Madrigal Pharmaceuticals Announces New Data from the Phase 3 MAESTRO-NASH Study of Rezdiffra™ (resmetirom) Presented at the EASL Congress

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- *Late-breaking AI-based analysis of MAESTRO-NASH biopsy data demonstrates Rezdiffra improved key fibrotic features that are predictive of progression to decompensated cirrhosis*
- *Noninvasive test data through three years of treatment demonstrate durable treatment response to Rezdiffra; 91% of patients achieved improvement or stabilization of liver stiffness*
- *First analysis of health-related quality of life data from MAESTRO-NASH demonstrates Rezdiffra improved patient worry, health distress and stigma*
- *First analysis of Rezdiffra treatment in MetALD demonstrates patients achieved similar rates of fibrosis improvement and steatohepatitis resolution compared to the NASH population*

CONSHOHOCKEN, Pa., June 06, 2024 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a biopharmaceutical company focused on delivering novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced results from new analyses of the Phase 3 MAESTRO-NASH trial of Rezdiffra being presented at the EASL Congress, which takes place from June 5-8, 2024 in Milan, Italy.

Rezdiffra is a once-daily, oral, liver-directed thyroid hormone receptor (THR)-β agonist designed to target key underlying causes of NASH. It is the first approved medication for the treatment of NASH. In the pivotal Phase 3 MAESTRO-NASH biopsy trial, Rezdiffra achieved both fibrosis improvement and NASH resolution primary endpoints, and 80% of patients treated with Rezdiffra 100 mg experienced improvement or stabilization of fibrosis. Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). Continued approval for this indication may be contingent upon verification and description of clinical benefit in ongoing confirmatory trials.

Bill Sibold, Chief Executive Officer of Madrigal, stated, “The ten abstracts Madrigal will be presenting at the EASL Congress further advance our leadership position in NASH. Our late-breaking oral presentation leverages innovative AI technology to provide deeper insight into the antifibrotic effects of Rezdiffra and the critical role of THR-β as a suppressor of NASH disease progression. This analysis is particularly meaningful in light of emerging health economics data indicating patients with NASH can progress more rapidly than previously thought to decompensated cirrhosis. Additionally, new analyses of the MAESTRO-NASH data broaden our understanding of Rezdiffra treatment response across a range of parameters, including noninvasive measures of fibrosis and steatosis through three years of therapy and health-related quality of life. These data reinforce Rezdiffra’s role as the foundational therapy in NASH.”

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, added, “Madrigal continues to advance ambitious scientific research that will help shape the future of the NASH field. We also look forward to presenting our first abstract examining Rezdiffra treatment in patients with probable metabolic dysfunction and alcohol-associated liver disease (MetALD), a population that has historically been underrepresented in clinical research.”

Late-breaking AI-based analysis of MAESTRO-NASH biopsy data demonstrates Rezdiffra improved key fibrotic features that may be predictive of progression to decompensated cirrhosis

An AI-driven fibrosis assessment methodology, qFibrosis (Histoindex), has identified 30 specific fibrotic features on NASH liver biopsies that may be predictive of progression to cirrhosis and decompensated cirrhosis based on the SteatoSITE database. SteatoSITE contains integrated clinical and pathological data from 940 cases across the NASH spectrum with outcome data from electronic health record and pathologist-assigned fibrosis stage and RNA on baseline biopsy.

In an analysis of MAESTRO-NASH data featured in a late-breaking presentation at EASL, total qFibrosis score showed a highly significant improvement in fibrosis with Rezdiffra treatment and less progression of fibrosis as compared with placebo; results were similar to pathologist scoring. Six qFibrosis progression features with the strongest correlations between baseline pathologist scoring and noninvasive tests were identified. At week 52, patients treated with Rezdiffra showed reduction from baseline in these key features compared to placebo, with the most marked reductions occurring in the F3 population.

In a previous study, baseline biopsy RNA analyses and annotated patient timelines from SteatoSITE in histologically identical high risk fibrosis stages (F3 and F4) identified THR-β as a potential master regulator of fibrosis progression. Patients with low THR-β activity in their liver at baseline had the highest chance of progression to decompensated cirrhosis.

“The qFibrosis data provide support for Rezdiffra’s potential in benefiting patients with NASH with moderate to advanced liver fibrosis by reversing fibrosis and preventing progression to more advanced liver disease,” said Jörn M. Schattenberg, M.D., Professor of Medicine and Director of the Department of Medicine at the University Medical Center Homburg and University of the

Saarland in Germany. “These results, coupled with earlier analyses of the SteatoSITE database which found that reduced THR-β activity predicts future hepatic decompensation in patients with NASH, are highly encouraging as we await results from two ongoing Phase 3 outcomes studies of Rezdiffra, a THR-β agonist.”

