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A SPECIAL MEETING REVIEW EDITION

Highlights in MASH From the American College of Gastroenterology 2026 Annual Scientific Meeting

A Review of Selected Presentations From the ACG 2026 Annual Scientific Meeting
October 9-14, 2026 • Nashville, Tennessee

Special Reporting on:

- Machine Learning Models of Noninvasive Tests to Predict MASH and Fibrosis Stage Based on MAESTRO-NAFLD-1 and MAESTRO-NASH Liver Biopsies
- Efruxifermin Induced a Rapid and Direct Antifibrotic Response That Was Sustained Through 96 Weeks in Phase 2b Trials of Participants With MASH and F2/F3 Fibrosis or Cirrhosis
- Reducing Cardiovascular Risk in Patients With MASH Independent of Baseline Based on Lipoprotein(a) and Low-Density Lipoprotein Lowering by Resmetirom
- Semaglutide and Tirzepatide Are Associated With Lower Risk of Cirrhosis and Liver Decompensation in MASH
- Efruxifermin in MASH With F2/F3 Fibrosis: Post Hoc Analysis Indicated Early Histologic Features of Regression Were Associated With Week 96 Fibrosis Improvement

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.

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 Interaction Effects of Strong or Moderate CYP2C8 Inhibitors on Rezdiffra

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

Please see Brief Summary on the following pages and full Prescribing Information at https://www.madrigalpharma.com/Rezdiffra-us-prescribing-information.

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



IMPROVING FIBROSIS & MASH is no longer wishful thinking.

Rezdiffra is the **first and only** treatment for MASH with moderate to advanced fibrosis that **activates THR-β directly in the liver**[1]

For adults with noncirrhotic MASH with moderate to advanced fibrosis, in conjunction with diet and exercise. 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.

Liver-Directed[1]

Dual Efficacy[1]

Demonstrated Safety[1]

Oral, Once-Daily Dosing[1]

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

MASH=metabolic dysfunction-associated steatohepatitis.

IMPORTANT SAFETY INFORMATION (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 to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Report pregnancies to Madrigal Pharmaceuticals, Inc. Adverse Event Reporting line at 1-800-905-0324 and visit https://pregnancyregistry.madrigalpharma.com for information about a pregnancy safety study.

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

The recommended dosage of Rezdiffra in patients with mild, moderate, or severe renal impairment is the same as in patients with normal kidney function.

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 of Rezdiffra 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 MASH with liver fibrosis (F2 or F3). Patients were randomized 1:1:1 to Rezdiffra (80 mg or 100 mg) or placebo to evaluate the efficacy and safety at 52 weeks.[1,2]

*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]

THR-β=thyroid hormone receptor beta.

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

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US-PP-RES-00716-v3 02/26

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 than 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 or https://pregnancyregistry.madrigalpharma.com.

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 of REZDIFFRA in patients with mild, moderate, or severe renal impairment is the same as in patients with normal kidney function *[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.

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Machine Learning Models of Noninvasive Tests to Predict MASH and Fibrosis Stage Based on MAESTRO-NAFLD-1 and MAESTRO-NASH Liver Biopsies

Metabolic dysfunction-associated steatotic disease (MASLD) can progress to metabolic dysfunction-associated steatohepatitis (MASH), a progressive liver disease associated with hepatic inflammation, hepatocyte ballooning, and varying degrees of fibrosis.[1] In patients with MASH, advanced fibrosis is associated with a higher risk of adverse clinical outcomes, including hepatocellular carcinoma.[2] As a result, there is a need to accurately assess the extent of fibrosis in patients with MASH.

