRO studies will help identify NASH patients in the real world and provide foundation for monitoring treatment response to resmetirom, if approved.”

Additional MAESTRO-NASH Biopsy Results

All baseline and Week 52 biopsies in MAESTRO-NASH were read independently by two central pathologists (glass slides) for the primary analysis read. Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both liver biopsy endpoints. The results were combined statistically to generate a single treatment effect.

As a supportive analysis, a “consensus read” of digitized biopsy images was conducted in cases where the two pathologists scores disagreed as to whether the there was a response for either NASH resolution (ballooning 0, inflammation 0,1; ≥2-point NAS reduction and no worsening of fibrosis) OR ≥1 stage fibrosis reduction with no worsening of NAS (primary endpoints). The consensus read by the two central pathologists reinforced the positive results observed in the primary analysis (Tables 1-2).

Table 1. Dual Primary Endpoints (52 Weeks) – Primary Analysis

Primary Endpoint	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%

Table 2. Dual Primary Endpoints (52 Weeks) – Consensus Read Supportive Analysis

Primary Endpoint	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	24%	<0.0001	28%	<0.0001	8%
≥1-stage improvement in fibrosis with no worsening of NAS	24 %	<0.0001	26%	<0.0001	12%

As previously reported, biopsy endpoints were achieved independent of baseline fibrosis stage or diabetes status, including similar statistical significance and magnitude of response at both doses in subgroups of F2, F3, and F2/F3 biopsies.

Other secondary liver biopsy endpoints were achieved at both doses including ≥2 point reduction in NAS (with ≥1 point improvement in ballooning and/or inflammation) and no worsening of fibrosis; ≥2 point reduction in NAS (with ≥1 point improvement in ballooning and/or inflammation) AND ≥1-stage improvement in fibrosis; NASH resolution (with ≥2 point reduction in NAS) AND ≥1-stage improvement in fibrosis; a 2-stage reduction in fibrosis without worsening of NAS; and reduction in all 3 NAS components (ballooning, inflammation and steatosis) without worsening of fibrosis (the steatosis response included ≥1-point improvement in biopsy steatosis grade and/or, for this endpoint only, a MRI-PDFF reduction of ≥30%).

MAESTRO-NASH is an ongoing blinded Phase 3 clinical trial, and enrolled patients continue on therapy after the Week 52 liver biopsy for up to a total of 54 months to accrue hepatic clinical outcome events including histologic conversion to cirrhosis and hepatic decompensation events.

In the first half of 2023, Madrigal intends to file a new drug application seeking accelerated approval of resmetirom. In addition to the efficacy and safety results from MAESTRO-NASH, the filing will be supported by a robust safety database, which also includes the Phase 3 MAESTRO-NAFLD-1 safety study, and two ongoing outcomes studies designed to confirm clinical benefit.

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 (up to 2,000 in total) 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 for a potential 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). NAFLD is estimated to afflict more than 20% of adults globally, about 30% in the United States. Of that population, 20% may have 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 Current Report 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; 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," "continue," "could," "demonstrates," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "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, 2021, filed with the SEC on February 24, 2022, as updated by the risk factors discussed in Part II, Item 1A of the Quarterly Report on Form 10-Q filed with the SEC on May 9, 2022, as well as in Madrigal's other filings with the SEC.

Investor Contact
Alex Howarth, Madrigal Pharmaceuticals, Inc., IR@madrigalpharma.com

Media Contact
Christopher Frates, Madrigal Pharmaceuticals, Inc., media@madrigalpharma.com

Source: Madrigal Pharmaceuticals, Inc.