



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

December 19, 2022

- In MAESTRO-NASH, a 52-week serial liver biopsy Phase 3 study in more than 950 patients, resmetirom achieved both primary endpoints and potentially clinically meaningful effects with both daily oral doses, 80 mg and 100 mg, relative to placebo
 - NASH resolution (ballooning of 0, inflammation of 0-1) and ≥ 2 -point NAS reduction with no worsening of fibrosis ($p < 0.0001$ at both doses)
 - Fibrosis improvement by at least one stage with no worsening of NAS ($p = 0.0002$ and < 0.0001 at 80 and 100 mg, respectively)
- Potentially clinically meaningful LDL-lowering, a key secondary endpoint ($p < 0.0001$)
- Multiple positive effects on NASH biomarkers and imaging
- Resmetirom was safe and well-tolerated in the MAESTRO-NASH study, consistent with the overall safety in Phase 3 MAESTRO trials, expanding the large safety database
- Madrigal intends to file a new drug application seeking accelerated approval of resmetirom for the treatment of non-cirrhotic NASH with liver fibrosis

Madrigal to host conference call at 8:00 am ET to review the results

CONSHOHOCKEN, Pa., Dec. 19, 2022 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced positive topline results from the pivotal Phase 3 MAESTRO-NASH biopsy clinical trial of resmetirom, a liver-directed selective thyroid hormone receptor agonist. MAESTRO-NASH, a registrational Phase 3 trial, has 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.

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, "These pivotal Phase 3 results demonstrate the potential for resmetirom to help patients achieve improvement in both the underlying steatohepatitis that drives this disease and the resulting fibrosis that is associated with progression to cirrhosis and its complications. The topline data also reinforce our confidence in the safety and tolerability profile of resmetirom. We believe the Phase 3 MAESTRO clinical development program, including the MAESTRO-NAFLD-1 and MAESTRO-NAFLD-OLE safety clinical trials and the recently initiated MAESTRO-NASH-OUTCOMES clinical trial, provides a strong foundation for our new drug application (NDA) and the potential accelerated approval of resmetirom for the treatment of non-cirrhotic NASH with liver fibrosis."

Dr. Taub added, "I want to thank the MAESTRO-NASH investigators and study sites participating in the study, my colleagues on the R&D team at Madrigal, and, most of all, the patients who made achievement of this important milestone possible."

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, "NASH with liver fibrosis puts patients at risk of progressing to liver failure, liver cancer, need for liver transplant, and premature mortality; with no approved treatment, this disease represents one of the most urgent unmet needs in healthcare today. These unprecedented results from the MAESTRO-NASH clinical trial signal a major turning point for the field."

Paul Friedman, M.D., Chief Executive Officer of Madrigal, stated, "MAESTRO-NASH achieved both primary endpoints proposed by the FDA as reasonably likely to predict clinical benefit and we have established a large safety database, supported by a second Phase 3 clinical trial (MAESTRO-NAFLD-1) and MAESTRO-NAFLD-OLE, to inform benefit-risk assessment. With these unequivocally positive Phase 3 data in hand, our path forward is clear. In the first half of 2023, we intend to file a new drug application seeking accelerated approval of resmetirom. I want to thank my colleagues for their sustained efforts and strong execution; our team is committed to delivering resmetirom to patients in need."

MAESTRO-NASH Week 52 Results

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.

Efficacy Results

Patients meeting eligibility requirements for MAESTRO-NASH were randomized 1:1:1 to receive resmetirom 80 mg, resmetirom 100 mg, or placebo taken orally once daily. Baseline characteristics in the 966 randomized patients in the primary analysis NASH population (ITT, safety population) were balanced across treatment arms and include age 57 (10) (mean (SD)), female 56%, white 89%, Hispanic 21%, BMI 36 (7) kg/m², type 2 diabetes 67%, hypertension 78%, dyslipidemia 71%, hypothyroidism 13%, FibroScan, kilopascals (kPa) 13 (7), CAP 348 (38), MRI-PDFF 18% (7), FIB-4 1.4 (0.7), ALT 55 (32) IU, AST 41 (23) IU, LDL 99 (40) mg/dL, triglycerides 188 (132) mg/dL, hemoglobin A1C 6.6 (1) %, ELF 9.8 (0.9). Medications included 49% on statins, 14% on GLP-1 agonists, 14% on SGLT2 inhibitors. Baseline liver biopsy fibrosis scores included F3 (~60%), F2 (~35%), F1B (~5%) (primary analysis population) with 84% with NAS ≥ 5 based on independent primary glass slide reads of the entire study by two central pathologists.

