



Madrigal Announces Publication in the Journal of Hepatology Demonstrating Consistent Rezdiffra Efficacy Across Common MASH Genetic Risk Variants

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- *Secondary analysis of the Phase 3 MAESTRO-NASH trial demonstrated Rezdiffra improved histology and MRI-PDFF across common genetic variants associated with MASH progression*

CONSHOHOCKEN, Pa., Oct. 06, 2026 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ: MDGL), a biopharmaceutical company focused on delivering novel therapeutics for metabolic dysfunction-associated steatohepatitis (MASH), today announced the publication of a pre-specified secondary analysis from the Phase 3 MAESTRO-NASH trial in the [Journal of Hepatology](#) evaluating whether common genetic risk variants associated with MASH altered patient response to Rezdiffra® (resmetirom).

The analysis demonstrated that treatment with Rezdiffra resulted in fibrosis improvement, MASH resolution and liver fat and biomarker reductions across patients with several well-established genetic variants associated with MASH progression, including PNPLA3, HSD17B13, TM6SF2, MTARC1 and MBOAT7. The findings suggest that Rezdiffra may have a therapeutic effect regardless of genetic risk factors that contribute to more severe disease.

"Understanding how common MASH risk alleles may influence a patient's response to treatment will be increasingly important as the treatment landscape and number of diagnosed patients continue to evolve. For example, there is emerging evidence suggesting that response to various therapies could differ in individuals with MASH carrying the PNPLA3 allele, and it will be important to perform similar analyses for other approved and investigational MASH therapies moving forward," said Naga Chalasani, M.D., David W. Crabb Professor of Gastroenterology and Hepatology at Indiana University School of Medicine and lead author of the study. "It is encouraging to see that Rezdiffra demonstrated consistent effects on liver histology and biomarkers across the genetic risk subgroups evaluated, supporting broad applicability across patients with this serious liver disease."

"MASH is a complex, heterogeneous disease driven by both metabolic and genetic factors," said David Soergel, M.D., Chief Medical Officer of Madrigal. "These data reinforce that Rezdiffra provides broad benefit across patients with MASH, including those with the most common genetic risk variants that may put them at higher risk of disease progression, cirrhosis and liver cancer, strengthening its position as a foundation of MASH treatment. These results also support our pipeline strategy of developing precision approaches targeting well-defined genetic drivers of disease that may complement Rezdiffra in specific patient populations."

About the Analysis

The publication, "*Effects of select MASH risk genotypes on resmetirom efficacy on liver histology and biomarkers in patients with MASH and liver fibrosis: a secondary analysis of the MAESTRO-NASH trial*," reports results from a pre-specified secondary analysis of 738 patients from the Phase 3 MAESTRO-NASH trial who consented to genetic testing and completed baseline and Week 52 liver biopsies. The analysis was not prospectively powered to detect small genotype-by-treatment interactions, and only select common variants were assessed. Across all major efficacy endpoints, including MASH resolution, fibrosis improvement, MRI-PDFF reduction and multiple biomarkers, there was no meaningful difference in treatment response based on MASH genetic risk variants or a composite genetic risk score.

Among the findings:

- Resmetirom responses were consistent across PNPLA3, HSD17B13, TM6SF2, MTARC1 and MBOAT7 risk groups for MASH resolution, fibrosis improvement and MRI-PDFF reduction.
- The treatment effect remained consistent after accounting for sex and Hispanic ethnicity.
- Results suggested Rezdiffra's mechanism of action as a thyroid hormone receptor-beta (THR- β) agonist is not affected by common genetic pathways associated with MASH progression and severity.
- Patients with high-risk genotypes of PNPLA3 or HSD17B13 demonstrated reduced frequency of metabolic risk factors, including diabetes and hypertension, suggesting patients with greater genetic risk could still have high stages of fibrosis, even if they had fewer traditional metabolic risk factors.
- Because this was a secondary analysis with limited numbers in some genotype groups, smaller genotype-specific effects or rarer variants cannot be excluded.
- In the overall MAESTRO-NASH trial (n=966), Rezdiffra was generally well tolerated, with the frequency of serious adverse events similar across treatment groups. See additional risk information below.