The gold standard approach for assessing hepatic fibrosis is liver biopsy; however, biopsy is associated with limitations, including high costs, susceptibility to sampling error, variability in pathologic interpretation, and a risk of procedure-related adverse outcomes.[1] There has been significant interest in the development of noninvasive biomarker tests as alternatives to serial liver biopsies.[3]

Loomba and colleagues developed machine learning methods to predict MASH and/or the extent of fibrosis using various noninvasive tests in

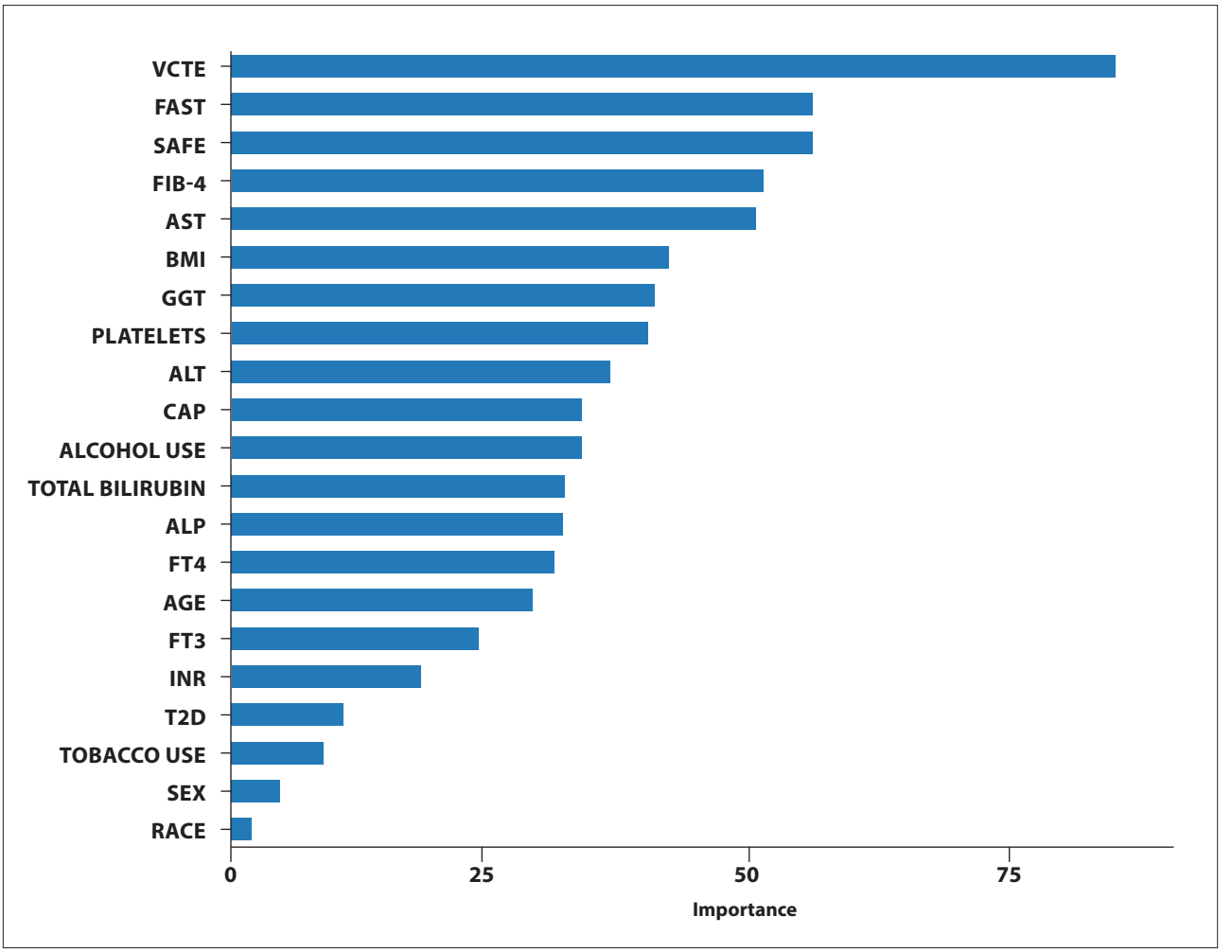


Figure 1. Lean model 1, random forest–based variable importance for fibrosis stage prediction, showing the factors that contributed most to predicting fibrosis stage, from a retrospective analysis of the MAESTRO-NAFLD-1 and MAESTRO-NASH trials. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter score; FAST, FibroScan-AST; FIB-4; Fibrosis-4 index; FT3, free triiodothyronine; FT4, free thyroxine; GGT, gamma-glutamyl transferase; INR, international normalized ratio; SAFE, Steatosis-Associated Fibrosis Estimator Score; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography. Adapted from Loomba R, et al. Abstract P6074. Presented at: ACG 2026; October 9-14, 2026; Nashville, Tennessee.[3]

