Madrigal Adds Clinical-Stage siRNA Asset Targeting PNPLA3 to its MASH Pipeline

May 5, 2026

- *Company advances its leadership in MASH with clinical-stage, genetically targeted siRNA asset from Arrowhead Pharmaceuticals*
- *Precision approach targets patients who have a mutation in the PNPLA3 gene, which is highly prevalent among Hispanic patients with MASH*
- *Phase 1 data published in The New England Journal of Medicine demonstrated a 46% liver fat reduction in homozygous patients and a well-tolerated safety profile*
- *Madrigal's pipeline includes more than 10 programs at multiple stages of development, anchored by Rezdiffra ® (resmetirom) as the foundational treatment*

CONSHOHOCKEN, Pa., May 05, 2026 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ: MDGL), a biopharmaceutical company focused on delivering novel therapeutics for metabolic dysfunction-associated steatohepatitis (MASH), today announced an exclusive global license agreement with Arrowhead Pharmaceuticals for ARO-PNPLA3, a clinical-stage, small interfering RNA (siRNA) asset targeting patatin-like phospholipase domain-containing protein 3 (PNPLA3), a key genetic driver of MASH.

The license of ARO-PNPLA3 adds to Madrigal's pipeline with a precision medicine approach for patients at high risk of MASH. PNPLA3 I148M, a well-established genetic contributor to MASH progression, is associated with increased liver fat, inflammation, fibrosis, cirrhosis and hepatocellular carcinoma. Approximately 30% of patients with MASH with moderate to advanced fibrosis (consistent with stages F2 to F3 fibrosis) carry two identical copies of this variant (known as homozygous patients), and it is highly prevalent in Hispanic populations.

"The addition of an siRNA program targeting PNPLA3 to our pipeline reflects Madrigal's commitment to shaping the future of MASH patient care," said Bill Sibold, Chief Executive Officer of Madrigal. "MASH is a complex, heterogeneous disease, and we believe patients will benefit from personalized treatment strategies targeting key genetic risk factors that drive disease progression and adverse outcomes. We're particularly excited about the potential to advance research for members of the Hispanic community, who are disproportionately affected by MASH."

"We are pleased to add ARO-PNPLA3 to our pipeline as we continue to expand Madrigal's leadership in MASH," said David Soergel, M.D., Chief Medical Officer of Madrigal. "This licensing agreement advances our R&D strategy of developing therapies that target validated disease mechanisms and may complement Rezdiffra's broad therapeutic effects, especially in patient populations with specific needs. Encouraging Phase 1 data support continued development of this targeted approach for patients with a well-defined genetic driver of disease, and we will begin planning for combination studies with Rezdiffra."

Phase 1 trials provide proof-of-concept for ARO-PNPLA3 as a potential precision-medicine approach in MASH
A Phase 1, first-in-human, double-blind, placebo-controlled trial of ARO-PNPLA3 was conducted in the United States in 55 patients with Metabolic dysfunction-associated fatty liver disease (MAFLD) who were either homozygous or heterozygous carriers of the PNPLA3 I148M variant. Approximately 93% of participants were Hispanic or Latino. Data from this study, published in *The New England Journal of Medicine*, demonstrated:

- Reductions in liver fat up to 46% (as measured by MRI-PDFF) at 12 weeks following a single dose at the highest dose level tested in PNPLA3 I148M homozygous patients
- Rapid onset of effect, with reductions observed at six weeks and sustained through at least 24 weeks
- No clinically meaningful adverse events were observed
- No effect on liver fat content was observed in heterozygous participants at any of the doses studied
- Results from a second Phase 1 trial conducted in Japan (n=9) support these findings

siRNA: Potential for an Effective, Genetically Targeted Treatment Approach
Small interfering RNAs (siRNAs) offer a precision approach to gene silencing in MASH by selectively reducing the production of disease-driving proteins. When linked to a GalNAc ligand, siRNA molecules are delivered directly into hepatocytes, where they silence genes that have been identified as key risk factors for MASH by breaking down targeted mRNA. By pairing this precise gene-silencing approach with Rezdiffra, the company aims to explore whether reducing drivers of disease at the genetic level can complement Rezdiffra's therapeutic effects. Madrigal currently has seven siRNA programs in its pipeline.

ARO-PNPLA3 is a GalNAc-conjugated siRNA designed to reduce expression of PNPLA3, a genetically validated driver of MASH. Mutations in the PNPLA3 gene have been shown to disrupt the liver's ability to properly process fat. This leads to increased fat accumulation in hepatocytes, and is strongly associated with MASH progression and a high risk of developing hepatocellular carcinoma (HCC). The results of two Phase 1 trials suggested that a single dose of ARO-PNPLA3 reduced liver fat content in homozygous carriers of the PNPLA3 I148M variant, providing proof-of-concept for ARO-PNPLA3 as a precision-medicine

approach in this patient population. Madrigal will consult with the FDA on design of a Phase 2 combination trial with Rezdiffra.

Deal Terms
Arrowhead has granted Madrigal an exclusive global license to develop, manufacture and commercialize ARO-PNPLA3. Arrowhead will receive an upfront payment of $25 million, additional payments of up to $975M if certain milestones are achieved and royalties on net sales.

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 diagnosed patients 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 Madrigal's development goals and timelines for its pipeline candidates, the potential benefit of ARO-PNPLA3 in the treatment of MASH and Madrigal's ability to advance its leadership position in MASH treatment. Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: the assumptions underlying the forward-looking statements; Madrigal's ability to successfully commercialize Rezdiffra; 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; Madrigal's history of operating losses and the possibility that it 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) or any product candidate's mechanism of action; market demand for and acceptance of Rezdiffra; Madrigal's ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitive trials; future topline data timing or results; Madrigal's 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; Madrigal's ability to protect its intellectual property; and changes in laws and regulations applicable to Madrigal's business and its 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, filed with the SEC on February 19, 2026, 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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