UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): March 14, 2024

MADRIGAL PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-33277**	**04-3508648**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

Four Tower Bridge
200 Barr Harbor Drive, Suite 200
West Conshohocken, Pennsylvania **19428**
(Address of principal executive offices) **(Zip Code)**

Registrant's telephone number, including area code: (267) 824-2827

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 Par Value Per Share	MDGL	The NASDAQ Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure

On March 14, 2024, Madrigal Pharmaceuticals, Inc. (the "Company") issued a press release announcing that the U.S. Food and Drug Administration ("FDA") has granted accelerated approval of Rezdiffra™ (resmetirom) in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis ("NASH") with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K. In addition, the Company posted to its website a corporate presentation in connection with the approval. A copy of the corporate presentation is attached hereto as Exhibit 99.2.

The information in Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.1 and 99.2 hereto, is being furnished pursuant to Item 7.01 and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, and it shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or under the Exchange Act, whether made before or after the date hereof, except as expressly set forth by specific reference in such filing to this item of this report.

Item 8.01 Other Events

On March 14, 2024, the Company announced that the FDA has granted accelerated approval of 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.

Item 9.01. Financial Statements and Exhibits.

(d) The following exhibits are filed as part of this report:

Exhibit Number	Description
99.1	Press Release of Madrigal Pharmaceuticals, Inc. (March 14, 2024)
99.2	Corporate Presentation of Madrigal Pharmaceuticals, Inc. (March 14, 2024)
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

MADRIGAL PHARMACEUTICALS, INC.

By: /s/ Mardi Dier
Name: Mardi Dier
Title: Senior Vice President and Chief Financial Officer

Date: March 14, 2024

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

- *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 – 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-ß 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-ß 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.

Investor Contact

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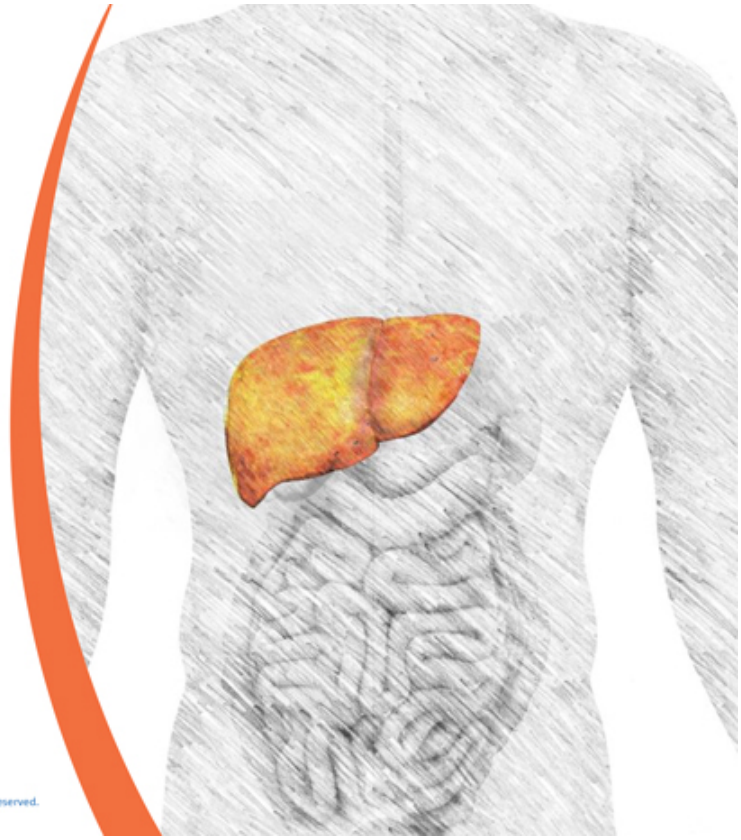
Madrigal Pharmaceuticals

Rezdiffra™ (resmetirom) FDA Approval Conference Call

March 2024



NASDAQ: MDGL

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Agenda

1	Introduction	***Bill Sibold*** *Chief Executive Officer* *Madrigal Pharmaceuticals*
2	Disease Overview and Current Treatment Paradigm	***Stephen Harrison, M.D.*** *Medical Director, Pinnacle Clinical Research; Visiting Professor of Hepatology, Oxford; Lead Principal Investigator of the MAESTRO studies*
3	Review of Rezdiffra Label and Clinical Data	***Becky Taub, M.D.*** *Chief Medical Officer and President of R&D* *Madrigal Pharmaceuticals*
4	Rezdiffra Commercial Strategy	***Bill Sibold***
5	Q&A	***Bill Sibold, Stephen Harrison, Becky Taub and Mardi Dier*** *Chief Financial Officer* *Madrigal Pharmaceuticals*

