Madrigal Announces New Two-Year Data from the Compensated MASH Cirrhosis Arm of the MAESTRO-NAFLD-1 Trial Demonstrating Potential Benefit of Rezdiffra™ (resmetirom) in Patients with Compensated MASH Cirrhosis

February 26, 2025 at 6:30 AM EST

- *Patients achieved a mean 6.7 kPa reduction in liver stiffness as measured by vibration-controlled transient elastography (VCTE); this represents the largest reduction in liver stiffness reported in a compensated MASH cirrhosis patient population*
- *51% of patients achieved a ≥25% reduction in liver stiffness; a reduction of this magnitude has been associated with reduced progression to end-stage liver disease*
- *Company to review topline data during its fourth-quarter and full-year 2024 financial results conference call today, February 26, 2025, at 8 a.m. EST*

CONSHOHOCKEN, Pa., Feb. 26, 2025 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a biopharmaceutical company focused on delivering novel therapeutics for metabolic dysfunction-associated steatohepatitis (MASH), today reported positive two-year results from the open-label compensated MASH cirrhosis (F4c) arm of the Phase 3 MAESTRO-NAFLD-1 trial of Rezdiffra (resmetirom). Patients treated with Rezdiffra achieved marked reductions in liver stiffness, a surrogate for fibrosis, measured by vibration-controlled transient elastography (VCTE).

The Phase 3 MAESTRO-NAFLD-1 trial of Rezdiffra included an open-label active treatment arm of patients with compensated MASH cirrhosis. Madrigal previously reported one-year results from this cohort. Following two years of treatment, 101 patients had VCTE results for analysis. Mean liver stiffness at baseline was 25 kPa and patients achieved a mean 6.7 kPa reduction in liver stiffness at two years (6.1 kPa at one year), which was statistically significant compared to baseline. This represents the largest reduction in liver stiffness reported to date in an F4c MASH population.

Mazen Noureddin, M.D., M.H.Sc., Professor of Medicine, Director Houston Research Institute and C.S.O. Summit Clinical Research, stated, “These data demonstrating patients with compensated MASH cirrhosis achieved marked reductions in VCTE are highly encouraging. We use the ‘Baveno rule of 5 kPa’ to stratify risk of liver-related events in patients with MASH, so a mean 6.7 kPa reduction suggests that many patients are moving into a lower risk category. The results are particularly meaningful in light of recently published, multi-center, longitudinal studies[1,2] demonstrating VCTE is a strong predictor of clinical outcomes and may be more predictive of clinical outcomes than fibrosis stage assessed by liver biopsy.”

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]

The safety and tolerability profile of Rezdiffra in the compensated MASH cohort of MAESTRO-NAFLD-1 was consistent with other Rezdiffra clinical trials, with a low rate of discontinuations due to adverse events.

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, “Patients with MASH who progress to cirrhosis face a 42 times higher risk of liver-related mortality, so there is an urgent need to improve care for this underserved population with no approved treatment options. The new two-year data from MAESTRO-NAFLD-1 reinforce our confidence in the ongoing, fully enrolled MAESTRO-NASH OUTCOMES trial of Rezdiffra in patients with compensated MASH cirrhosis. If our OUTCOMES trial is successful, Rezdiffra has the potential to become the first therapy for F2-F4c MASH. It is important to remember that Rezdiffra should not be used for the treatment of patients with compensated MASH cirrhosis until safety and efficacy are established in our Phase 3 trial and the medication receives approval for this indication from regulatory authorities.”

Draft FDA guidance recommends that Phase 3 clinical trials in MASH cirrhosis use outcomes as an endpoint, as opposed to biopsy-based surrogate endpoints. This guidance, along with data from the open-label compensated MASH cirrhosis arm of MAESTRO-NAFLD-1, informed the design of the ongoing Phase 3 MAESTRO-NASH OUTCOMES trial.

Madrigal plans to present additional results from the compensated MASH cirrhosis arm of the MAESTRO-NAFLD-1 trial at a future medical conference.

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 for the treatment of patients with MASH cirrhosis.

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
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 the Rezdiffra Phase 3 Program
Madrigal is currently conducting multiple Phase 3 clinical trials to evaluate the safety and efficacy of Rezdiffra for the treatment of moderate to advanced fibrosis (consistent with fibrosis stages F2-F3) and compensated MASH cirrhosis (consistent with F4c):

1. The pivotal **MAESTRO-NASH (Moderate to Advanced Fibrosis)** trial included a 52-week biopsy assessment that supported accelerated approval and an ongoing 54-month outcomes trial designed to generate confirmatory data that, if positive, will help verify the clinical benefit of Rezdiffra and support full approval. The primary results of the MAESTRO-NASH trial were published in the *New England Journal of Medicine* in February 2024.
2. **MAESTRO-NASH OUTCOMES (Compensated Cirrhosis)** evaluates 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.
3. The **MAESTRO-NAFLD-1 (Safety)** trial was designed to noninvasively evaluate the safety and tolerability of Rezdiffra and

provide a larger safety database to support regulatory benefit-risk assessment. The primary results from the MAESTRO-NAFLD-1 trial were published in *Nature Medicine* in October 2023. MAESTRO-NAFLD-OLE, an open-label active treatment extension of MAESTRO-NAFLD-1, is ongoing to collect additional safety data in patients with noncirrhotic NASH and patients with compensated NASH cirrhosis.

Data from the 52-week portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, Phase 2 and Phase 1 data, including safety parameters, formed the basis for accelerated approval of Rezdiffra for treatment of MASH with moderate to advanced liver fibrosis.

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 Rezdiffra's potential ability to treat patients with compensated MASH cirrhosis, Madrigals intentions to present data from the MAESTRO-NAFLD-1 trial at a medical conference and expectations regarding the MAESTRO NASH OUTCOMES trial. 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 does not have commercial experience; 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 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 Rezdiffra's (resmetirom's) mechanism of action; enrollment and trial conclusion uncertainties; 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; the ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitive studies; future topline data timing or results; our ability to prevent and/or mitigate cyber-attacks; the timing and outcomes of clinical studies of Rezdiffra (resmetirom); 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, 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 sections appearing in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2023, filed with the SEC on February 28, 2024, and Part II, Item 1A of its Quarterly Report on Form 10-Q for the quarter ended September 30, 2024, filed with the SEC on October 31, 2024, 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. Gawrieh, S, et al. Increases and Decreases in Liver Stiffness Measurement are independently associated with the risk of liver-related events in NAFLD. Journal of Hepatology. 2024;81(4):600–608.

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