patients with MASLD.[3] The authors retrospectively analyzed data from 1970 biopsy-confirmed patients in the phase 3 MAESTRO-NASH and MAESTRO-NAFLD-1 trials who met the criteria of having 3 of 4 defined metabolic risk factors (diabetes/insulin resistance, hypertension, obesity/overweight, and dyslipidemia) and with evidence of hepatic steatosis and fibrosis from recent assessments.

Two outcomes were accessed: fibrosis stage, categorized as F0/F1, F2/F3, or F4; and the presence of MASH with F2/3 fibrosis, or at-risk MASH, which was defined as a baseline nonalcoholic fatty liver disease activity score (NAS) of 4 or higher and moderate to advanced fibrosis without cirrhosis. Models were developed using the random forest method for the full predictor model that incorporated 37 demographic and clinical variables and a lean model that included 20 to 24 routinely available parameters.

Among the 1970 patients included, 71.8% had moderate to advanced fibrosis and 74.7% had MASH (baseline NAS ≥4). Investigators reported that the machine learning models accurately predicted fibrosis stage and MASH with F2/F3 fibrosis. Using the full data model, the cross-validation mean area under the curve (AUC) for predicting the 3 fibrosis categories was 0.76 for predicting F0/F1, 0.75 for predicting F2/F3, and 0.94 for predicting F4. The investigators noted the particularly high mean AUC of 0.94 for discriminating patients with cirrhosis (F4). Using the best-performing lean model (Figure 1), the mean AUCs for predicting F0/F1, F2/F3, and F4 were 0.83, 0.78, and 0.89, respectively.

> The main limitation of these new machine learning models for predicting fibrosis stage and diagnosing MASH with F2/F3 fibrosis is the need for imaging with VCTE or MRE, which is not readily available. These models need to be validated in real-world practice and outside of clinical trial settings.
>
> — Naim Alkhouri, MD

The mean AUC for predicting MASH with significant (stage F2/F3) liver fibrosis was 0.75 using the full model and 0.79 using the lean model. The sensitivity of the full model for predicting F4 fibrosis was 82.3% and the negative predictive value (NPV) was 98.1%. The lean model 1 was found to perform as well as the full model for sensitivity (72.5% vs 65.3%), specificity (73.7% vs 71.1%), positive predictive value (PPV) (78.3% vs 74.6%), and NPV (67.4% vs 61.2%). The factors that contributed most to predicting fibrosis stage were liver stiffness measures from imaging with magnetic resonance elastography (MRE) or vibration-controlled transient elastography (VCTE) and MASH composite algorithms such as FAST score (FibroScan measurements with aspartate aminotransferase levels), SAFE (Steatosis-Associated Fibrosis Estimator), and FIB-4 (Fibrosis-4) index.

The findings support potential use of machine learning models of noninvasive biomarkers to identifying patients with MASH and moderate to advanced liver fibrosis for clinical trial enrollment. However, the authors cautioned that there is a need for additional external and prospective validation of these tools before implementing them in clinical practice.

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Efruxifermin Induced a Rapid and Direct Antifibrotic Response That Was Sustained Through 96 Weeks in Phase 2b Trials of Participants With MASH and F2/F3 Fibrosis or Cirrhosis

Efruxifermin, an investigational fibroblast growth factor 21 analog, has been evaluated in two randomized phase 2b trials of patients with MASH. In the HARMONY trial in patients with moderate or severe (F2/F3) fibrosis, efruxifermin was associated with a significant improvement in fibrosis at Week 24 (the primary outcome) and at Week 96.[1] In the SYMMETRY trial in patients with compensated cirrhosis (F4c), efruxifermin was not associated with a significant improvement in fibrosis at Week 36 (the primary outcome) but was associated with a significant improvement at Week 96.[2]