Terri's Story

Terri is a patient leader in the NASH community

Her story illustrates the serious burden of NASH progression

- She was told: *"You have fatty liver, but don't worry about it"*
- NASH cirrhosis was later detected during gallbladder surgery
- Developed ascites, hepatic encephalopathy and then hepatocellular carcinoma
- Ultimately had liver transplant, but difficult post-transplant experience

NASH, nonalcoholic steatohepatitis. **Ascites,** excess abdominal fluid and swelling. **Hepatic encephalopathy,** impaired cognitive function due to the liver's inability to filter toxins from the blood. **Hepatocellular carcinoma,** liver cancer.

Key Takeaways for Today's Call

- Rezdiffra approval is an **unprecedented milestone**
- **First-in-class label** positions Rezdiffra as **foundational therapy**
- Set to deliver **successful launch** and **maximize potential**

Strong Label Positions Rezdiffra as Foundational Therapy

- Indicated for the treatment of NASH with moderate to advanced liver fibrosis (F2/F3)
- No biopsy requirement in label
- Once-daily, oral; simple dosing
- No contraindications; no boxed warning; no monitoring requirements beyond SOC

Landmark label for first FDA-approved medicine for NASH
sets standard for potential future treatments

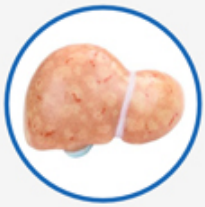
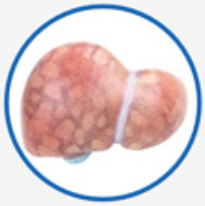
Source: Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024. **SOC,** standard of care

Disease Overview and Current Treatment Paradigm

Madrigal

NASH is a Chronic and Progressive Liver Disease

NAFLD: Nonalcoholic Fatty Liver Disease:
Entire spectrum of fatty liver disease in individuals without significant alcohol consumption

Normal Liver	NAFL: Nonalcoholic Fatty Liver	NASH: Nonalcoholic Steatohepatitis	NASH with Fibrosis	Cirrhosis
				
Fat accumulation	▪ Isolated steatosis (fat in ≥5% of hepatocytes)	▪ Steatosis ▪ Ballooning ▪ Inflammation	▪ **F1:** fibrosis stage 1 = **Mild** *Moderate to Advanced* ▪ **F2:** fibrosis stage 2 ▪ **F3:** fibrosis stage 3	▪ **F4:** fibrosis stage 4 = **Cirrhosis**

NASH is the more advanced form of NAFLD, which can progress to cirrhosis, liver failure, or result in premature death[1-5]

Hepatocytes, liver cells. **Steatosis,** excess fat in liver cells. **Steatohepatitis,** build up of excess fat in liver cells causing inflammation and damage.

1. Sheka AC, et al. JAMA. 2020;323(12):1175-83. 2. Alkhouri N, McCullough AJ. Gastroenterol Hepatol (N Y). 2012;8(10):661-8. 3. EASL–EASD–EASO. J Hepatol. 2016;64:1388-402. 4. Diehl AM, Day C. NEJM. 2017;377:3063-72. 5. Honda et al. Int J Mol Sci. 2020;21:4039.

The NASH Patient Journey, Diagnosis and Treatment

Initial Suspicion & Referral

Initial suspicion at primary care › **Referral to a specialist (Hep/GI)**

Diagnosis & Risk Assessment at Hep/GI

Confirmation of NASH diagnosis and fibrosis using NITs

Treatment for Moderate to Advanced (F2/F3) NASH Patients

+ Ongoing Diet, Exercise and Co-morbidity management

Prior Approach: No treatments available to halt or improve fibrosis; resolve NASH

TODAY'S Approach:

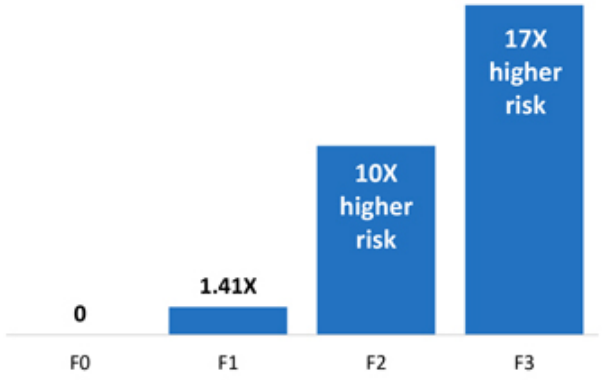
Rezdiffra: resmetirom tablets

60mg · 80mg · 100mg

Hep, hepatologist; **GI**, gastroenterologist; **NITs**, noninvasive tests.

Goal: Treat Before Negative Patient Outcomes Occur

Up to 17X Higher Risk of Liver-Related Mortality in Patients with NASH with Moderate to Advanced Fibrosis[1]

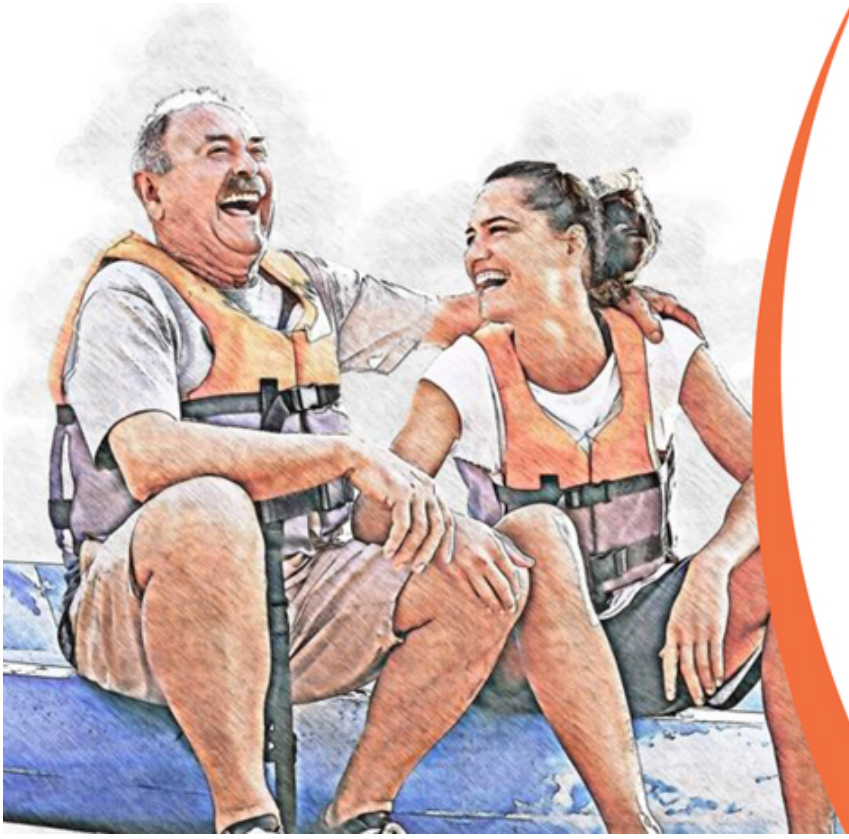


~22%

of patients with F3 fibrosis **progress to cirrhosis within 2 years**[2]

Goal: Treat NASH with moderate to advanced fibrosis **before negative patient outcomes occur**

1. Angulo P, et al. Gastroenterology. 2015;149:389-397. 2. Loomba R, Adams L. Hepatology. 2019;70(6):1885-1888.



Review of Rezdiffra Label and Clinical Data

Madrigal

Rezdiffra Approval Supported by One of the Most Comprehensive Clinical Development Programs in NASH

MAESTRO-NAFLD-1 Safety	MAESTRO-NASH Moderate to Advanced Fibrosis	MAESTRO-NASH OUTCOMES Compensated Cirrhosis
Evaluates safety and tolerability as measured by incidence of adverse events	Evaluates NASH resolution and/or fibrosis improvement on liver biopsy and composite clinical events	Event-driven trial evaluating progression to hepatic decompensation
52 weeks (completed)	52 weeks biopsy (completed) 54 months clinical outcomes	~36 months
~1,200 patients, including 200 with compensated cirrhosis	**~1,750** patients (ongoing)	**~700** patients (recruiting)

