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A SPECIAL MEETING REVIEW EDITION

Highlights in MASH From the American College of Gastroenterology 2025 Annual Scientific Meeting

A Review of Selected Presentations From the ACG 2025 Annual Scientific Meeting
October 24-29, 2025 • Phoenix, Arizona

Special Reporting on:

- Treatment With Resmetirom for Up to 2 Years Led to Improvement in Liver Stiffness, Fibrosis Biomarkers, Fibrosis Scores, and Portal Hypertension Risk in 122 Patients With Compensated MASH Cirrhosis
- Comparative Efficacy of Tirzepatide vs Semaglutide on Liver and Cardiovascular Related Outcomes in Patients with MASLD/MASH, Obesity, and Type 2 Diabetes Mellitus: A Real-World Cohort Study
- Changes in Health-Related Quality of Life, Cognitive Dysfunction, and Worry Domains in Patients With MASLD and MASH Treated With Resmetirom
- Efficacy and Safety of Efruxifermin in Patients With MASH: A Meta-Analysis of Randomized Controlled Trials
- Distinct Lipid and Liver Enzyme Trajectories in Diabetic vs Nondiabetic MASLD/MASH Patients Treated With Resmetirom: A Multicenter Propensity-Matched Analysis
- Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in MASH Resolution and Fibrosis Reduction: A Meta-Analysis
- Real-World Safety and Monitoring Practices in Patients Receiving Resmetirom for MASH: A Single Center Retrospective Review

PLUS Meeting Abstract Summaries

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Rezdiffra™
resmetirom tablets
60 mg · 80 mg · 100 mg

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

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

Limitation of Use: Avoid use in patients with decompensated cirrhosis.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Hepatotoxicity has been observed with the use of Rezdiffra. One patient developed substantial elevations of liver biochemistries that resolved when treatment was interrupted. *Please see full Prescribing Information for more details on this specific case of Hepatotoxicity [see Warnings and Precautions (5.1)].*

Monitor for elevations in liver tests, liver-related adverse reactions, and symptoms/signs of hepatotoxicity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]). If hepatotoxicity is suspected, discontinue Rezdiffra and monitor. If laboratory values return to baseline, weigh the potential risks against the benefits of restarting Rezdiffra. If laboratory values do not return to baseline, consider drug-induced autoimmune-like hepatitis (DI-ALH) or autoimmune liver disease in the evaluation of elevations in liver tests.

Gallbladder-Related Adverse Reactions

Cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) were observed more often in Rezdiffra-treated patients than in placebo-treated patients. The exposure-adjusted incidence rates (EAIRs) for these events were less than 1 per 100 person-years (PY) for all treatment arms. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event is suspected, interrupt treatment until the event is resolved.

Drug Interaction with Certain Statins

An increase in exposure of atorvastatin, pravastatin, rosuvastatin and simvastatin was observed when concomitantly administered with Rezdiffra, which may increase the risk of adverse reactions related to these drugs.

Dosage adjustment for certain statins is recommended. Monitor for statin-related adverse reactions including, but not limited to, elevation of liver tests, myopathy, and rhabdomyolysis. *Please see the upcoming* Drug Interactions *section of the Important Safety Information for more details.*

ADVERSE REACTIONS

The most common adverse reactions with Rezdiffra (reported in ≥ 5% of patients and higher compared to placebo) are diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness. Diarrhea and nausea were the most common causes of treatment discontinuation.

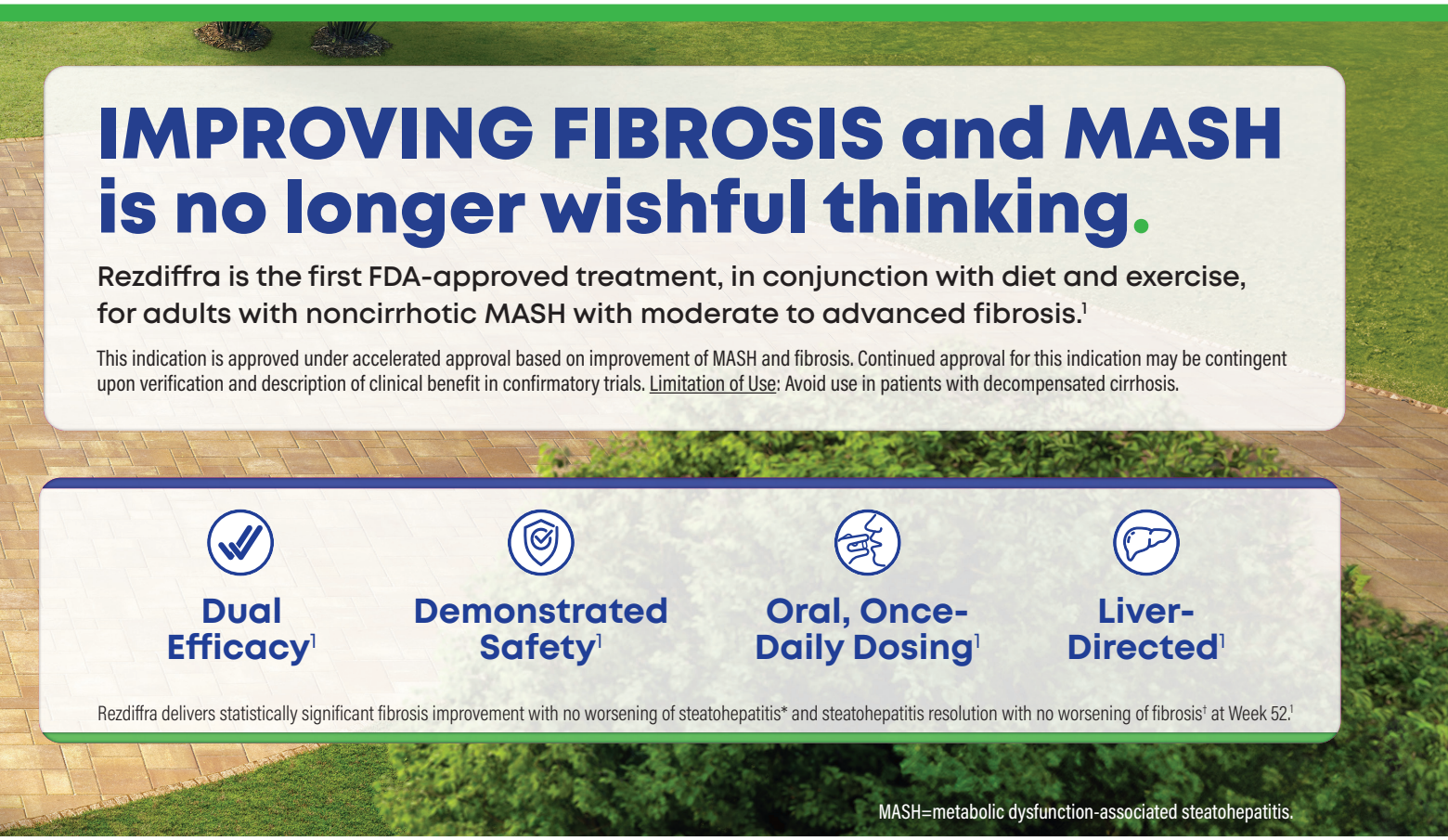
DRUG INTERACTIONS

Clinically Significant Interactions Affecting Rezdiffra

- Concomitant use with strong CYP2C8 inhibitors (eg, gemfibrozil) is not recommended. Reduce dosage if used concomitantly with a moderate CYP2C8 inhibitor (eg, clopidogrel).
- Concomitant use with OATP1B1 or OATP1B3 inhibitors (eg, cyclosporine) is not recommended.

Please see Brief Summary on the following pages and full Prescribing Information at www.madrigalpharma.com/Rezdiffra-USPI.

Visit **RezdiffraHCP.com** to learn more and get patients started.



IMPROVING FIBROSIS and MASH is no longer wishful thinking.

Rezdiffra is the first FDA-approved treatment, in conjunction with diet and exercise, for adults with noncirrhotic MASH with moderate to advanced fibrosis.[1]

This indication is approved under accelerated approval based on improvement of MASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Limitation of Use: Avoid use in patients with decompensated cirrhosis.

Dual Efficacy[1]

Demonstrated Safety[1]

Oral, Once-Daily Dosing[1]

Liver-Directed[1]

Rezdiffra delivers statistically significant fibrosis improvement with no worsening of steatohepatitis* and steatohepatitis resolution with no worsening of fibrosis† at Week 52.[1]

MASH=metabolic dysfunction-associated steatohepatitis.

IMPORTANT SAFETY INFORMATION (cont.)