Sanyal and colleagues evaluated the time course of fibrosis improvement with efruxifermin in patients enrolled in the HARMONY and SYMMETRY trials.[3]

The HARMONY trial enrolled 126 patients with F2/F3 MASH who

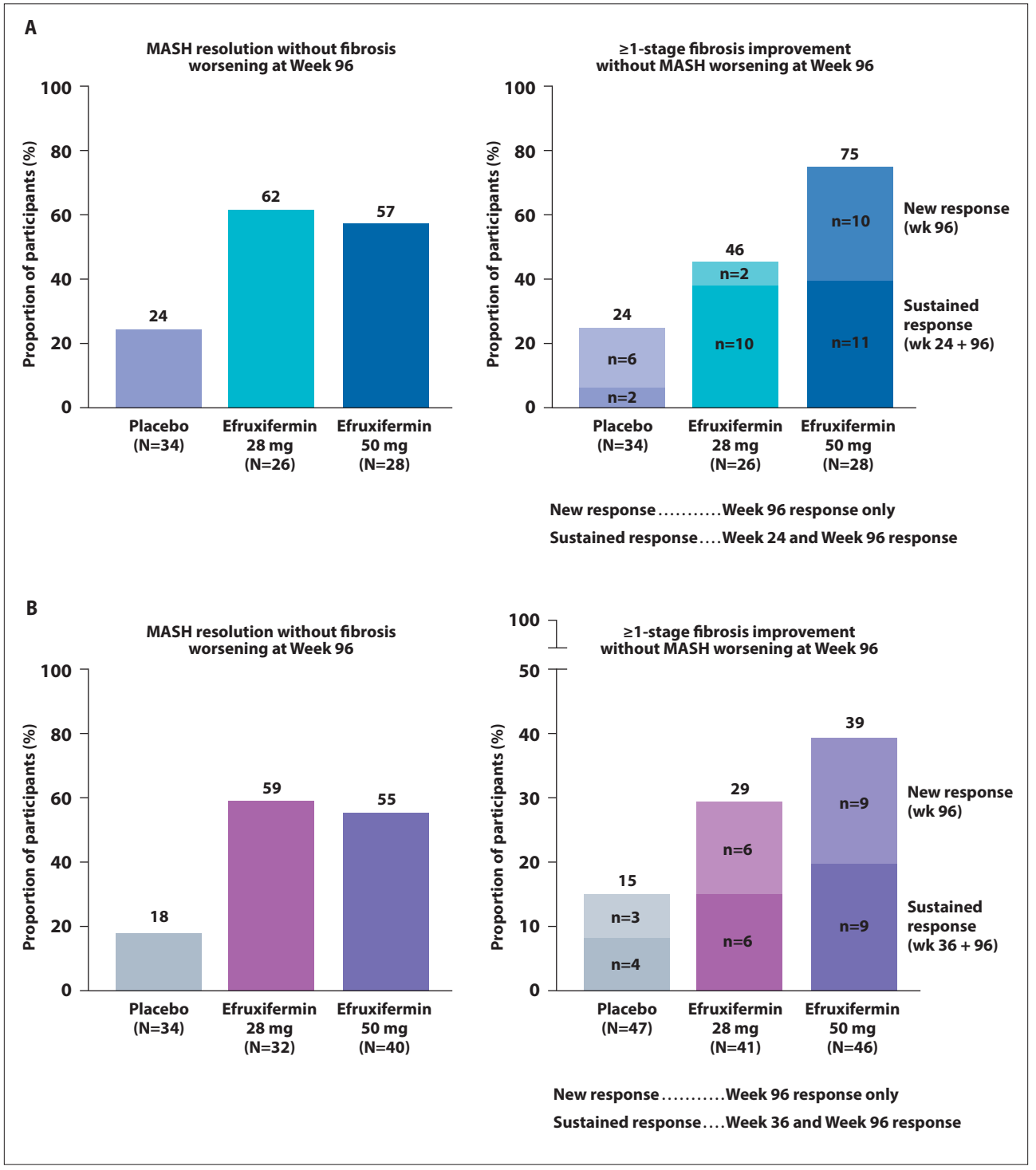


Figure 2. Efruxifermin improved MASH and fibrosis through 96 weeks in the phase 2b HARMONY (A) and SYMMETRY (B) trials. MASH, metabolic dysfunction-associated steatohepatitis. Adapted from Sanyal AJ, et al. Abstract 28. Presented at: ACG 2026; October 9-14, 2026; Nashville, Tennessee.[3]