Phase 3 Data in *New England Journal of Medicine* Demonstrate Broad Response

50% of Rezdiffra-treated patients showed either **NASH resolution or fibrosis improvement**[1]

>70% of patients achieved a **>30% reduction in non-invasive test results (MRI-PDFF)**[2]

> 80% of Rezdiffra-treated patients achieved **fibrosis reversal or no fibrosis progression**[3]

MRI-PDFF, magnetic resonance imaging-proton density fat fraction. Source: Harrison S, et al. *N Engl J Med*. 2024 Feb;390(6):497-509. 1. 50% of patients on 100mg with eligible biopsies at 52 weeks achieved NASH resolution or fibrosis improvement. *NEJM* supplement Table S9. 2. >70% of patients on 100mg achieved >30% reduction in MRI-PDFF at 52 weeks. *NEJM* supplement Table S10. 3. >80% of Rezdiffra-treated patients (F1B or F2 at baseline) achieved fibrosis reversal or no fibrosis progression at 52 weeks. *NEJM* supplement Figure S5.

Rezdiffra Indication: No Biopsy; Defined Patient Population

INDICATIONS AND USAGE[1]

REZDIFFRA is a thyroid hormone receptor beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- NASH with moderate to advanced liver fibrosis (consistent with F2/F3)
- No biopsy requirement
- No contraindications; no boxed warning; no monitoring requirements beyond SOC

1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024. **SOC,** standard of care.

Rezdiffra Indication: Clearly States Where Rezdiffra Should Not Be Used

INDICATIONS AND USAGE[1]

REZDIFFRA is a thyroid hormone receptor beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitations of Use
Avoid use of REZDIFFRA in patients with decompensated cirrhosis

Avoid use of Rezdiffra in patients with decompensated cirrhosis

1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024.

Rezdiffra Label: Simple Dosing Profile

DOSING AND ADMINISTRATION[1]

The recommended dosage of REZDIFFRA is based on actual body weight. For patients weighing:

- <100 kg, the recommended dosage is 80 mg orally once daily.
- ≥100 kg, the recommended dosage is 100 mg orally once daily.

Administer REZDIFFRA with or without food.

DOSING FORMS AND STRENGTHS[1]

Tablets: 60 mg, 80 mg, or 100 mg

- Simple, weight-based, no titration
- Oral, once-daily
- 3 strengths: 60 mg, 80 mg, 100 mg

1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024.

Rezdiffra Label: No Contraindications; Warnings and Precautions Reinforce Standard of Care

CONTRAINDICATIONS[1]

None.

WARNINGS AND PRECAUTIONS[1]

- Hepatotoxicity: Monitor patients during treatment with REZDIFFRA for elevations in liver tests and for the development of liver-related adverse reactions. Discontinue REZDIFFRA and continue to monitor the patient if hepatotoxicity is suspected.
- Gallbladder-Related Adverse Reactions: Cholelithiasis and cholecystitis were observed more often in REZDIFFRA-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event such as acute cholecystitis is suspected, interrupt REZDIFFRA treatment until the event is resolved.

- No contraindications; no boxed warning
- Hepatoxicity; one patient from safety trial (did not have NASH); label reinforces standard of care
- Gallbladder-related AEs; higher incidence in NASH patients; overall incidence low with Rezdiffra (<1%)

1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024.

Rezdiffra Label: Strong Clinical Efficacy on Fibrosis Improvement and NASH Resolution

Clinical Efficacy in Rezdiffra Label[1]

	Placebo N=294	80 mg N=298	100 mg N=296
	Improvement in liver fibrosis and no worsening of steatohepatitis		
Response rate, Pathologist A (%)	15	23	28
Difference in response rate vs. placebo (95% CI)		8 (2, 14)	13 (7, 20)
Response rate, Pathologist B (%)	13	23	24
Difference in response rate vs. placebo (95% CI)		11 (5, 17)	11 (5, 7)
	Resolution of steatohepatitis and no worsening of liver fibrosis		
Response rate, Pathologist A (%)	13	27	36
Difference in response rate vs. placebo (95% CI)		14 (8, 20)	23 (16, 30)
Response rate, Pathologist B (%)	9	26	24
Difference in response rate vs. placebo (95% CI)		17 (11, 23)	15 (9, 21)

From Rezdiffra Label[1]