DRUG INTERACTIONS (cont.)

Clinically Significant Interactions Affecting Other Drugs

- **Statins:** Limit daily rosuvastatin and simvastatin dosage to 20 mg. Limit pravastatin and atorvastatin dosage to 40 mg.
- **CYP2C8 Substrates:** Monitor patients more frequently for substrate-related adverse reactions if Rezdiffra is co-administered with CYP2C8 substrates where minimal concentration changes may lead to serious adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Rezdiffra use in pregnant women. Report pregnancies to Madrigal Pharmaceuticals, Inc.'s Adverse Event reporting line at 1-800-905-0324 and https://www.madrigalpharma.com/contact/.

Lactation

There is no information regarding the presence of Rezdiffra in human or animal milk, the effects on the breast-fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rezdiffra and any potential adverse effects on the breastfed infant from Rezdiffra or from the underlying maternal condition.

Geriatric Use

Numerically higher incidence of adverse reactions have been observed in patients ≥65 years of age compared to younger adult patients.

Renal Impairment

Rezdiffra has not been studied in patients with severe renal impairment.

Hepatic Impairment

Avoid use in patients with decompensated cirrhosis (consistent with moderate to severe hepatic impairment). Moderate or severe hepatic impairment (Child-Pugh Class B or C) may increase the risk of adverse reactions.

The safety and effectiveness have not been established in patients with cirrhosis.

Trial design: MAESTRO-NASH is an ongoing pivotal Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in 888 patients with biopsy-confirmed NASH with liver fibrosis (F2 or F3).[1] Patients were randomized 1:1:1 to Rezdiffra (80 mg or 100 mg) or placebo to evaluate the efficacy and safety at 52 weeks.[2]

*Fibrosis improvement: ≥1-stage improvement in fibrosis with no worsening of steatohepatitis (defined as no increase in score for ballooning, inflammation, or steatosis).[1]

†Steatohepatitis resolution: Resolution of steatohepatitis (score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with no worsening of fibrosis.[1]

References: 1. Rezdiffra. Prescribing Information. Madrigal Pharmaceuticals, Inc. **2.** Harrison SA et al. *N Engl J Med.* 2024;390(6):497-509.

REZDIFFRA™ (resmetirom)

Brief Summary of full Prescribing Information

INDICATIONS AND USAGE

REZDIFFRA is 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 *[see Clinical Studies (14) in the full Prescribing Information]*. 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 *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Hepatotoxicity has been observed with use of REZDIFFRA. One patient had normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB) levels at baseline, who received REZDIFFRA 80 mg daily, developed substantial elevations of liver biochemistries that resolved when treatment was interrupted. After reinitiating REZDIFFRA, the patient had elevations of ALT, AST, and TB. Peak values observed were 58 x upper limit of normal (ULN) for ALT, 66 x ULN for AST, 15 x ULN for TB, with no elevation of alkaline phosphatase (ALP). Elevations in liver enzymes were accompanied by elevations in immunoglobulin G levels, suggesting drug-induced autoimmune-like hepatitis (DI-ALH). The liver tests returned to baseline following hospitalization and discontinuation of REZDIFFRA without any therapeutic intervention.

Monitor patients during treatment with REZDIFFRA for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]). If hepatotoxicity is suspected, discontinue REZDIFFRA and continue to monitor the patient. If laboratory values return to baseline, weigh the potential risks against the benefits of restarting REZDIFFRA. If laboratory values do not return to baseline, consider DI-ALH or autoimmune liver disease in the evaluation of elevations in liver tests.

Gallbladder-Related Adverse Reactions

In clinical trials, cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) were observed more often in REZDIFFRA-treated patients than in placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event is suspected, interrupt REZDIFFRA treatment until the event is resolved *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

Drug Interaction with Certain Statins

An increase in exposure of atorvastatin, pravastatin, rosuvastatin and simvastatin was observed when concomitantly administered with REZDIFFRA *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*, which may increase the risk of adverse reactions related to these drugs. Dosage adjustment for certain statins is recommended *[see Drug Interactions (7.2) in the full Prescribing Information]*. Monitor for statin-related adverse reactions including but not limited to elevation of liver tests, myopathy, and rhabdomyolysis.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Gallbladder-Related Adverse Reactions *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of REZDIFFRA was evaluated in two randomized, double-blind, placebo-controlled trials that enrolled a total of 2019 patients.

Trial 1

Trial 1 included patients who had noncirrhotic NASH with stages F2 and F3 fibrosis at eligibility (n=888) *[see Clinical Studies (14) in the full Prescribing Information]*.

Adverse Reactions Leading to Discontinuations

The exposure-adjusted incidence rates (EAIRs) per 100 person-years (PY) for treatment discontinuation due to any adverse reaction were higher in the REZDIFFRA dosage arms: 4 per 100 PY, 5 per 100 PY, and 8 per 100 PY in placebo, REZDIFFRA 80 mg once daily, and REZDIFFRA 100 mg once daily arms, respectively. Diarrhea and nausea were the most common causes of treatment discontinuation.

Common Adverse Reactions

Table 1 displays EAIRs per 100 PY for the common adverse reactions that occurred in at least 5% of patients with F2 or F3 fibrosis treated in either drug arm with REZDIFFRA and were greater than that reported for placebo.

Table 1: Exposure-Adjusted Incidence Rates (EAIR) of Common Adverse Reactions Reported with REZDIFFRA in Adult Patients with Noncirrhotic NASH (Trial 1)[a, b, c]

Adverse Reaction	Placebo N=294 n (EAIR[d])	REZDIFFRA 80 mg Once Daily N=298 n (EAIR[d])	REZDIFFRA 100 mg Once Daily N=296 n (EAIR[d])
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)

[a] Population includes adult patients with noncirrhotic NASH with liver fibrosis (stages F2 and F3 at eligibility).

[b] Median exposure duration was 68 weeks for placebo, 74 weeks for REZDIFFRA 80 mg once daily, and 66 weeks for REZDIFFRA 100 mg once daily.

[c] EAIRs are per 100 person-years (PY) where total PYs were 435, 435, and 407 for placebo, 80 mg once daily, and 100 mg once daily arms, respectively.

[d] 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.

Abbreviations: EAIR, exposure-adjusted incidence rate; PY, person-years; NASH, nonalcoholic steatohepatitis

Gastrointestinal Adverse Reactions

The incidence of gastrointestinal adverse reactions was higher for the REZDIFFRA drug arms compared to placebo. The EAIRs for gastrointestinal adverse reactions were 57 per 100 PY, 73 per 100 PY, and 89 per 100 PY in the placebo, REZDIFFRA 80 mg once daily, REZDIFFRA 100 mg once daily arms, respectively.

Diarrhea typically began early in treatment initiation and was mild to moderate in severity. The median time (Q1 to Q3) to a diarrheal event was 39 (2 to 195) days, 17 (3 to 70) days, and 6 (2 to 54) days in the placebo, REZDIFFRA 80 mg once daily, and REZDIFFRA 100 mg once daily arms, respectively.

Median duration of diarrhea was 9 days for placebo compared to 20 days for both REZDIFFRA 80 mg once daily and REZDIFFRA 100 mg once daily dosage arms.

Nausea also began early in treatment and was mild to moderate in severity. Among patients with nausea, the median time (Q1 to Q3) to a nausea event was 85 (24 to 347) days, 28 (2 to 162) days, and 5 (2 to 40) days in the placebo, REZDIFFRA 80 mg once daily, and REZDIFFRA 100 mg once daily arms, respectively. Median duration of nausea was 17 days, 26 days, and 28 days for patients in the placebo, REZDIFFRA 80 mg once daily, and REZDIFFRA 100 mg once daily arms, respectively. Vomiting and abdominal pain adverse reactions were mild to moderate in severity.

Hypersensitivity Reactions

Reactions such as urticaria and rash, which may reflect drug hypersensitivity, were observed in patients receiving REZDIFFRA. The EAIRs for urticaria were 0.2 per 100 PY, 0.7 per 100 PY, and 1.5 per 100 PY in the placebo, REZDIFFRA 80 mg once daily, and REZDIFFRA 100 mg once daily arms, respectively. The EAIRs for rash were 3 per 100 PY in the placebo and REZDIFFRA 80 mg once daily arms compared to 5 per 100 PY in the REZDIFFRA 100 mg once daily arm.

Gallbladder-Related Adverse Reactions

A higher incidence of cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) was observed in the treatment arms compared to placebo. However, the EAIRs for these events were less than 1 per 100 PY for all treatment arms.

