Madrigal Pharmaceuticals Announces FDA Approval of Rezdiffra™ (resmetirom) for the Treatment of Patients with Noncirrhotic Nonalcoholic Steatohepatitis (NASH) with Moderate to Advanced Liver Fibrosis

March 14, 2024

- *Rezdiffra becomes the first and only medication approved by the FDA for the treatment of NASH (also known as "MASH")*
- *Accelerated approval was based on Phase 3 data demonstrating that Rezdiffra improved liver fibrosis and resolved NASH in patients with noncirrhotic NASH with moderate to advanced liver fibrosis*
- *Rezdiffra prescribing information does not include a liver biopsy requirement for diagnosis*
- *Madrigal conference call scheduled for March 14, 2024, at 5:15 pm ET*

CONSHOHOCKEN, Pa., March 14, 2024 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), a biopharmaceutical company focused on delivering novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval for Rezdiffra (resmetirom) 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, "NASH with moderate to advanced liver fibrosis is a serious and progressive liver disease that, until now, has not had an FDA-approved therapy. The accelerated approval of Rezdiffra is a culmination of more than 15 years of research from our founder Dr. Becky Taub and a small R&D team that took on one of the biggest challenges in drug development. This is a historic moment for the NASH field and represents the best of what our industry is capable of. We're excited to deliver Rezdiffra to patients in need."

Becky Taub, M.D., the Founder, Chief Medical Officer and President of Research & Development of Madrigal, stated, "Madrigal would like to thank the many patients who made the accelerated approval of Rezdiffra possible by participating in our clinical studies. We believe Rezdiffra will change the treatment paradigm for NASH with moderate to advanced liver fibrosis, giving physicians a liver-directed therapy to help improve fibrosis and resolve NASH before their patients progress to cirrhosis."

Wayne Eskridge, Co-Founder and Chief Executive Officer of the Fatty Liver Foundation, stated, "This is a day of celebration for patients with NASH who have been waiting many years for the first approved therapy. I believe this approval milestone will bring new energy and momentum to the NASH community, accelerating our efforts to improve disease education, build care pathways, and expand investment in NASH research."

Rezdiffra is a once-daily, oral THR-β agonist designed to target key underlying causes of NASH. The accelerated approval of Rezdiffra was based on results from the Phase 3 MAESTRO-NASH trial, which was recently published in the *New England Journal of Medicine*. MAESTRO-NASH is an ongoing pivotal, multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1,759 patients with biopsy-confirmed NASH. Following 52 weeks of treatment, both 100 mg and 80 mg doses of Rezdiffra demonstrated statistically significant improvement compared to placebo on two primary endpoints: NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points) with no worsening of fibrosis, and an improvement in fibrosis by at least one stage with no worsening of the NAFLD activity score. Fibrosis improvement and NASH resolution were consistent regardless of age, gender, type 2 diabetes status, or fibrosis stage.

The Rezdiffra prescribing information does not include a liver biopsy requirement for diagnosis. The recommended dosage of Rezdiffra is based on actual body weight. For patients weighing <100 kg (220 lbs.), the recommended dosage is 80 mg orally once daily. For patients weighing ≥100 kg (220 lbs.), the recommended dosage is 100 mg orally once daily.

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 approval of the first medication for NASH is a true game-changer for healthcare providers, the research community and, most importantly, patients living with this serious liver condition. Based on the robust efficacy and safety data generated in two large Phase 3 MAESTRO studies, I believe Rezdiffra will become the foundational therapy for patients with NASH with moderate to advanced liver fibrosis."

Dr. Harrison continued, "Importantly, we continue to study Rezdiffra to determine if the positive results observed in the MAESTRO studies will lead to reduced risk of progression to cirrhosis, liver failure, need for liver transplant and premature mortality."

MAESTRO-NASH remains ongoing as an outcomes study designed to generate confirmatory data that, if positive, will help verify clinical benefit and may support full approval. A second ongoing outcomes trial is evaluating progression to liver decompensation events in patients with well-compensated NASH cirrhosis treated with Rezdiffra versus placebo.

Rezdiffra should not be used in patients with decompensated cirrhosis. The most common adverse reactions reported in patients treated with Rezdiffra included diarrhea, nausea, pruritis, abdominal pain, vomiting, constipation, and dizziness. Diarrhea and nausea typically began early in treatment initiation and were mild to moderate in severity. A separate, noninvasive Phase 3 trial, MAESTRO-NAFLD-1, evaluated the safety and tolerability of Rezdiffra and contributed to the safety database supporting regulatory benefit-risk assessment.

Rezdiffra is expected to be available to patients in the U.S. in April and will be distributed through a limited specialty pharmacy network. Madrigal is committed to helping appropriate patients who may benefit from Rezdiffra access the medication through the *Madrigal Patient Support* program. This program is designed to help patients navigate insurance and affordability challenges and provide co-pay support for eligible patients. Madrigal has also established a patient assistance program (PAP) to help patients with no insurance access Rezdiffra.

Conference Call and Webcast

Madrigal will host a conference call and webcast today at 5:15 PM ET to discuss the accelerated approval of Rezdiffra. To access the webcast of the call with slides please visit the Investors section of Madrigal's website or click here. An archived webcast will be available on the Madrigal website after the event.

Phase 3 MAESTRO-NASH Trial Results

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 presentation 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; and statements regarding: Rezdiffra (resmetirom) and its expected use for treating NASH with moderate to advanced fibrosis; the initiation of the commercial launch of Rezdiffra, including statements regarding commercial insurance and the anticipated time to fill prescriptions; 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; possible or assumed future results of operations and expenses, business strategies and plans (including ex-US.

Launch/partnering plans); 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 can be identified by terms such as "accelerate," "achieve," "allow," "anticipates," "appear," "be," "believes," "can," "confidence," "continue," "could," "demonstrates," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "inform," 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; the challenges with the commercial launch of a new product, particularly for a company that does not have commercial experience; 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 our product; 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; 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; and uncertainties concerning analyses or assessments outside of a controlled clinical trial. 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 as updated from time to time by Madrigal's other filings with the SEC.

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A photo accompanying this announcement is available at https://www.globenewswire.com/NewsRoom/AttachmentNg/699742ee-b5cf-4bac-8fe0-131c989b4210

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Rezdiffra




Rezdiffra product image