were randomly assigned to efruxifermin 28 mg (n=40), efruxifermin 50 mg (n=43), or placebo (n=43).[1] The mean age of enrolled patients was 55 years; 62% of patients were female, 70% had type 2 diabetes, 16% were receiving a glucagon-like peptide-1 receptor agonist (GLP-1 RA), and the mean body mass index (BMI) was 38 kg/m^2. Week 96 liver biopsies were available for 88 patients.

In the HARMONY trial, at Week 96, rates of MASH resolution without fibrosis worsening were 62% and 57% in the efruxifermin 28 mg and

Efruxifermin demonstrated robust antifibrotic effects after 96 weeks of treatment, including improvement by 1 fibrosis stage or more in up to 75% of patients with F2/F3 fibrosis and reversal of cirrhosis in up to 39% of patients with MASH cirrhosis, providing further support for the possibility of reversing disease even in the most advanced cases. The adverse events were mainly gastrointestinal, but there was a reduction in bone density as well.

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50 mg arms and 24% in the placebo arm (*P*<.001 for each efruxifermin group vs placebo).[3] Improvement in fibrosis of at least 1 stage without MASH worsening occurred in 46% of patients receiving efruxifermin 28 mg (12/26), including 10 patients (38%) with a sustained response at Weeks 24 and 96 and 2 patients (8%) with a new response at Week 96. In the efruxifermin 50-mg arm, 75% of patients (21/28) attained an improvement in fibrosis of at least 1 stage without MASH worsening (*P*<.001 vs placebo), including 11 patients (42%) with a sustained response at Weeks 24 and 96 and 10 patients (38%) with a new response at Week 96. In the placebo arm, 24% of patients had an improvement in fibrosis of at least 1 stage without MASH worsening at Week 96 (Figure 2, A).

The SYMMETRY trial enrolled 181 patients with F4c MASH who were randomly assigned to efruxifermin 28 mg (n=57), efruxifermin 50 mg (n=63), or placebo (n=61).[2] The mean age of enrolled patients was 61 years; 67% were female, 80% had type 2 diabetes, 35% were receiving a GLP-1 RA, and the mean BMI was 36 mg/m^2. Week 96 liver biopsies were available for 134 patients.

In the SYMMETRY trial, at Week 96, rates of MASH resolution without fibrosis worsening were 59% and 55% with efruxifermin 28 mg and 50 mg, respectively, and 18% in the placebo arm (*P*<.001 and *P*<.01, respectively). Improvement in fibrosis of at least 1 stage without MASH worsening occurred in 29% of patients receiving efruxifermin 28 mg (12/41), including 6 patients (14.6%) with a sustained response at Weeks 36 and 96 and 6 patients (14.6%) with a new response at Week 96. In the efruxifermin 50-mg arm, 39% of patients (18/46) attained an improvement in fibrosis of at least 1 stage without MASH worsening (*P*<.01 vs placebo), including 9 patients (19.5%) with a sustained response at Weeks 36 and 96 and 9 patients (19.5%) with a new response at Week 96. In the placebo arm, 15% of patients had an improvement in fibrosis of at least 1 stage without MASH worsening at Week 96 (Figure 2, B).

In both trials, efruxifermin was associated with rapid reductions in liver stiffness by VCTE that improved over time. In the HARMONY trial, the mean change in liver stiffness from baseline to Week 96 was +1% with placebo, -20% with efruxifermin 28 mg (*P*<.05 vs placebo), and -39% with efruxifermin 50 mg (*P*<.001 vs placebo). In the SYMMETRY trial, the mean change in liver stiffness from baseline to Week 96 was -10% with placebo, -19% with efruxifermin 28 mg, and -25% with efruxifermin 50 mg (*P*<.05 vs placebo).