Less Common Adverse Reactions

Additional adverse reactions that occurred more frequently in the REZDIFFRA arms compared to placebo, in less 5% of patients, included decreased appetite, flatulence, abnormal feces, dysgeusia, vertigo, arrhythmia, palpitations, depression, erythema, hypoglycemia, tendinopathy, abnormal uterine bleeding.

Laboratory Abnormalities

Liver Tests

Increases in mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed in the first 4 weeks after initiating treatment with REZDIFFRA. In both REZDIFFRA dosage arms, the mean elevation in ALT and AST values was less than 1.5 times baseline at 4 weeks after treatment initiation. These values returned to baseline around 8 weeks after initiating treatment.

Table 2 presents the frequency of liver test elevations during Trial 1.

Table 2: Frequency of Liver Test Elevations in Trial 1

	Placebo (%)	REZDIFFRA 80 mg Once Daily (%)	REZDIFFRA 100 mg Once Daily (%)
ALT > 3x ULN	10	11	13
ALT > 5x ULN	2	2	2
AST > 3x ULN	10	9	12
AST > 5x ULN	2	1	4
TB[a] > 2x ULN	2	1	3

[a] TB elevations include patients with Gilbert syndrome.

Thyroid Function Tests

A decrease in levels of prohormone free T4 (FT4) of mean 2%, 13%, and 17% was seen at 12 months in patients treated with placebo, REZDIFFRA 80 mg once daily, and REZDIFFRA 100 mg once daily, respectively, with minimal changes in active hormone T3 or in TSH. There were no clinical findings associated with FT4 decreases.

Additional Safety Data

The safety evaluation of REZDIFFRA also included an analysis of an additional randomized placebo-controlled safety trial which included 969 patients from a relevant patient population (placebo [n=318], REZDIFFRA 80 mg once daily [n=327], and REZDIFFRA 100 mg once daily [n=324]).

Data from the safety trial was combined with data from NASH patients with F2 and F3 fibrosis at eligibility (n=888) and data from an additional 162 patients from a relevant patient population enrolled in Trial 1. In the combined safety population (n=2019), the median (Q1 to Q3) age of patients at baseline was 58 (50 to 65) years; 55% were female, 28% were Hispanic, 89% were White, 2% were Asian, and 4% were Black or African American.

The safety profile from this combined analysis was similar to that in Trial 1, other than the one case of hepatotoxicity in the safety trial *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on REZDIFFRA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus related to underlying NASH with liver fibrosis *(see Clinical Considerations)*. In animal reproduction studies, adverse effects on embryo-fetal development occurred in pregnant rabbits treated with resmetirom at 3.5 times the maximum recommended dose during organogenesis. These effects were associated with maternal toxicity, whereas no embryo-fetal effects were observed at lower dose levels with better tolerance in pregnant rabbits. No embryo-fetal developmental effects occurred in pregnant rats treated with resmetirom or the metabolite MGL-3623. A pre- and postnatal development study in rats with maternal dosing of resmetirom during organogenesis through lactation showed a decrease in birthweight and increased incidence of stillbirths and mortality (postnatal days 1-4) at 37 times the maximum recommended dose *(see Data)*. These effects were associated with marked suppression of maternal T4, T3, and TSH levels.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Report pregnancies to Madrigal Pharmaceuticals, Inc. Adverse Event reporting line at 1-800-905-0324 and https://www.madrigalpharma.com/contact/.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

There are risks to the mother and fetus related to underlying maternal NASH with liver fibrosis, such as increased risks of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage.

Data

Animal Data

No effects on embryo-fetal development were observed in pregnant rats treated orally with up to 100 mg/kg/day (21 times the maximum recommended dose based on AUC [area under the plasma concentration-time curve]) or in pregnant rabbits treated orally with up to 30 mg/kg/day (2.8 times the maximum recommended dose based on AUC) during the period of organogenesis. Oral administration of 75 mg/kg/day in pregnant rabbits (3.5 times the maximum recommended dose based on AUC) produced an increase in post-implantation loss and decreases in viable fetuses and fetal weight. These effects were likely due to maternal toxicity (i.e., marked reductions in weight gain and food consumption).

A pre- and postnatal development study was performed using oral administration of 3, 30, or 100 mg/kg/day in female rats during organogenesis through lactation. Treatment with 100 mg/kg/day (37 times the maximum recommended dose based on AUC) produced increases in number of stillborn, pup deaths during postnatal days 1-4, and pups with absence of milk in stomach. Birthweight was decreased by 10% in this dose group, with recovery to normal body weight thereafter. The effects in offspring were associated with marked reductions in maternal plasma levels of T4 (88% decrease), T3 (79% decrease), and TSH (44% decrease). No effects on postnatal development were observed at doses up to 30 mg/kg/day (7.2 times the maximum recommended dose based on AUC). This study lacked a complete evaluation of physical and neurobehavioral development in offspring; however, no effects of resmetirom were noted in tests of learning and memory.

The metabolite MGL-3623 was tested for its effects on embryo-fetal development. No effects were observed in pregnant rats treated orally with up to 100 mg/kg/day MGL-3623 (4.7 times the maximum recommended dose based on AUC for MGL-3623) during the period of organogenesis.

Lactation

Risk Summary

There is no information regarding the presence of REZDIFFRA in human or animal milk, the effects on the breast-fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REZDIFFRA and any potential adverse effects on the breastfed infant from REZDIFFRA or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of REZDIFFRA have not been established in pediatric patients.

Geriatric Use

In Trial 1, of the 594 patients with NASH who received at least one dose of REZDIFFRA, 149 (25%) were 65 years of age and older and 13 (2%) were 75 years of age and older *[see Clinical Studies (14) in the full Prescribing Information]*. No overall differences in effectiveness but numerically higher incidence of adverse reactions have been observed in patients 65 years of age and older compared to younger adult patients.

Renal Impairment

The recommended dosage in patients with mild or moderate renal impairment is the same as in patients with normal kidney function. REZDIFFRA has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

Avoid use of REZDIFFRA in patients with decompensated cirrhosis (consistent with moderate to severe hepatic impairment). Moderate or severe hepatic impairment (Child-Pugh Class B or C) increases resmetirom C_{max} and AUC *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*, which may increase the risk of adverse reactions.

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

The safety and effectiveness of REZDIFFRA have not been established in patients with NASH cirrhosis.

For more detailed information, please read the full Prescribing Information.

Manufactured by: UPM Pharmaceuticals (Bristol, TN)
Manufactured for: Madrigal Pharmaceuticals, Inc. (West Conshohocken, PA)

REZDIFFRA™ (resmetirom)

 Issued: 03/24 US-PP-RES-00148 v2

Treatment With Resmetirom for Up to 2 Years Led to Improvement in Liver Stiffness, Fibrosis Biomarkers, Fibrosis Scores, and Portal Hypertension Risk in 122 Patients With Compensated MASH Cirrhosis

Resmetirom is an oral, once-daily, liver-directed thyroid hormone receptor β agonist currently approved by the US Food and Drug Administration for adults with metabolic dysfunction-associated steatohepatitis (MASH), characterized by moderate to advanced liver scarring without cirrhosis.[1] There is an unmet need for effective therapies for patients with MASH and compensated cirrhosis, as no therapies have been approved for this subset of patients, and stage F4 fibrosis is associated with an increased risk of adverse outcomes, including liver-related complications, need for transplantation, and death.[2] It has been proposed that by restoring thyroid hormone receptor β signaling, resmetirom may promote fibrosis regression through its effects on mitogenesis, reductions in oxidative stress, and effects on hepatic stellate cells.[3]

Alkhouri and colleagues presented results from the MAESTRO-NAFLD-1 trial evaluating the safety and efficacy of resmetirom in an open-label cohort of patients with compensated MASH cirrhosis (Child-Pugh A).[4] These patients received resmetirom 80 mg for 52 weeks, and after a variable gap of 1 month to 1 year off treatment, entered a 1-year open-label extension. The cohort comprised 122 patients with F4 fibrosis on liver biopsy or noninvasive clinical assessments with a platelet count of 70,000/μL or higher. Most patients (n=93) had classic MASH cirrhosis, with a baseline magnetic resonance imaging-proton density fat fraction (MRI-PDFF) greater than 5%; the remaining 21 patients had an MRI-PDFF of 5% or less. This cryptogenic MASH cirrhosis is associated with a more aggressive disease course, and patients tend to have more liver stiffness, larger spleens, lower platelet counts, and higher fibrosis-4 index (FIB-4).