- *Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient.*
  - *Both the 80 mg once daily and the 100 mg once daily dosages of REZDIFFRA **demonstrated improvement on these histopathology endpoints** at Month 12 compared to placebo.*
- *In a statistical analysis incorporating both pathologists' independent readings, REZDIFFRA **achieved statistical significance on both histopathology endpoints for both doses**.*

1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024. Label: The 888 population was based on patients determined to be F2/F3 based on scoring of the baseline liver biopsy by a central reviewer at the time of randomization into the study. FDA Endpoints: Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4. Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis was defined as no increase in score for ballooning, inflammation, or steatosis. Estimated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). 95% stratified Newcombe confidence intervals (CIs) are provided. Patients with missing liver biopsy at Month 12 are considered a non-responder.

Consistent Efficacy Across All Endpoints, Doses, Patient Populations

	Label F2/F3 Population[1,2]						Madrigal F1B/F2/F3 Population[1,2]					
	MAESTRO-NASH *Label Endpoints*			MAESTRO-NASH *Prespecified Endpoints*			MAESTRO-NASH *Label Endpoints*			MAESTRO-NASH *Prespecified Endpoints (NEJM)*		
	Placebo	*80 mg*	*100 mg*	*Placebo*	*80 mg*	*100 mg*	*Placebo*	*80 mg*	*100 mg*	*Placebo*	*80 mg*	*100 mg*
Fibrosis Improvement	14%	23% p < 0.001	26% p < 0.001	16%	25% p = 0.002	27% p < 0.001	12%	23% p < 0.001	24% p < 0.001	14%	24% p < 0.001	26% p < 0.001
NASH Resolution	11%	25% p < 0.001	30% p < 0.001	9%	24% p < 0.001	29% p < 0.001	12%	27% p < 0.001	32% p < 0.001	10%	26% p < 0.001	30% p < 0.001
Number of Patients		888			888			966			966	

1. Label: The 888 population was based on patients determined to be F2/F3 based on scoring of the baseline liver biopsy by a central reviewer at the time of randomization into the study. Label Endpoints: Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4. Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis was defined as no increase in score for ballooning, inflammation, or steatosis. Estimated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). 95% stratified Newcombe confidence intervals (CIs) are provided. Patients with missing liver biopsy at Month 12 are considered a non-responder.
2. MADRIGAL: 966 population of F1B, F2, F3 patients was based on the primary efficacy read of baseline slides that was conducted by Path A and Path B near the Week 52 completion date. Madrigal Endpoints: Resolution of NASH Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis with no worsening of fibrosis stage and at least a 2-point reduction in NAS. Fibrosis improvement, at least a 1 stage improvement in fibrosis with no worsening of NAS. NAS, NAFLD Activity Score, the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); thus ranging from 0 to 8.

Rezdiffra Sets the Safety Bar in NASH

Common Adverse Reactions Reported with Rezdiffra[1,2]

Adverse Reaction	Placebo	Rezdiffra 80 mg Once Daily	Rezdiffra 100 mg Once Daily
	N=294	N=298	N=296
	n (EAIR[1])	n (EAIR[1])	n (EAIR[1])
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18(4)	24(6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

- Most frequent AEs were GI-related and generally transient with resolution over time
- Diarrhea lasted on average 2-3 weeks often characterized as loose stools or worsening of underlying diarrhea

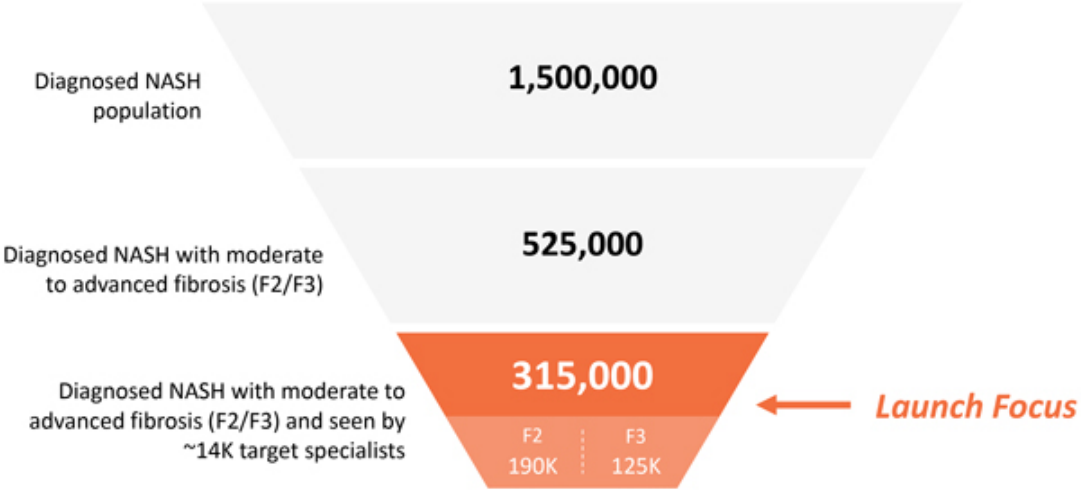
Pruritus, itchiness of skin; **AEs,** adverse events; **EAIR,** exposure-adjusted incidence rate; **PY,** person-years.
1. The EAIR per 100 PY can be interpreted as an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for one year. 2. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024.