Noninvasive test data through three years of treatment demonstrate durable treatment response to Rezdiffra

In analyses of noninvasive test results from MAESTRO-NASH, changes in vibration-controlled transient elastography (VCTE; an ultrasound-based measure of liver stiffness, a surrogate for fibrosis), controlled attenuation parameter (CAP; an ultrasound-derived measure of fat content in the liver), and magnetic resonance imaging-proton density fat fraction (MRI-PDFF; an MRI-based measure of triglyceride content in the liver) were assessed in the Rezdiffra 80mg, Rezdiffra 100mg, and placebo groups.

Liver stiffness as measured by VCTE improved over time (up to three years) relative to placebo in Rezdiffra-treated patients, with both doses showing a similar durable response. At year three, 91% of patients treated with Rezdiffra had improved or stable liver stiffness, as compared to 9% who experienced a ≥30% increase in liver stiffness.

CAP improvement was also stable over time, with both Rezdiffra doses showing a similar durable response through three years of treatment. CAP and MRI-PDFF improvements in patients treated with Rezdiffra predicted achieving both fibrosis improvement and NASH resolution responses on histology. However, CAP and MRI-PDFF improvements in placebo-treated patients did not predict fibrosis improvement, highlighting the importance of reducing liver fat directly in hepatocytes through THR-β agonism.

Rezdiffra improved health-related quality of life in patients with NASH

In the first analysis of health-related quality of life (HRQL) data from patients participating in the MAESTRO-NASH trial, changes in HRQL scores from baseline were evaluated in patients receiving Rezdiffra versus placebo and compared between patients with versus without biopsy response.

By weeks 24 and 52, patients receiving both doses of Rezdiffra experienced improvement of HRQL scores in the Worry domain of the Chronic Liver Disease Questionnaire-NASH. At week 52, Rezdiffra-treated patients who achieved fibrosis improvement or NASH resolution experienced improvement in several HRQL domains, including domains for Worry, Health Distress and Stigma. The improvement in HRQL among Rezdiffra biopsy responders was contrasted by no similar improvement in the placebo group. Biopsy responders with stage F3 fibrosis at baseline had similar or more pronounced improvements of HRQL in comparison to those responders with F2 or F1B fibrosis at baseline.

Rezdiffra improved fibrosis and resolved steatohepatitis in patients with MetALD

The first analysis of Rezdiffra treatment in MetALD included 75 patients from the Phase 3 MAESTRO-NASH study who were believed to have significant alcohol consumption in addition to NASH. Patients with probable MetALD were identified based on Carbohydrate Deficient Transferrin (CDT), a biomarker for chronic alcohol consumption, collected longitudinally through the study, and phosphatidylethanol (PEth) tests performed in patients suspected of increased alcohol consumption.

Rezdiffra-treated patients in the MetALD group achieved rates of fibrosis improvement and steatohepatitis resolution that were similar to the positive results observed in the overall MAESTRO-NASH population and to patients with NASH with low alcohol consumption. In the MetALD group, 88% of patients treated with Rezdiffra 100 mg and 81% treated with Rezdiffra 80 mg showed a ≥30% reduction from baseline in MRI-PDFF, compared to 14% in the placebo group.

About the Phase 3 MAESTRO-NASH Trial of Rezdiffra

MAESTRO-NASH is an ongoing Phase 3 trial that enrolled 1759 patients with biopsy-confirmed NASH. Patients were randomly assigned in a 1:1:1 ratio to receive once-daily Rezdiffra at a dose of 80 mg or 100 mg or placebo. The two primary endpoints at week 52 were NASH resolution with no worsening of fibrosis and an improvement in fibrosis by at least one stage with no worsening of the NAFLD activity score. The key secondary endpoint was the percent change from baseline in LDL cholesterol at week 24.

Rezdiffra achieved both primary endpoints and the key secondary endpoint of the MAESTRO-NASH trial. Additionally, Rezdiffra improved liver enzymes, fibrosis biomarkers and imaging tests as compared with placebo. The primary results of the trial were published in the *New England Journal of Medicine* in February 2024.

Patients enrolled in the MAESTRO-NASH trial 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 and hepatic decompensation events, as well as all-cause mortality. The 54-month outcomes portion of the trial is designed to generate confirmatory data that, if positive, will help verify Rezdiffra’s clinical benefit and may support full approval.

About NASH

Nonalcoholic steatohepatitis (NASH) is a more advanced form of nonalcoholic fatty liver disease (NAFLD). 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 patients progress to NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), the risk of adverse liver outcomes increases dramatically. NASH is rapidly becoming the leading cause of liver transplantation in the U.S.

Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with moderate to advanced liver fibrosis. Madrigal plans to focus on approximately 315,000 diagnosed patients with NASH with moderate to advanced liver fibrosis under the care of the liver specialist physicians during the launch of Rezdiffra.

NASH is also known as metabolic dysfunction associated steatohepatitis (MASH). In 2023, global liver disease medical societies and patient groups came together to rename the disease, with the goal of establishing an affirmative, non-stigmatizing name and diagnosis. Nonalcoholic fatty liver disease (NAFLD) was renamed metabolic dysfunction-associated steatotic liver disease (MASLD); NASH was renamed MASH; and an overarching term, steatotic liver disease (SLD), was established to capture multiple types of liver diseases associated with fat buildup in the liver. In addition to liver disease, patients with MASH have at least one related comorbid condition (e.g., obesity, hypertension, dyslipidemia, or type 2 diabetes).