In the efficacy analysis, resmetirom was associated with significant sustained reductions in liver stiffness measurement (LSM). After 1 year, 47% of patients achieved a 25% or more reduction in LSM assessed with vibration-controlled transient elastography (VCTE), increasing to 51% at 2 years. The mean change in VCTE was -6.4 kilopascals (kPa) after 1 year (n=116) and -6.7 kPa after 2 years (n=101). Among patients with confirmed F4 fibrosis at baseline, 35% had a potential transition to F3 at year 2 as defined by VCTE (<15 kPa and ≥25% decrease from baseline).

Reductions in portal hypertension risk category were also observed in patients receiving resmetirom. At baseline, clinically significant portal

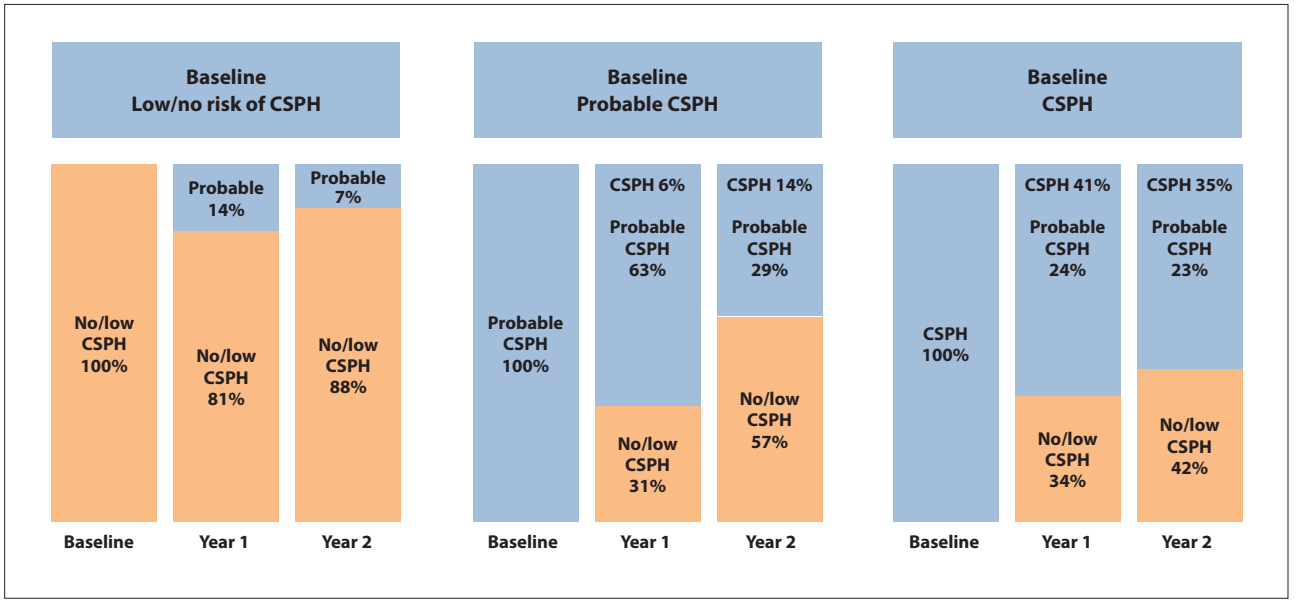


Figure 1. Improvements in portal hypertension risk category with resmetirom. High, statistically significant percentage of patients with probable CSPH and CSPH at baseline shift to lower risk category at Year 1 and Year 2 whether Baveno (shown) or modified Baveno criteria for CSPH are used.

CSPH, clinically significant portal hypertension.

Adapted from Alkhouri N. Abstract 7. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[4]

hypertension (CSPH) was present in 35% of patients as assessed using Baveno criteria. This decreased to 17% after 1 year and to 15% after 2 years. Conversely, the proportion of patients with no or low CSPH increased from 51% at baseline to 58% at 1 year and 70% at 2 years. Similar reductions in portal hypertension risk were observed using modified Baveno criteria, which add requirements for CSPH in patients with VCTE of 25 kPa or higher. A subgroup analysis found significant shifts in portal hypertension risk across baseline CSPH risk categories (Figure 1).

Resmetirom was also associated with sustained reductions in liver fat and liver stiffness at 2 years as assessed by changes from baseline in MRI-PDFF greater than 5% (n=83; median change, -37%), controlled attenuation parameter (CAP) score (n=79; mean change, -43 dBM), and magnetic resonance elastography (MRE) (n=77; mean change, -0.48 kPa). An improved MRE response (≥19%) was noted in 29% of patients with a baseline MRI-PDFF greater than 5% and in 43% of patients with a baseline MRI-PDFF of 5% or less.

Other biomarkers that improved after 2 years of resmetirom included alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT). In patients with MRI-PDFF greater than 5% (n=64) and MRI-PDFF of 5% or less (n=8) at baseline, mean percent change from baseline in ALT (≥30 at baseline) was -20% and -11%, respectively, and in GGT was -36% and -27%, respectively. Reductions in fibrosis and liver injury biomarkers as well as in atherogenic lipids were also observed. Finally, MRI-based assessments showed a decrease in liver volume (mean) of 22% to 25% and reduced mean spleen volume in patients with a baseline platelet count greater than 100,000/µL.

In the safety analysis, resmetirom was well tolerated. There were no serious adverse events (AEs) related to resmetirom, with the most frequent AEs being diarrhea (38%), COVID-19 (31%), nausea (31%), and urinary tract infection (27%). Decompensation events occurred in 6 of 122 patients, all of whom had elevated baseline Model for End-Stage Liver Disease score and/or platelets less than 100,000/µL.

> In an open-label trial of patients with compensated MASH cirrhosis who received resmetirom 80 mg daily, there was significant decrease in liver stiffness as assessed by vibration-controlled transient elastography, with potentially up to one-third of patients achieving reversal of cirrhosis and a significant percentage experiencing resolution of clinically significant portal hypertension. Resmetirom was associated with reasonable safety in this cohort of patients with advanced disease and with low discontinuation rate in the trial.
>
> —Naim Alkhouri, MD

The potential clinical benefit of resmetirom in patients with MASH cirrhosis is being evaluated in the ongoing phase 3 MAESTRO-NASH-OUTCOMES trial (NCT05500222).

References

1. Rezdiffra [package insert]. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc; 2024.
2. Sanyal AJ, Van Natta ML, Clark J, et al; NASH Clinical Research Network (CRN). Prospective Study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med*. 2021;385(17):1559-1569.
3. Arvanitakis K, Koufakis T, Cholongitas E, Francque S, Germanidis G. Insights into the results of resmetirom trials: can a thyroid hormone receptor agonist be the holy grail of MASH therapy? *Pharmacol Ther*. 2025;268:108811.
4. Alkhouri N, Taub R, Lu X, et al. Treatment with resmetirom for up to 2 years led to improvement in liver stiffness, fibrosis biomarkers, fibrosis scores, and portal hypertension risk in 122 patients with compensated MASH cirrhosis. Abstract 7. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.

Comparative Efficacy of Tirzepatide vs Semaglutide on Liver and Cardiovascular Related Outcomes in Patients with MASLD/MASH, Obesity, and Type 2 Diabetes Mellitus: A Real-World Cohort Study

Type 2 diabetes mellitus (T2DM) commonly occurs in patients who have metabolic dysfunction-associated steatotic liver disease (MASLD) and/or MASH.[1] Glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide have demonstrated benefits in patients with T2DM, including reduced body weight, improved glycemia, and a lower incidence of major adverse cardiovascular events.[2,3] In the SURPASS-2 trial, the dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide demonstrated superiority over semaglutide in weight loss and in glycated hemoglobin (A1c) levels.[4] The cardioprotective benefits of dual GIP/GLP-1 receptor agonists compared with selective GLP-1 receptor agonists have not been directly compared.