Rezdiffra Commercial Strategy

Madrigal

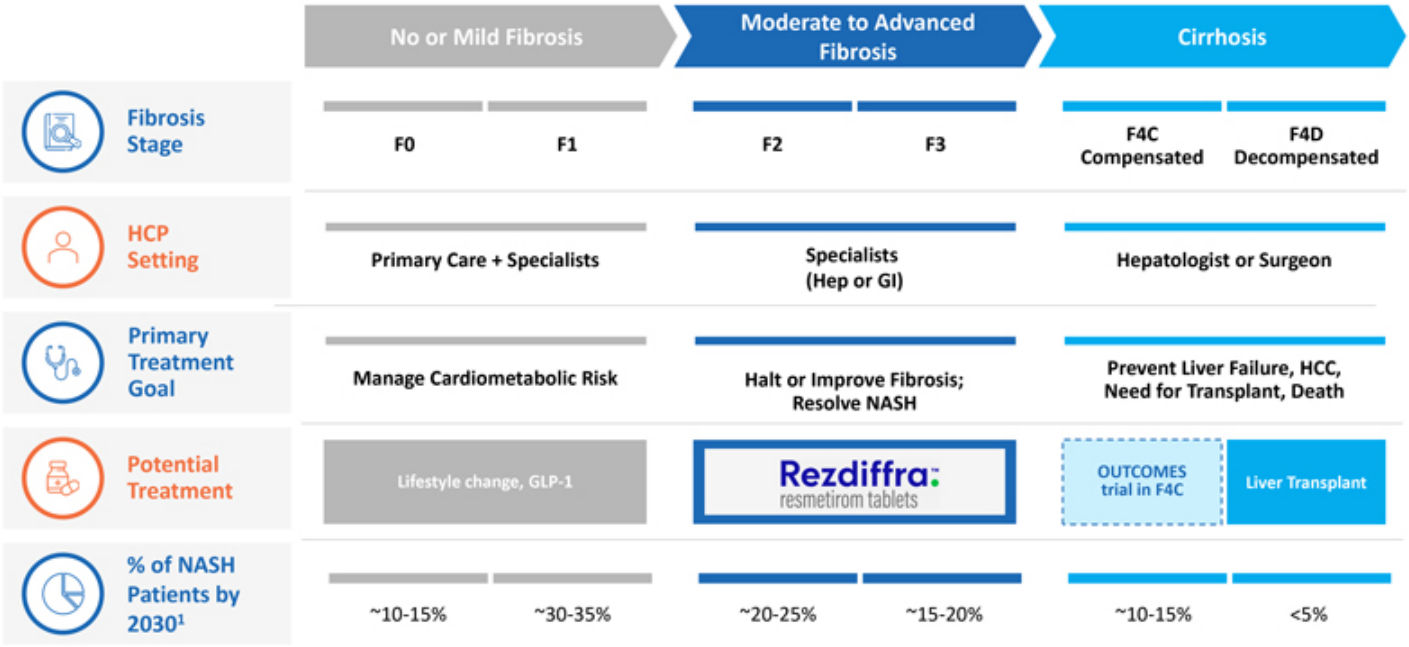
Specialty Launch Designed to Focus on 315,000 U.S. Patients

U.S. NASH Waterfall at Launch[1]



1. Forian Claims Data; Clearview Analysis; Fishman J, et al. Poster presented at: ISPOR 2023; May 7-10, 2023; Boston, MA. Data on file: REF-00571.