Madrigal's R&D strategy includes developing therapies that target validated disease mechanisms and may complement Rezdiffra's broad therapeutic effects, especially in patient populations with specific needs. In May 2026, [the company announced](#) the addition of MGL-0795 (formerly ARO-PNPLA3), a clinical-stage, small interfering RNA (siRNA) asset targeting PNPLA3 to its pipeline as a potential precision-medicine approach. Mutations in the PNPLA3 gene are strongly associated with MASH progression and a high

risk of developing hepatocellular carcinoma (HCC). Madrigal will consult with the FDA on design of a Phase 2 combination trial with Rezdiffra.

In this analysis, MASH resolution in the PNPLA3 subgroup was achieved in 38.4%, 30.8% and 30.5% of Rezdiffra-treated patients, versus 12.9%, 5.1% and 11.7% in patients in the placebo group across low, intermediate and high-risk genotypes, respectively, while fibrosis improvement was 34.2%, 29.5% and 31.4% versus 14.1%, 13.7% and 15.0%, respectively.

About MASH

Metabolic dysfunction-associated steatohepatitis (MASH) is a serious liver disease that can progress to cirrhosis, liver failure, liver cancer, the need for liver transplantation and premature mortality. MASH is the leading cause of liver transplantation in women and the second leading cause of all liver transplantation in the U.S., and the fastest-growing indication for liver transplantation in Europe.

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 to 17 times higher risk of liver-related mortality as compared to patients without fibrosis.

Patients with MASH 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.

As disease awareness improves and disease prevalence increases, the number of patients diagnosed with F2 to F4c MASH is growing.

About Rezdiffra

What is Rezdiffra?

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

This indication is approved based on improvement of MASH 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 MASH.
- 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.
 - A pregnancy safety study for women who take Rezdiffra during pregnancy collects information about the health of you and your baby. You or your healthcare provider can report your pregnancy by visiting <https://pregnancyregistry.madrigalpharma.com/> or calling 1-800-905-0324.
- 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, 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) or stomach pain/tenderness.
- gallbladder problems. Gallbladder problems such as gallstones, or inflammation of the gallbladder, or inflammation of the pancreas from gallstones can occur with MASH 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 pain, vomiting, dizziness and 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 was the first medication approved by both the FDA and European Commission for the treatment of MASH with moderate to advanced fibrosis (F2 to F3). An ongoing Phase 3 outcomes trial is evaluating Rezdiffra for the treatment of compensated MASH cirrhosis (F4c). For more information, visit www.madrigalpharma.com and follow us [on LinkedIn](#).

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 therapeutic effect of Rezdiffra across genetic variants associated with MASH, Madrigal's ability to develop its pipeline and the potential benefit of Madrigal's pipeline candidates for the treatment of MASH. Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: the assumptions underlying the forward-looking statements; our ability to successfully commercialize Rezdiffra in the U.S. and Europe; risks related to obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections; our history of operating losses and the possibility that we may never achieve or maintain profitability; risks associated with meeting the objectives of our clinical trials, including, but not limited to our ability to achieve enrollment objectives concerning patient numbers (including an adequate safety database), outcomes objectives and/or timing objectives for our 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 or of any other product candidate; market demand for and acceptance of Rezdiffra; our ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitors; future topline data timing or results; our ability to prevent and/or mitigate cyber-attacks; our ability to protect our intellectual property rights; 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, 2025, and as updated from time to time by Madrigal's other filings with the SEC.

Madrigal may use its website to comply with its disclosure obligations under Regulation FD. Therefore, investors should monitor Madrigal's website in addition to following its press releases, filings with the SEC, public conference calls, and webcasts.

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