Liver fibrosis as assessed using the Enhanced Liver Fibrosis (ELF) score also improved significantly and rapidly with efruxifermin. In both trials, improvements from baseline in mean ELF score were significantly greater with either efruxifermin dose compared with placebo at Week 24 and these differences were sustained at Week 96.

The most common adverse events across both trials were gastrointestinal, including diarrhea and nausea. Investigators noted that these were mild to moderate, transient, and generally occurred early in the treatment course. There were reports of increased appetite, but mean body weight did not generally change. Small but statistically significant reductions in bone mineral density at Week 96 were also reported, although investigators noted that the clinical relevance of these is to be determined, and the incidence of fractures was not increased. Markers of liver function and hemostasis were stable.

Efruxifermin was associated with improvements in MASH and fibrosis in patients with MASH and F2/F3 fibrosis or compensated cirrhosis. Most early responses were maintained for 96 weeks, and some patients without an early response gained a response by Week 96. Ongoing phase 3 trials evaluating efruxifermin in patients with MASH include the SYNCHRONY Histology trial in patients with F2/F3 fibrosis (NCT06215716) and the SYNCHRONY Outcomes trial in patients with compensated cirrhosis (NCT06528314).

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Reducing Cardiovascular Risk in Patients With MASH Independent of Baseline Based on Lipoprotein(a) and Low-Density Lipoprotein Lowering by Resmetirom

MASH is associated with a high prevalence of cardiovascular (CV) disease driven partially by atherogenic dyslipidemia.[1,2] Resmetirom, a thyroid hormone receptor-β agonist, is indicated in conjunction with diet and exercise for treatment of adults with MASH with moderate to advanced liver scarring without cirrhosis.[3] In the randomized phase 3 MAESTRO-NASH and MAESTRO-NAFLD-1 trials, resmetirom was associated with significant reductions in atherogenic lipid and lipoprotein (Lp) levels, including low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and Lp(a), in patients with MASH.[4,5]

Bansal and colleagues presented the results of an analysis of the effects of resmetirom on lipid-related parameters and safety based on use of statins at baseline among patients in the MAESTRO-NASH trial.[6] The analysis included patients with fibrosis stages F1B, F2, and F3 who were randomly assigned to resmetirom 80 mg, resmetirom 100 mg, or placebo.

Because the blinded MAESTRO-NASH trial is still ongoing, a pharmacokinetic analysis was not completed on this population. Instead, pharmacokinetics were analyzed for patients in MAESTRO-NAFLD-1, a completed 52-week trial that enrolled a similar population of patients with MASLD without cirrhosis.[5]

Of the 473 patients enrolled in MAESTRO-NASH, 49% were receiving statins at baseline—most commonly atorvastatin—and 26.9% were receiving high-intensity statin therapy. Compared with patients not receiving statins, those receiving statins were more likely to have diabetes (79.5% vs 55.0%), dyslipidemia (100% vs 43.8%), and advanced fibrosis (F3: 64.3% vs 56.6%).

In a modified intention-to-treat analysis, the dual primary endpoints from MAESTRO-NASH at Week 52 of MASH resolution (defined as a reduction in NAS by ≥2 points) and improvement in fibrosis (by ≥1 stage with no worsening of NAS) were similar regardless of baseline statin

> Although many patients with MASLD are treated with statins and other lipid-lowering agents, CV disease remains the most common cause of death in these patients. The authors of this study demonstrated that resmetirom significantly lowered atherogenic lipid levels independent of baseline statin use. These findings support the need to design a large CV outcomes trial with resmetirom in patients with MASLD at high risk for major adverse CV events.
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> — Naim Alkhouri, MD