Rezdiffra's Differentiated Position in the NASH Treatment Paradigm



Hep, hepatologist; **GI**, gastroenterologist; **HCC**, hepatocellular carcinoma. 1. Estes C, et al. Hepatology. 2018 Jan;67(1):123-133.

Our Stakeholders Are Ready and Waiting for a Therapy Like Rezdiffra

Physicians

In the treatment of NASH with moderate to advanced fibrosis:

~88% of heps/GIs see a high urgency to treat

~85% of heps/GIs see Rezdiffra offering high clinical utility

Patients

When seeking a treatment for NASH with moderate to advanced fibrosis:

89% would proactively seek resmetirom if it were available

"There is a ticking time bomb inside me, I don't know when it will go off."

Payers

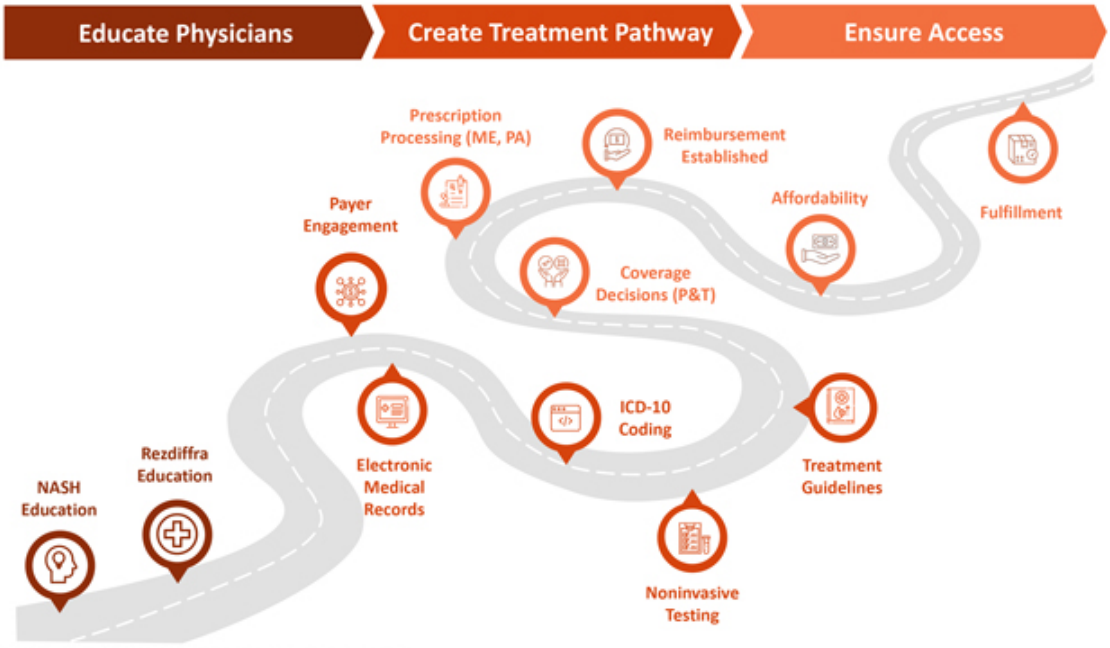
Vast majority of payers have a good understanding of disease state

Nearly 100% viewed need to treat NASH with moderate to advanced fibrosis as high to very high

Early insights: No biopsy requirement expected

Hep, hepatologist; **GI**, gastroenterologist.
Source: US Quant HCP Research, SRI, n= 172 HCPs, Q4 2023; US Quant HCP Research, ClearView, n=360 HCPs, Q4 2022; US Quant Patient Research, ClearView, n=140 patients, Q3 2021; US Payer Research, ClearView, n=24 payers, Q4 2023

Establishing Pathway for Blockbuster, First-in-Disease Medicine



Key Goals

Commercial coverage to ~80% by YE24

Time to fill Rx from ~60 days to ~30 days at 6 mos. post launch

P&T, pharmacy and therapeutics; **ME,** medical exception; **PA,** prior authorization.