Through the TriNetX database, Jalamneh and colleagues identified

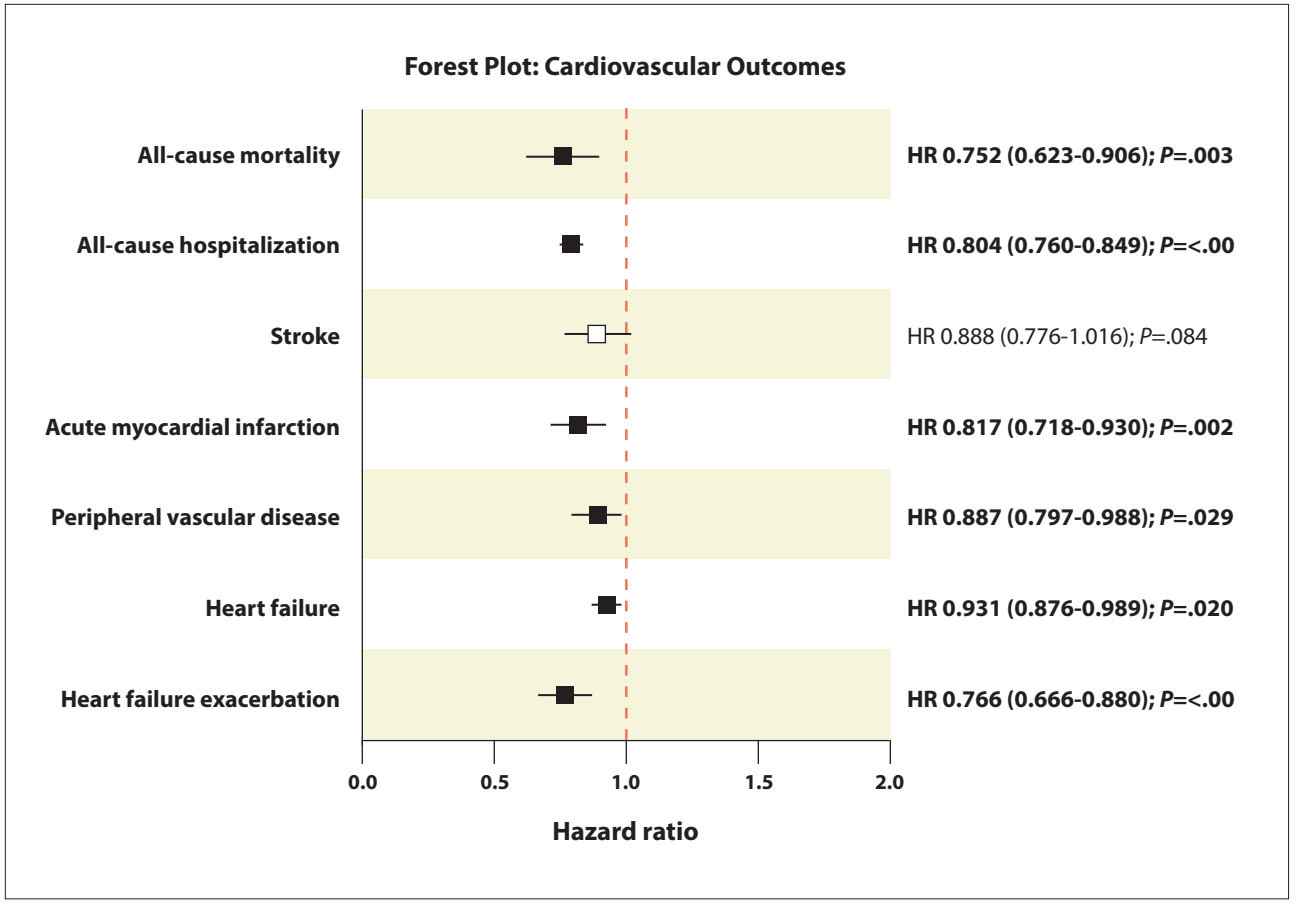


Figure 2. Large real-world comparison of tirzepatide vs semaglutide in MASLD, T2DM, and obesity showing favorable cardiovascular outcomes. Filled in squares indicate *P*<.05.

HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

Adapted from Jalamneh et al. Abstract 31. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[5]

adults with MASLD, T2DM, and a body mass index (BMI) of 30 kg/m^2 or higher receiving tirzepatide (n=21,517) or semaglutide (n=66,084) and conducted a retrospective, propensity score–matched analysis comparing cardiovascular and other outcomes.[5] The analysis was balanced for 43 demographic, diagnostic, medication-related, and laboratory-related variables to yield a final cohort of 21,513 patients in each arm. Outcomes were assessed at 6 months, 1 year, and 2 years.

Compared with semaglutide, tirzepatide was associated with lower risks of multiple cardiovascular-related outcomes (Figure 2). The cumulative probability curves showed sustained separation toward the end, stopping at about 6 months, with *P* values of less than .05 for all-cause mortality, all-cause hospitalization, acute myocardial infarction, peripheral vascular disease, heart failure, and heart failure exacerbation. The only safety parameter that was significantly different between arms was acute kidney injury, which significantly favored the tirzepatide arm (hazard ratio [HR], 0.880; 95% CI, 0.812-0.953; *P*=.002); other outcomes, including pancreatitis, cholelithiasis, cholecystitis, hypoglycemia, and gastroparesis, were not significantly

The finding of this study should be interpreted with caution given the reliance on coding-based outcomes and the relatively short follow-up period. The data did not include laboratory values such as liver enzyme levels or the results of imaging tests; therefore, no conclusions can be made regarding the severity of MASLD at baseline.

—Naim Alkhouri, MD

different between arms.

Although confounding bias was addressed in the analysis, the study had several limitations, including the potential for misclassification, residual confounding bias from unmeasured variables, the retrospective design, and short follow-up available for tirzepatide. The analysis showed favorable cardiovascular outcomes and decreased acute kidney injury events with tirzepatide compared with semaglutide. Patients with established coronary artery disease/heart failure or with frequent hospital admissions may obtain the most clinically meaningful benefit from tirzepatide.

References

1. Le P, Tatar M, Dasarathy S, et al. Estimated burden of metabolic dysfunction-associated steatotic liver disease in US Adults, 2020 to 2050. *JAMA Netw Open*. 2025;8(1):e2454707.
2. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
3. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776-785.
4. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515.
5. Jalamneh B, Abu-Hammour MN, Alabbas M, et al. Comparative efficacy of tirzepatide vs semaglutide on liver and cardiovascular related outcomes in patients with MASLD/MASH, obesity, and type 2 diabetes mellitus: a real-world cohort study. Abstract 31. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.

Changes in Health-Related Quality of Life, Cognitive Dysfunction, and Worry Domains in Patients With MASLD and MASH Treated With Resmetirom

Patients with MASLD can experience cognitive impairment that may relate to inflammation, oxidative stress, and dysregulation of the brain-liver-gut axis.[1] Cognitive changes and their effects on health-related quality of life (HRQL) have not been well characterized by the standard assessments for HRQL in patients with liver disease.

Younossi and colleagues developed a new Cognitive Function Self-Report domain, which was utilized to evaluate cognitive changes in patients with MASLD or MASH enrolled in the MAESTRO-NAFLD and MAESTRO-NASH clinical trials of resmetirom.[2] In both trials, patients completed the Liver Disease Quality of Life Questionnaire and Chronic Liver Disease Questionnaire-nonalcoholic fatty liver disease (CLDQ-NAFLD) at baseline, Week 24, and Week 52. Patients' data from these HRQL instruments were used to develop a surrogate Cognitive Function Self-Report domain. The domain asks patients to rate how often during the past 4 weeks they have had difficulties related to concentration, memory, and thinking. The validated CLDQ-NAFLD Worry domain was also assessed at baseline and during treatment.

Across the 2 trials, 2243 patients completed the HRQL instruments, including 50% with early MASH, 42% with F2 or F3 MASH, and 8% with MASH cirrhosis. Throughout

Table 1. Cognitive Function Self-Report Scores in Patients With MASH Treated With Resmetirom vs Placebo

	100 mg	80 mg	Placebo	All early MASH
Baseline (mean ± SD)	81.85 ± 19.96	80.51 ± 19.93	83.30 ± 17.75	81.86 ± 19.37
Week 24 (mean ± SD)	81.55 ± 19.47	81.58 ± 18.55	81.26 ± 19.24	81.48 ± 19.14
Change from baseline to week 24, mean (95% CI)	-0.20 (-1.77 to 1.37)	-0.06 (-1.83 to 1.71)	-2.95 (-4.86 to -1.04)[a]	-0.90 (-1.91 to 0.11)[a]
Week 52 (mean ± SD)	81.77 ± 19.20	80.81 ± 19.69	81.72 ± 18.35	81.50 ± 19.08
Change from baseline to week 52, mean (95% CI)	-0.55 (-2.18 to 1.08)	-1.51 (-3.50 to 0.48)	-2.66 (-4.69 to -0.63)[a]	-1.40 (-2.47 to -0.33)[a]

[a]Low score = bottom quartile in the study sample. MASH, metabolic dysfunction-associated steatohepatitis; SD, standard deviation.
Adapted from Younossi et al. Abstract P3697. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[2]

In this large cohort of patients with MASLD and MASH who were enrolled in the resmetirom phase 3 trials, a new Cognitive Function Self-Report domain was developed from health-related quality of life (HRQL) instruments. Patients treated with resmetirom maintained their Cognitive Function Self-Report domain score, whereas patients treated with placebo had a significant decrease in their score, indicating potential decline in their HRQL.