About Rezdiffra

What is Rezdiffra?

Rezdiffra is a prescribed medicine used along with diet and exercise to treat adults with nonalcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis), but not with cirrhosis of the liver.

It is not known if Rezdiffra is safe and effective in children (under 18 years old).

This indication is approved based on improvement of NASH and liver scarring (fibrosis). There are ongoing studies to confirm the clinical benefit of Rezdiffra.

Before you take Rezdiffra, tell your healthcare provider about all of your medical conditions, including if you:

- have any liver problems other than NASH.
- have gallbladder problems or have been told you have gallbladder problems, including gallstones.
- are pregnant or plan to become pregnant. It is not known if Rezdiffra will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Rezdiffra passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take Rezdiffra.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

- Rezdiffra and other medicines may affect each other, causing side effects. Rezdiffra may affect the way other medicines work, and other medicines may affect how Rezdiffra works.
- Especially tell your healthcare provider if you take medicines that contain gemfibrozil to help lower your triglycerides, or cyclosporine to suppress your immune system, because Rezdiffra is not recommended in patients taking these medicines.
- Tell your healthcare provider if you are taking medicines such as clopidogrel to thin your blood or statin medicines to help lower your cholesterol.
- Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

What are the possible side effects of Rezdiffra?

Rezdiffra may cause serious side effects, including:

- liver injury (hepatotoxicity). Stop taking Rezdiffra and call your healthcare provider right away if you develop the following signs or symptoms of hepatotoxicity: tiredness, nausea, vomiting, fever, rash, your skin or the white part of your eyes turns yellow (jaundice), pain or tenderness in the upper middle or upper right area of your stomach (abdomen).
- gallbladder problems. Gallbladder problems such as gallstones, inflammation of the gallbladder, or inflammation of the pancreas from gallstones can occur with NASH and may occur if you take Rezdiffra. Call your healthcare provider right away if you develop any signs or symptoms of these conditions including nausea, vomiting, fever, or pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back and the pain may happen with or without vomiting.

The most common side effects of Rezdiffra include: diarrhea, nausea, itching, stomach (abdominal) pain, vomiting, dizziness, constipation.

These are not all the possible side effects of Rezdiffra. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Madrigal at 1-800-905-0324.

Please see the full Prescribing Information, including Patient Information, for Rezdiffra.

About Madrigal Pharmaceuticals
Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), a liver disease with high unmet medical need. Madrigal's medication, Rezdiffra (resmetirom), is a once-daily, oral, liver-directed THR-β agonist designed to target key underlying causes of NASH. For more information, visit www.madrigalpharma.com.

Forward Looking Statements
This press release 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 can be identified by terms such as "anticipates," "believes," "can,""could," "demonstrates," "estimates," "expects," "forecasts," "future," "goal," "help," "hopeful," "intends," "may," "might," "on track," "plans," "positions," "potential," "predicts," "projects," "seeks," "should," "will," "would" or similar expressions and the negatives of those terms. 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; and statements regarding: Rezdiffra (resmetirom) and its expected use for treating NASH with moderate to advanced fibrosis; analysis of Rezdiffra treatment in MetALD; estimates of patients diagnosed with NASH and market opportunities; the relationship between NASH progression and adverse patient outcomes; the estimated clinical burden of uncontrolled NASH; analyses for patients with NASH with moderate to advanced fibrosis concerning potential progression to cirrhosis, decompensated cirrhosis, liver transplant or death; cardiovascular risks, comorbidities and outcomes; health economics assessments or projections; indicating Rezdiffra has been shown to improve the fibrosis that is associated with progression to cirrhosis and its complications and resolve the underlying inflammation that drives the disease; projections or objectives for obtaining full approval for Rezdiffra (resmetirom), including those concerning potential clinical benefit to support potential full approval; regarding post-approval requirements and commitments; reduced risk of progression to cirrhosis, liver failure, need for liver transplant and premature mortality; treatment paradigm; improved liver enzymes, fibrosis biomarkers and imaging tests; the potential efficacy and safety of Rezdiffra (resmetirom) for noncirrhotic NASH patients and cirrhotic NASH patients; research and development activities, the timing and results associated with the future development of Rezdiffra (resmetirom), the timing and completion of projected future clinical milestone events, including enrollment, additional studies, the potential to support an additional indication for Rezdiffra (resmetirom) in patients with well-compensated NASH cirrhosis; optimal dosing levels for Rezdiffra (resmetirom); potential NASH or NAFLD and potential patient benefits with Rezdiffra (resmetirom), including future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment, and/or biomarker effects with Rezdiffra (resmetirom); and strategies, objectives and commercial opportunities, including potential prospects or results.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to those risks and uncertainties discussed in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission, or SEC, on February 28, 2024, and Part II, Item 1A of its Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, filed with the SEC on May 7, 2024, and as updated from time to time by Madrigal's other filings with the SEC.. 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 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.

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