Built a Winning Team Ready for Launch

Commercial and Medical leadership team; each with 25+ years industry experience; numerous blockbuster launches

Sales
- 17 yrs. experience
- Top performers
- Hep/GI experience

Medical Affairs
- 8 yrs. in practice; 14 yrs. in industry
- M.D.s, Pharm.Ds., Ph.D.s
- Hep/GI experience

Patient Support
- 18 yrs. experience
- Expert support in access and affordability solutions

Market Access
- 15 yrs. experience
- Best-in-class HEOR data
- Robust disease, cost and NIT education leading up to launch

Key Account Team
- IDNs, large GI/hep health systems
- Hep/GI experience

Right People, Right Skills, Right Size

Hep, hepatologist; **GI**, gastroenterologist; **TA**, therapeutic area; **NITs**, noninvasive tests; **IDN**, integrated delivery network.

Pricing is Grounded in Benefit to Patients and Value to the Health System

Targeting a Costly Disease for the Health System

~$120B Annual direct costs of NASH[1]

4X Higher cost of cirrhosis vs. halting NASH at F3[2]

Delivering a Cost-Effective Therapy

$76,000
ICER cost-effectiveness assessment

$39,600 – $50,100
ICER cost-effectiveness threshold range[3]

Rezdiffra Price

$47,400
Annual WAC price

Price reflects value as first-and-only therapy for NASH

WAC, wholesale acquisition cost; 1. O'Hara J, et al. JHEP Rep. 2020 Oct; 2(5): 100142. 2. Qian C, et al. Poster presented at: AMCP Nexus; October 16–19, 2023; Orlando, FL. 3. Fahim SM, et al. J Manag Care Spec Pharm. 2023 Oct;29(10):1169-1172.

Madrigal Patient Support to Provide Access Support and Education

Helping patients, no matter where they are in the Rezdiffra treatment journey

- Educational resources
- Coverage navigation
- Financial support
- Direct-to-patient delivery

Madrigal Patient Support

Madrigal plans to focus on equitable access and affordability as the launch progresses:

- **$10 co-pays** for **Commercial** patients
- Patients with **no insurance or no coverage for Rezdiffra** may be eligible to receive the medication for free

Key Takeaways for Today's Call

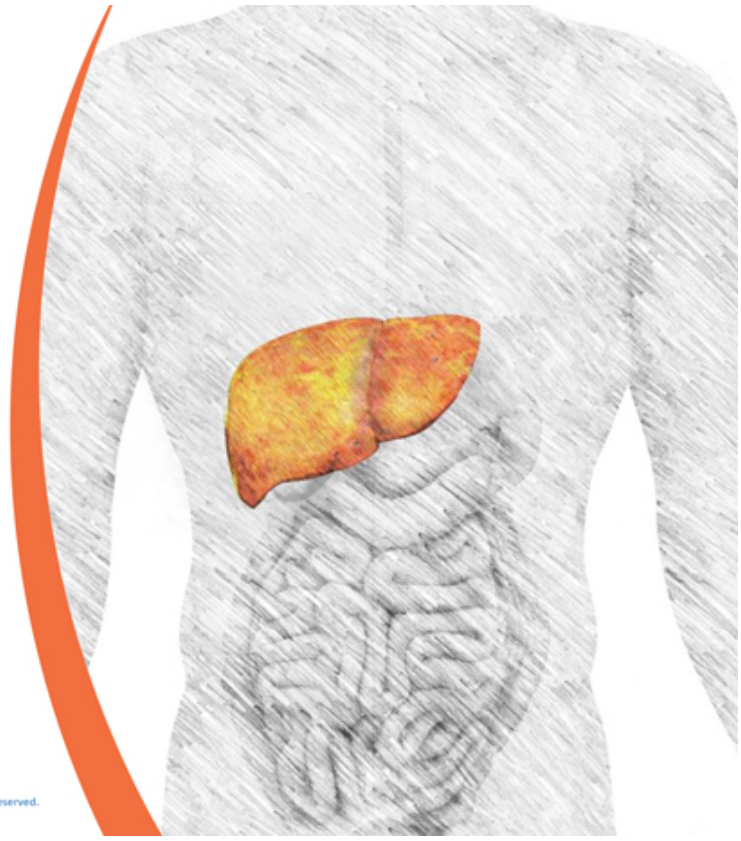
- Rezdiffra approval is an **unprecedented milestone**
- **First-in-class label** positions Rezdiffra as **foundational therapy**
- Set to deliver **successful launch** and **maximize potential**

Q&A

Madrigal

Rezdiffra™ (resmetirom) FDA Approval Conference Call

March 2024



NASDAQ: MDGL