—Naim Alkhouri, MD

the study, Cognitive Function Self-Report scores were significantly higher in patients with early MASH than in patients with F2 or F3 MASH or those with cirrhosis, as were the CLDQ-NAFLD Worry domain scores.

Multiple factors were significantly and independently associated with low (in the bottom quartile) Worry scores: younger age, female sex, history of depression, and higher LSM. These factors, plus a history of clinically overt fatigue, also independently predicted low Cognitive Function Self-Report scores, which were significantly and strongly associated with overall HRQL.

During the 1-year resmetirom study, average Cognitive Function Self-Report scores declined in patients receiving placebo but did not decline in patients treated with 80 mg or 100 mg of resmetirom (Table 1). The Cognitive Function Self-Report and Worry domains capture different aspects of HRQL, and both patient characteristics and treatment can affect these domains. The Cognitive Function Self-Report domain has the potential to be used clinically as a practical way for tracking patient-perceived cognitive deficits.

References

1. Meroni M, Longo M, Paolini E, Dongiovanni P. A narrative review about cognitive impairment in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): another matter to face through a holistic approach. *J Adv Res*. 2025;68:231-240.
2. Younossi ZM, Nader F, Labriola D, et al. Changes in health-related quality of life, cognitive dysfunction, and worry domains in patients with MASLD and MASH treated with resmetirom. Abstract P3697. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.

Efficacy and Safety of Efruxifermin in Patients With MASH: A Meta-Analysis of Randomized Controlled Trials

Efruxifermin is a novel engineered fibroblast growth factor 21 (FGF21) fusion protein being evaluated for the treatment of MASH. Rajab and colleagues conducted a systematic review and meta-analysis of 4 randomized controlled trials of efruxifermin compared with placebo in patients with MASH to evaluate key histologic outcomes.[1]

The 4 trials analyzed were the phase 2b BALANCED study of 80 patients with MASH, the phase 2b HARMONY trial of 747 patients with MASH and F2 or F3 fibrosis, a study of a cohort of patients with MASH and stage 4 fibrosis from the BALANCED trial (n=30), and a phase 2b trial of 181 patients with MASH and compensated cirrhosis.[2-5]

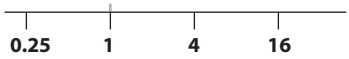
Efruxifermin was associated with significant improvements in multiple outcomes (Figure 3). Overall, 39.7% of patients receiving efruxifermin experienced an improvement in fibrosis stage by at least 1 category without MASH worsening, compared with 17.1% in the placebo arm (risk ratio [RR], 1.83; 95% CI, 1.17-2.84; *P*=.01). Patients receiving efruxifermin were also significantly more likely than those receiving placebo to attain MASH resolution without worsening (45.1% and 13.5%; RR, 2.42; 95% CI, 1.48-3.94) and to attain a combined outcome of MASH resolution and improvement (28.8% vs 4%; RR, 3.77; 95% CI, 1.10-12.87; *P*=.03).

Fibroblast growth factor 21 agonists such as efruxifermin have shown promising results in treating patients with at-risk MASH and those with MASH cirrhosis. This meta-analysis of 4 randomized controlled trials demonstrated the potential efficacy of efruxifermin in achieving histologic improvement in patients with MASH. Compared with placebo, efruxifermin was associated with higher rates of adverse events and discontinuation rate.

—Naim Alkhouri, MD

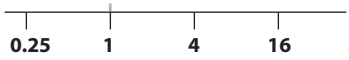
A ≥1 Stage fibrosis improvement

	Efruxifermin		Placebo		
Study	**Event**	**Total**	**Event**	**Total**	**Risk ratio (95% CI)**
Stage 2 or 3 fibrosis					
Harrison et al 2023	29	85	8	43	1.62 (0.80-3.30)
Harrison et al 2021	19	40	0	2	1.95 (0.15-25.14)
Heterogeneity: τ^2=0.00, I^2=0.00%, H^2=1.00					1.64 (0.83-3.26)
Stage 4 fibrosis					
Noureddin et al 2025	50	120	11	61	1.93 (1.07-3.48)
Harrison et al 2022	4	12	0	5	3.18 (0.20-50.67)
Heterogeneity: τ^2=0.00, I^2=0.00%, H^2=1.00					1.97 (1.10-3.51)
Overall					1.83 (1.17-2.84)



B MASH resolution without worsening

	Efruxifermin		Placebo		
Study	**Event**	**Total**	**Event**	**Total**	**Risk ratio (95% CI)**
Stage 2 or 3 fibrosis					
Harrison et al 2023	44	85	6	43	2.79 (1.27-6.12)
Harrison et al 2021	19	40	1	2	0.97 (0.19-4.99)
Heterogeneity: τ^2=0.13, I^2=22.99%, H^2=1.30					2.12 (0.85-5.26)
Stage 4 fibrosis					
Noureddin et al 2025	50	120	8	61	2.54 (1.27-5.07)
Harrison et al 2022	3	12	0	5	2.62 (0.16-43.63)
Heterogeneity: τ^2=0.00, I^2=0.00%, H^2=1.00					2.54 (1.30-4.98)
Overall					2.42 (1.48-3.94)



C MASH resolution and improvement

	Efruxifermin		Control		
Study	**Event**	**Total**	**Event**	**Total**	**Risk ratio (95% CI)**
Harrison et al 2023	25	85	2	43	5.11 (1.26-20.69)
Harrison et al 2021	11	40	0	2	1.33 (0.10-17.53)
Heterogeneity: τ^2=0.00, I^2=0.00%, H^2=1.00					3.77 (1.10-12.87)

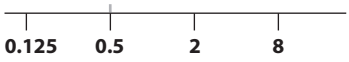


Figure 3. Efruxifermin significantly improved stage 1 or higher fibrosis without MASH worsening (A), MASH resolution without worsening (B), and combined MASH resolution and improvement (C), shown in a random effects DerSimonian Laird model.

MASH, metabolic dysfunction-associated steatohepatitis.

Adapted from Rajab et al. Abstract P5882. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[1]

ABSTRACT SUMMARY Semaglutide's Dose Dependent Effect on MASH Resolution: Updated Meta-Analysis of 5 RCTs With Histologic and Metabolic Improvements

The association between the dose of semaglutide and its effects on MASH-related outcomes was assessed in a meta-analysis that included 1366 patients with biopsy-proven MASH from 5 randomized controlled trials (Abstract P3740). Across 3 evaluable studies (n=1191), patients receiving semaglutide were significantly more likely than those receiving placebo to attain MASH resolution (OR, 4.56; 95% CI, 1.78-11.67). Moreover, there was a nonsignificant trend toward a higher likelihood of attaining fibrosis improvement with semaglutide vs placebo (OR, 1.56; 95% CI, 0.55-4.41). A comparison of dosing in a phase 2 trial and the phase 3 ESSENCE trial found that semaglutide dosed at 0.4 mg/day was associated with a 26.2% increase in the likelihood of attaining MASH resolution compared with standard 2.4 mg/week dosing. Assessments of changes in MRI-PDFF, body weight, and ALT/AST levels across the 5 trials found consistent benefits with use of semaglutide. Additional research is needed to further characterize the long-term dose-response relationship of semaglutide and the optimal treatment duration in patients with MASH.

The likelihood of attaining a fibrosis improvement of at least 2 stage categories was not significantly different between arms.

In the safety analysis, the incidence of drug-related AEs was significantly higher with efruxifermin vs placebo (71.2% vs 43.7%; RR, 1.35; 59% CI, 1.06-1.71; $P<.05$), as was the rate of discontinuations owing to AEs (10.3% vs 2.2%; RR, 3.13; 95% CI, 1.12-8.76; $P<.05$). Rates of serious AEs, deaths, and overall treatment-emergent AEs were not significantly different between arms.

The meta-analysis suggests that efruxifermin may have a therapeutic role in MASH, and toxicities appear manageable. However, additional randomized trials are needed to establish its efficacy and safety in the long term.

References

1. Rajab I, Elgendy MS, Emara A, et al. Efficacy and safety of efruxifermin in patients with MASH: a meta-analysis of randomized controlled trials. Abstract P5882. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.
2. Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat Med*. 2021;27(7):1262-1271.
3. Harrison SA, Frias JP, Neff G, et al; HARMONY Study Group. Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol*. 2023;8(12):1080-1093.
4. Noureddin M, Rinella ME, Chalasani NP, et al. Efruxifermin in compensated liver cirrhosis caused by MASH. *N Engl J Med*. 2025;392(24):2413-2424.
5. Harrison SA, Ruane PJ, Freilich B, et al. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. *JHEP Rep Innov Hepatol*. 2022;5(1):100563.