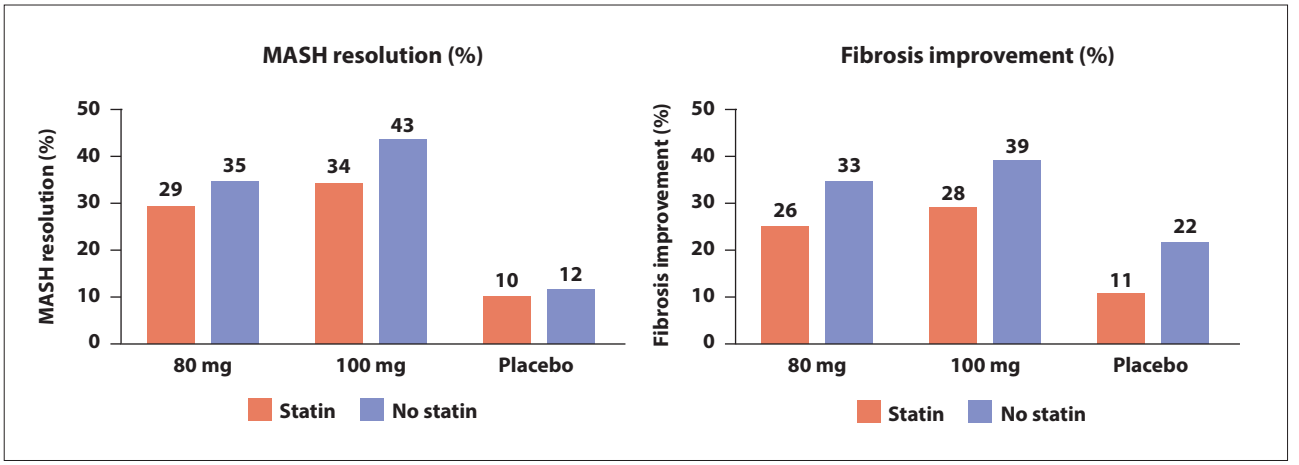


Figure 3. Dual liver biopsy primary endpoints at Week 52 by statin use from a secondary analysis of the phase 3 MAESTRO-NASH clinical trial. MASH, metabolic dysfunction-associated steatohepatitis. Adapted from Bansal M, et al. Abstract P6267. Presented at: ACG 2026; October 9-14, 2026; Nashville, Tennessee.[6]

ABSTRACT SUMMARY Cardiovascular Outcomes of Resmetirom vs Semaglutide in Patients With MASLD/MASH: A Propensity-Matched Real-World Analysis

Cardiovascular outcomes with resmetirom vs semaglutide were evaluated in patients with MASLD/MASH and hepatic fibrosis from the TriNetX database in a retrospective propensity-matched cohort study (Abstract P4038). The study included 6140 patients receiving resmetirom and 71,285 patients receiving semaglutide before matching, and 4253 patients per group after matching for demographic and clinical variables. At 1 year, resmetirom was associated with significant improvements over semaglutide in rates of major adverse CV events (MACE), including myocardial infarction (MI), atrial fibrillation (AF), and heart failure (HF) (HR, 0.50; 95% CI, 0.32-0.80; *P*=.003), all-cause mortality (HR, 0.29; 95% CI, 0.16-0.54; *P*<.001), and HF (HR, 0.64; 95% CI, 0.42-0.99; *P*=.042). At 2 years, resmetirom was associated with improvements over semaglutide in rates of MACE (HR, 0.61; 95% CI, 0.41-0.89; *P*=.011) and all-cause mortality (HR, 0.33; 95% CI, 0.20-0.55; *P*<.001) but not a significant difference in AF or HF. Differences in MI rates were not significant between groups at either time point. The researchers concluded that resmetirom may provide a cardiovascular benefit beyond its hepatic effects but added that prospective trials evaluating cardiovascular endpoints are warranted.

use, with both outcomes showing a nominally significant improvement with resmetirom at 80-mg and 100-mg doses vs placebo. Specifically, the Week 52 MASH resolution rates were 29% in patients receiving a statin and 35% in patients not receiving a statin in the resmetirom 80-mg arm; 34% and 43%, respectively, in the resmetirom 100-mg arm; and 10% and 12%, respectively, in the placebo arm. Week 52 fibrosis improvement rates were 26% in patients receiving a statin vs 33% in patients not receiving a statin in the resmetirom 80-mg arm, 28% and 39%, respectively, in the resmetirom 100-mg arm, and 11% and 22%, respectively, in the placebo arm (Figure 3).

