Madrigal Announces New Clinical Data Demonstrating Rezdiffra™ (resmetirom) Significantly Improved Multiple Noninvasive Tests and Portal Hypertension Risk in Patients with Compensated MASH Cirrhosis

May 10, 2025

- *Late-breaking results from the open-label compensated MASH cirrhosis (F4c) arm of the Phase 3 MAESTRO-NAFLD-1 trial presented at the EASL Congress*
- *65% of patients with clinically significant portal hypertension (CSPH) at baseline moved into lower risk categories by year two*
- *Patients achieved a mean 6.7 kPa reduction in liver stiffness, which was statistically significant compared to baseline*

CONSHOHOCKEN, Pa., May 10, 2025 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ: MDGL), a biopharmaceutical company focused on delivering novel therapeutics for metabolic dysfunction-associated steatohepatitis (MASH), today announced positive two-year results from the open-label compensated MASH cirrhosis (F4c) arm of the Phase 3 MAESTRO-NAFLD-1 trial of Rezdiffra. Patients (n=122) in the study achieved significant improvements from baseline in liver stiffness, liver fat, fibrosis biomarkers, liver volume and risk scores for clinically significant portal hypertension (CSPH).

“Rezdiffra demonstrated broad, sustained efficacy across multiple noninvasive parameters at two years of treatment. A high, statistically significant percentage of patients with CSPH or probable CSPH at baseline shifted to lower risk categories,” said Naim Alkhouri, M.D., Chief Academic Officer at Summit Clinical Research and the Director of the Steatotic Liver Disease Program at the Clinical Research Institute of Ohio. “A larger placebo-controlled study will be needed to confirm Rezdiffra’s benefit in F4c, but the totality of data in this high-risk population of patients on the cusp of progressing to liver decompensation is highly encouraging as we await results from the ongoing Phase 3 MAESTRO-NASH OUTCOMES trial of Rezdiffra.”

CSPH is a major consequence of cirrhosis and is responsible for its most severe complications, including ascites, variceal bleeding and hepatic encephalopathy. Patients with MASH who progress to cirrhosis face a 42 times higher risk of liver-related mortality.

MAESTRO-NAFLD-1 included an open-label active treatment arm of patients with compensated MASH cirrhosis. After one year, patients were given the option to enroll in an open-label extension trial; 122 patients enrolled and 113 completed two years of treatment. At baseline, 35% of patients met Baveno criteria for CSPH, 14% for probable CSPH and 51% for no/low CSPH. The Baveno criteria use a combination of vibration-controlled transient elastography (VCTE) and platelet count to assess CSPH risk.

Among patients with CSPH at baseline, 65% moved into lower risk categories by year two (42% to no/low CSPH and 23% to probable CSPH). Among patients with probable CSPH at baseline, 57% moved into the no/low CSPH category as compared to 14% who moved into the CSPH category by year two. Improvement in CSPH risk was statistically significant compared to baseline. Similar shifts to lower risk categories were observed in an analysis using a more stringent modified Baveno criteria that incorporates magnetic resonance elastography (MRE) and the Enhanced Liver Fibrosis (ELF) test as additional evidence for CSPH risk.

As previously reported, patients achieved a mean 6.7 kPa reduction in liver stiffness at two years, which was statistically significant compared to baseline. In a responder analysis examining ≥25% improvement or worsening of liver stiffness, 51% of patients achieved improvement. An improvement of this magnitude has been associated with reduced progression to end-stage liver disease.[1] Rezdiffra helped 35% of patients achieve liver stiffness measurements consistent with F3 fibrosis, suggesting reversal of cirrhosis.

Safety data were consistent with previous studies and Rezdiffra was well-tolerated with a low rate of discontinuation due to adverse events. The most common adverse events were diarrhea, COVID-19 and nausea. There were two deaths unrelated to Rezdiffra.

“Lower thyroid-hormone receptor-beta (THR-β) activity in the liver is predictive of hepatic decompensation[2] in patients with MASH, so there is a strong mechanistic rationale supporting the potential of Rezdiffra, a THR-β agonist, to improve outcomes in patients with compensated MASH cirrhosis,” said David Soergel, M.D., Chief Medical Officer of Madrigal. “These two-year open-label data from MAESTRO-NAFLD-1 add important clinical evidence that supports our confidence in the ongoing, fully enrolled Phase 3 outcomes trial of Rezdiffra in compensated MASH cirrhosis.”