Distinct Lipid and Liver Enzyme Trajectories in Diabetic vs Nondiabetic MASLD/MASH Patients Treated With Resmetirom: A Multicenter Propensity-Matched Analysis

Diabetes mellitus and MASLD share overlapping pathophysiologies and often co-occur.[1] Treatment with resmetirom has been shown to reduce liver fat and improve lipid profiles, including low-density lipoprotein (LDL) levels.[2] Lee and colleagues compared laboratory parameters over time in MASLD/MASH patients with or without DM who were prescribed resmetirom.[3] After propensity score matching to adjust for age, race, gender, BMI, and use of lipid-lowering agents, the cohort included 461 patients with DM and 461 patients without DM.

Mean laboratory trends were compared at baseline and at 1 month, 6 months, and 12 months using a cox proportional hazards model. Patients with DM treated with resmetirom had statistically lower LDL and total cholesterol levels at all time points ($P<.05$) (Table 2). High-density lipoprotein levels were not significantly different after the baseline reading, whereas triglyceride levels between the patients

These results are consistent with the results that have been seen in the MAESTRO-NASH trial in terms of improvement in total cholesterol and LDL cholesterol and the fact that patients are expected to experience a slight increase in ALT and AST after 1 month of treatment with resmetirom. However, the results do not support a clear distinction between diabetics and nondiabetics, and the authors should consider adjusting for concomitant medications and glycemic control.

—Naim Alkhouri, MD

Table 2. Laboratory Parameters Compared at Various Time Points in Resmetirom Patients With and Without Diabetes

Lab value[a]	Cohort	Baseline (mean ± SD)	*P*	1 month (mean ± SD)	*P*	6 month (mean ± SD)	*P*	12 month (mean ± SD)	*P*
ALT	DM No DM	52.8 ± 36.9 48.2 ± 32.3	.06	52.3 ± 49.2 85.9 ± 180.6	.1	48.2 ± 36.2 61.2 ± 106.3	.08	46.1 ± 36.2 57.7 ± 103.3	.1
AST	DM No DM	42.4 ± 23.2 43.9 ± 30.7	.08	42.5 ± 28.4 59.8 ± 69.4	.06	38.3 ± 23.2 45.6 ± 44.9	.03	37.6 ± 24.4 43.7 ± 43.6	.06
LDL	DM No DM	72.2 ± 23.3 105.3 ± 41.1	.03	67.5 ± 40.1 108.7 ± 50.7	.004	73 ± 36.3 93.8 ± 49.1	.001	70.2 ± 31 92.7 ± 45.2	.0001
HDL	DM No DM	42.2 ± 8.2 57 ± 13.9	.006	39.9 ± 13.3 47.3 ± 16.6	.1	42.5 ± 13.7 44.8 ± 13.7	.2	42.1 ± 13.2 44.9 ± 13.9	.09
Cholesterol	DM No DM	142.4 ± 33.3 190.1 ± 46.4	.01	146.4 ± 48 182.2 ± 55.8	.02	145.3 ± 49.9 165.3 ± 53.5	.006	140.8 ± 44.6 163.5 ± 49.8	.0001
Triglyceride	DM No DM	148.4 ± 62.1 145.9 ± 57.3	.09	187.6 ± 88.2 140.3 ± 68.5	.05	162.8 ± 100.1 140.7 ± 85	.07	155.3 ± 91.7 141.2 ± 84.5	.2

[a]Gamma-glutamyl transferase (not shown) declined in both groups over 12 months; however, the greater reduction in diabetics was not statistically significant at each following time point. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Adapted from Lee et al. Abstract P5899. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[3]

with and without DM were only statistically different at 1 month.

The trajectories of ALT and AST differed between the 2 cohorts, with non-DM patients having a nonsignificant transient increase in the liver enzyme levels at 1 month, and patients with DM having stable levels throughout. Both groups of patients had improved AST and ALT at 6 and 12 months, but only AST was statistically significant at 6 months ($P<.05$).

The findings suggest distinct biochemical response patterns to resmetirom based on DM status of patients with MASLD/MASH. Additional research should assess whether glycemic control, insulin resistance, or antidiabetic therapies may affect the efficacy of resmetirom and lead to better outcomes.

References

1. Leith D, Lin YY, Brennan P. Metabolic dysfunction-associated steatotic liver disease and type 2 diabetes: a deadly synergy. *TouchREV Endocrinol*. 2024;20(2):5-9.
2. Harrison SA, Bedossa P, Guy CD, et al; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med*. 2024;390(6):497-509.
3. Lee R, Totah F, Solaimani P. Distinct lipid and liver enzyme trajectories in diabetic vs nondiabetic MASLD/MASH patients treated with resmetirom: a multicenter propensity-matched analysis. Abstract 5899. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.

Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in MASH Resolution and Fibrosis Reduction: A Meta-Analysis

Glucagon-like peptide-1 (GLP-1) receptor agonists have now been evaluated in patients with MASH in multiple randomized trials. To better understand the efficacy and safety of these agents in patients with MASH, Tripathi and colleagues conducted a meta-analysis of 6 randomized controlled trials.[1] The dataset included a study of liraglutide vs placebo in 14 patients with MASH; a phase 2 trial of semaglutide 2.4 mg once weekly vs placebo in 71 patients with MASH and compensated cirrhosis; the phase 2 SYNERGY-NASH trial of tirzepatide in 190 patients with MASH and stage F2 or F3 fibrosis; the phase 2 NN931-4296 trial of semaglutide vs placebo in 320 patients with MASH and F1 to F3 fibrosis; the phase 2 1404-0043 trial of survodutide vs placebo in 293 patients with MASH and F1 to F3 fibrosis; and the phase

GLP-1 receptor agonists have revolutionized the treatment of diabetes and obesity. In this systematic review, the authors analyzed data from 6 randomized controlled trials that included 1273 patients and demonstrated positive effects of GLP-1 receptor agonists on MASH resolution and fibrosis improvement with a good safety profile.

—Naim Alkhouri, MD

	GLP-1		Placebo		Odds ratio	
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**M-H, fixed (95% CI)**	
Armstrong 2016	9	23	2	22	6.43 (1.20-34.41)	
Loomba 2023	16	47	5	24	1.96 (0.62-6.23)	
Loomba 2024	30	48	5	48	14.33 (4.79-42.85)	
Newsome 2021	33	56	10	58	6.89 (2.90-16.35)	
Sanyal 2024	32	74	10	73	4.80 (2.13-10.79)	
Sanyal 2025	336	534	91	266	3.26 (2.40-4.44)	
Total		**782**		**491**	**3.94 (3.06-5.08)**	
Total events	456		123			
					0.01 0.1 1 10 100 Favors GLP-1 Favors placebo	
Heterogeneity: Chi^2 = 10.34, df = 5 (*P*=.07); I^2 = 52%						

Figure 4. Association of GLP-1 receptor agonists vs placebo with regards to MASH resolution.
GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; M-H, fixed, Mantel-Haenszel fixed-effects method.
Adapted from Tripathi et al. Abstract P3746. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[1]

3 ESSENCE trial of semaglutide vs placebo in 1196 patients with MASH and F2 to F3 fibrosis.[2-7]

A total of 1273 patients, 782 receiving GLP-1 receptor agonists and 491 receiving placebo, met the inclusion criteria. Patients were followed for an average of 57 weeks; the median patient age was 54 years, and 45% were male. Overall, patients receiving GLP-1 receptor agonists were significantly more likely than those receiving placebo to have resolution of MASH (odds ratio [OR], 3.94; 95% CI, 3.06-5.08; *P*<.0001) (Figure 4). Improvements in fibrosis were also associated with the GLP-1 receptor agonists compared with placebo in 5 of the 6 studies (OR, 1.81; 95% CI, 1.40-2.35; *P*<.0001). Gastrointestinal AEs, including nausea, vomiting, and diarrhea, occurred at a significantly higher rate in patients receiving GLP-1 receptor agonists than in patients receiving placebo (OR, 14.34; 95% CI, 7.98-25.79) across 3 studies.

The meta-analysis demonstrated that GLP-1 receptor agonists compared with placebo significantly enhance improvement of fibrosis in patients with MASH, suggesting that they have a role in mitigating disease progression. The results support the inclusion of GLP-1 receptor agonists into clinical management guidelines, granted that further studies assess their long-term safety and effectiveness.