A second biopsy was conducted after 52 weeks of treatment for assessment of the dual primary endpoints. The primary efficacy analysis assessed histological response at 52 weeks in 955 patients with biopsy-confirmed NASH with fibrosis (modified intent-to-treat (mITT) population) that excluded 11 ITT patients who had their Week 52 biopsy after Week 60 due to COVID-related reasons per regulatory guidelines. Patients without a second biopsy due to early study discontinuation or missing liver biopsy (~17% across treatment arms) were included and considered as non-responders in the primary efficacy analyses (mITT). The compliance to treatment was high and minimally impacted by COVID pandemic restrictions.

Dual Primary Endpoints (52 Weeks) and Key Secondary Endpoint (24 weeks)

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%
Key Secondary Endpoint					
LDL-C lowering (24 weeks)	-12%	<0.0001	-16%	<0.0001	1%

All biopsies were read independently by two central pathologists. Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both liver biopsy endpoints. Biopsy endpoints were achieved independent of baseline fibrosis stage or diabetes status, including similar statistical significance and magnitude of effect at both doses in subgroups of F2, F3, and F2/F3 patients. Other secondary liver biopsy endpoints that were achieved at both doses include ≥2 point reduction in NAS with no worsening of fibrosis, ≥2 point reduction in NAS with ≥1-stage improvement in fibrosis, NASH resolution (with ≥2 point reduction in NAS) with ≥1-stage improvement in fibrosis, and a 2-stage reduction in fibrosis without worsening of NAS.

Multiple secondary endpoints were achieved, including statistically significant reduction from baseline in liver enzymes (ALT, AST and GGT). Reductions in atherogenic lipids and lipoproteins, fibrosis biomarkers and imaging tests (MRI-PDFF, CAP and liver stiffness measures) were observed in resmetirom treatment arms as compared with placebo.

MAESTRO-NASH included many biomarker and imaging assessments that may be used in real world clinical practice to identify appropriate patients for treatment and monitor response to resmetirom, if approved.

Madrigal intends to submit primary results for publication in a peer-reviewed journal and present study results at a future scientific congress.

Safety Results

Resmetirom was safe and well-tolerated at both the 80 mg and 100 mg doses. The frequency of serious adverse events (SAEs) was similar across treatment arms: 11.8%, 12.7% and 12.1% for the 80 mg, 100 mg, and placebo groups, respectively. The rate of study discontinuation for adverse events was low: 2.8%, 7.7% and 3.7% for the 80 mg, 100 mg and placebo groups, respectively. SAEs occurred at expected rates based on the patient population.

Consistent with previous Phase 2 and Phase 3 data, the most common adverse events reported with greater frequency in the resmetirom groups vs placebo were an excess of generally mild and transient diarrhea at the beginning of therapy, in 28%, 34%, 16% in the 80 mg, 100 mg and placebo groups, respectively, and generally mild nausea that occurred at rates of 22%, 19% and 13% in the 80 mg, 100 mg and placebo arms, respectively.

Conference Call and Webcast at 8:00 am EST

Madrigal will hold a conference call and webcast at 8:00 am EST on December 19, 2022. To access the live webcast of the call with slides please visit the Investors section of Madrigal's website or click [here](#). To access the call by phone, please go to this link ([registration link](#)), and you will be provided with dial in details. To avoid delays, we encourage participants to dial into the conference call fifteen minutes ahead of the scheduled start time. 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 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 NAS. Achievement of either primary endpoint is considered a successful trial outcome. A key secondary endpoint is lowering of LDL-C.

All 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; include all statements that are not historical facts; include statements referenced by forward-looking statement identifiers, including the examples in the paragraph below; and include but are not limited to 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 plan (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 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 resmetirom; Madrigal’s primary and key secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections; 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.

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Source: Madrigal Pharmaceuticals, Inc.