Investor Webcast to Review New F4c Data
At 8 a.m. EDT May 13, 2025, Madrigal will host a webcast to review the detailed two-year data from the compensated MASH cirrhosis (F4c) arm of the Phase 3 MAESTRO-NAFLD-1 trial. To access the webcast, please visit the investor relations section of the Madrigal website or click here to register.

About MASH
Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), is a serious liver disease that can progress to cirrhosis, liver failure, liver cancer, need for liver transplantation, and premature mortality. MASH is expected to become the leading cause of liver transplantation in the U.S. and is already the leading cause of liver transplantation among women.

Once patients progress to MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), the risk of adverse liver outcomes increases dramatically: these patients have a 10-17 times higher risk of liver-related mortality as compared to patients without fibrosis. Those who progress to cirrhosis face a 42 times higher risk of liver-related mortality, underscoring the need to treat MASH before complications of cirrhosis develop. MASH is also an independent driver of cardiovascular disease, the leading cause of mortality for patients.

An estimated 1.5 million patients have been diagnosed with MASH in the U.S., and Madrigal is focused on reaching approximately 315,000 patients with moderate to advanced fibrosis who are under the care of liver specialists. As MASH disease awareness improves and disease prevalence increases, the number of diagnosed patients with MASH with moderate to advanced fibrosis is expected to grow.

About Rezdiffra
Rezdiffra is a once-daily, oral, liver-directed THR-β agonist designed to target key underlying causes of MASH. It is the first approved medication for the treatment of MASH in the U.S. In the pivotal Phase 3 MAESTRO-NASH biopsy trial, Rezdiffra achieved both fibrosis improvement and MASH resolution primary endpoints, and 91% of patients treated with Rezdiffra 100 mg experienced improvement or stabilization of liver stiffness. In the U.S., Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic MASH 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.

Rezdiffra is not approved in Europe for the treatment of patients with MASH with moderate to advanced liver fibrosis and not approved in any geography for the treatment of patients with cirrhosis. The ongoing, fully enrolled MAESTRO-NASH OUTCOMES trial is evaluating progression to liver decompensation events in patients with compensated NASH cirrhosis treated with Rezdiffra versus placebo. A positive outcome is expected to support the full approval of Rezdiffra for noncirrhotic MASH and expand the eligible patient population for Rezdiffra with an additional indication in patients with compensated MASH cirrhosis.

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
Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a biopharmaceutical company focused on delivering novel therapeutics for metabolic dysfunction-associated steatohepatitis (MASH), 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 MASH. Rezdiffra is the first and only medication approved by the FDA for the treatment of MASH with moderate to advanced fibrosis (consistent with stages F2 to F3). An ongoing Phase 3 outcomes trial is evaluating Rezdiffra for the treatment of compensated MASH cirrhosis (consistent with stage F4c). 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, as amended, including statements related to the potential benefit of Rezdiffra in patients with compensated MASH cirrhosis. 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; the challenges with the commercial launch of a new product, particularly for a company that did not have commercial experience prior to 2024; our history of operating losses and the possibility that we may never achieve or maintain profitability; risks associated with meeting the objectives of Madrigal's clinical trials, 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 trials; any delays or failures in enrollment, and the occurrence of adverse safety events; risks related to the effects of Rezdiffra's (resmetirom's) mechanism of action; market demand for and acceptance of Rezdiffra; the potential inability to raise sufficient capital to fund ongoing operations as currently planned or to obtain financing on acceptable terms; our ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitive trials; future topline data timing or results; our ability to prevent and/or mitigate cyber-attacks; the uncertainties inherent in clinical testing; uncertainties concerning analyses or assessments outside of a controlled clinical trial; and changes in laws and regulations applicable to our business and our ability to comply with such laws and regulations. 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("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 sections appearing in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2024, filed with the SEC on February 26, 2025, and as updated from time to time by Madrigal's other filings with the SEC.

1. Lin H, Lee HW, Yip TC, et al. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease. *JAMA*. 2024;331(15):1287–1297.
2. Kendall TJ, Jimenez-Ramos M, Turner F, et al. An integrated gene-to-outcome multimodal database for metabolic dysfunction-associated steatotic liver disease. *Nat Med*. 2023 Nov;29(11):2939-2953.

Investor Contact
Tina Ventura, IR@madrigalpharma.com

Media Contact
Christopher Frates, media@madrigalpharma.com

Source: Madrigal Pharmaceuticals, Inc.