ABSTRACT SUMMARY Incretin-Based Therapies in MASH: A Meta-Analysis of Hepatic and Metabolic Outcomes

A meta-analysis of 6 randomized controlled trials of incretin-based therapy in MASH was reported (Abstract P1582). The trials evaluated GLP-1 receptor agonist therapy (semaglutide), dual GLP-1 and glucagon agonists (pemvidutide, survodutide, and cotadutide), the GLP-1 + GIP agonist tirzepatide, and the triple agonist retatrutide. All included trials involved a treatment period of 12 or more weeks and assessed liver fat (by MRI-PDFF, liver fat content, or hepatic fat fraction). The analysis found significant reductions in liver fat in patients receiving incretin-based therapies, with results suggesting a dose-response effect. Across all agents tested, the pooled mean reduction in liver fat was 50%, which was a clinically meaningful effect. The greatest reductions, up to 83%, were observed with the triple agonist retatrutide 12 mg, followed by the dual GLP-1/glucagon agonists pemvidutide 1.8 mg (64%) and survodutide 6 mg (60%), followed by the GLP-1/GIP agonist tirzepatide 15 mg (47%). Semaglutide 2.4 mg was associated with a 39% reduction in liver fat, and the dual agonist cotadutide 0.6 mg was associated with a 27% reduction. In most studies, the risk of bias was considered low to moderate, however, there was substantial heterogeneity between studies.

References

1. Tripathi R, Gupta S, Jarnes L, Zeidan N, Tao M, Jamorabo D. Efficacy of GLP-1 receptor agonists in MASH resolution and fibrosis reduction: a meta-analysis. Abstract P3746. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.

2. Armstrong MJ, Hull D, Guo K, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *J Hepatol.* 2016;64(2):399-408.
3. Loomba R, Abdelmalek MF, Armstrong MJ, et al; NN9931-4492 investigators. Semaglutide 2.4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol.* 2023;8(6):511-522.
4. Loomba R, Hartman ML, Lawitz EJ, et al; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med.* 2024;391(4):299-310.
5. Newsome PN, Buchholtz K, Cusi K, et al; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384(12):1113-1124.
6. Sanyal AJ, Bedossa P, Fraessdorf M, et al; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med.* 2024;391(4):311-319.
7. Sanyal AJ, Newsome PN, Kliers I, et al; ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med.* 2025;392(21):2089-2099.

Real-World Safety and Monitoring Practices in Patients Receiving Resmetirom for MASH: A Single Center Retrospective Review

This study adds to the existing literature on the safety and efficacy of resmetirom in the real-world settings outside of clinical trials. It was interesting to see that while the majority of patients had their liver enzymes checked periodically, only a small percentage of patients had their thyroid function tests followed over time.

—Naim Alkhouri, MD

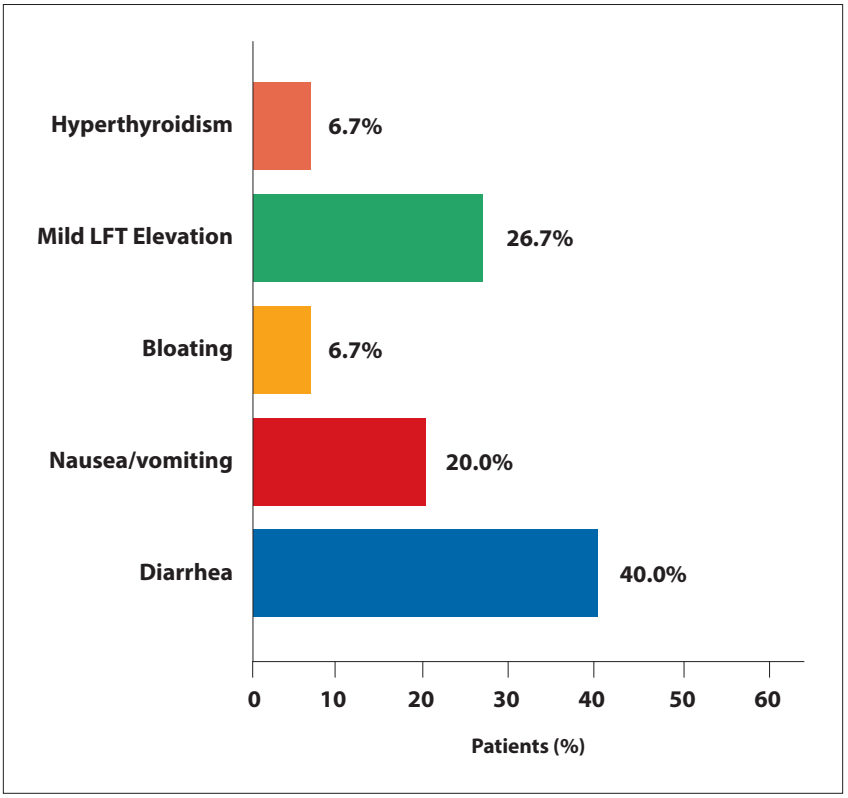


Figure 5. Documented adverse events after resmetirom start in patients with metabolic dysfunction-associated steatohepatitis.

LFT, left function test.

Adapted from Lora et al. Abstract P5938. Presented at: ACG 2025; October 24-29, 2025; Phoenix, Arizona.[1]

Although resmetirom demonstrated encouraging tolerability in clinical trials, there is limited evidence regarding safety outcomes and adherence to laboratory monitoring guideline recommendations among patients receiving resmetirom in clinical practice. Lora and colleagues presented results of a retrospective analysis evaluating patient characteristics, treatment duration, AEs, and adherence to laboratory monitoring guidelines in patients with MASH receiving resmetirom at a single academic center.[1]

The cohort initially included 56 patients who were prescribed resmetirom. However, 9 patients (16%) were excluded after they did not initiate resmetirom owing to insurance denial, and 13 additional patients were excluded because they had not started resmetirom or had no accessible laboratory data. The mean age of enrolled patients was 55 years, average BMI was 36.2 kg/m^2, and 44% were male. Most patients were Hispanic (44.1%) or White (35.3%); 1 patient (2.9%) was Black and the remaining 6 (17.7%) were other races/ethnicities. The mean duration of resmetirom therapy was 236.6 days.

At baseline, the mean fibrosis score (assessed in 27 patients) was F1 to F2 in 4 patients (14.8%), F2 in 3 patients (11.1%), F2 to F3 in 5 patients (18.5%), F3 in 9 patients (33.3%), F3 to F4 in 5 patients (18.5%), and F4 in 1 patient (3.7%). Mean NAFLD fibrosis scores did not change significantly from baseline to 3 to 6 months, likely because of short follow-up.

AEs were reported in 15 patients

ABSTRACT SUMMARY Safety and Efficacy of Semaglutide in MASLD and MASH: A Systematic Review and Meta-Analysis

A meta-analysis assessed the efficacy and safety of semaglutide in MASLD and MASH patients using a random-effects model in R and performing sensitivity and publication bias analyses (Abstract P1558). In the comparative analysis, semaglutide was associated with significant reductions in CAP score, ALT, AST, BMI, and A1c vs the control arm. Changes in liver stiffness were only significant after excluding for outliers. In the single-arm analysis, semaglutide was associated with reductions in CAP score, FIB-4, ALT, AST, BMI, A1c, and cholesterol. The single-arm analysis was characterized by moderate to high heterogeneity and minimal to moderate bias. In patients with MASLD/MASH, semaglutide was associated with significant improvements in liver fat and metabolic markers but limited effects on fibrosis, suggesting that patients with concomitant obesity or diabetes may gain the most benefit from semaglutide.

(44.1%) (Figure 5). The most common toxicities were gastrointestinal, with diarrhea being the most frequent (40%), followed by nausea/vomiting (20%) and bloating (6.7%). Other documented AEs included mild liver function test elevation (26.7%) and hyperthyroidism (6.7%). The 3 documented discontinuations from toxicity were all attributed to diarrhea.

Monitoring practices varied; although liver enzymes were tested at baseline and at 3 to 6 months in 70% of patients, thyroid function was only assessed in 38% of patients at baseline and in 14% at follow-up. In the one patient with preexisting hyperthyroidism, the dose of levothyroxine was adjusted after starting resmetirom.

Resmetirom was generally well tolerated, but there was a notable incidence of gastrointestinal events, especially diarrhea. The authors noted that monitoring practices frequently did not meet guidelines recommended by the American Association for the Study of Liver Diseases.

Reference

1. Lora DR, Blumenstein A, Post Z, Reau N. Real-world safety and monitoring practices in patients receiving resmetirom for MASH: a single-center retrospective review. Abstract P5938. Presented at: ACG 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona.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