Resmetirom was also associated with numerically greater reductions in liver fat assessed by magnetic resonance imaging–proton density fat fraction compared with placebo in both dose groups at Week 52, and reductions in LDL-C, ApoB, triglycerides, and Lp(a) at Week 24, regardless of baseline statin use. Overall, 44.4% of patients on statins at baseline with an LDL-C level of 70 mg/dL or higher who were assigned to resmetirom 100 mg attained an LDL-C reduction of less than 70 mg/dL; 36.3% and 37.5% of patients with an elevated Lp(a) level at baseline shifted to a lower level (≥30 or ≥50 mg/dL to <30 or <50 mg/dL).

Among patients in the highest quartile of CV risk based on Lp(a) at baseline (>18.75 mg/dL), resmetirom was associated with a significant reduction in Lp(a) regardless of baseline statin use. Investigators reported no significant statin-related adverse events in the trial and concluded that the findings support concomitant use of resmetirom and statins in these patients.

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Semaglutide and Tirzepatide Are Associated With Lower Risk of Cirrhosis and Liver Decompensation in MASH

Several recent randomized clinical trials have demonstrated histologic benefit with incretin-based therapy in patients with MASH and moderate or advanced (F2 or F3) fibrosis.[1,2] In the ESSENCE trial, semaglutide was associated with significant improvements over placebo at Week 72 in multiple liver histologic outcomes, including rates of resolution of steatohepatitis without worsening of fibrosis (62.9% vs 34.3%; *P*<.001), reduction in liver fibrosis without worsening of steatohepatitis (36.8% vs 22.4%; *P*<.001), and a combined outcome of resolution of steatohepatitis and reduction in liver fibrosis (32.7% vs 16.1%; *P*<.001).[1] In the SYNERGY-NASH trial, tirzepatide was associated with significant improvements over placebo at Week 52 in rates of MASH resolution without worsening of fibrosis (44% with tirzepatide 5 mg, 56% with tirzepatide 10 mg, and 62% with tirzepatide 15 mg, compared with 10% with placebo; *P*<.001 for all 3 comparisons) and higher rates of improvement of at least 1 fibrosis stage without worsening of MASH (55%, 51%, and 51%, respectively, with tirzepatide, compared with 30% with placebo).[2] In both trials, gastrointestinal adverse events were more common

with incretin-based therapy vs placebo.

Nyancho and colleagues evaluated the association between incretin-based therapy and liver outcomes in a real-world cohort of patients with MASH by using electronic health record data.[3] The cohort included 12,017 adults who had received semaglutide or tirzepatide and a control group of 47,343 adults who had not received either agent. In a 1:1 propensity matched analysis controlled for demographics, clinical variables, and treatment, outcomes were compared in 3558 patients receiving incretin-based therapy with semaglutide or tirzepatide and a control group of 3358 patients receiving neither agent.

The primary outcome, a composite of cirrhosis or hepatic decompensation, occurred at a significantly lower rate in the incretin-based therapy group vs the control group (hazard ratio [HR], 0.53; 95% CI, 0.44-0.64) (Figure 4). In terms of individual outcomes, incretin therapy was associated with significant reductions over the control group in rates of incident cirrhosis (4.0% vs 12.8%; odds ratio [OR], 0.29; 95% CI, 0.24-0.35) and liver decompensation (1.7% vs 9.8%; OR, 0.16; 95% CI, 0.12-0.22).

The researchers cautioned that

> The authors demonstrated that patients with MASH and moderate to advanced fibrosis who were treated with semaglutide or tirzepatide had significantly lower rates of developing cirrhosis or hepatic decompensation. These findings replicate the results of earlier studies that used different databases and should encourage physicians to start patients with MASH and multiple obesity-related comorbidities on GLP-1 RA therapy as a management tool that may change liver outcomes.
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> — Naim Alkhouri, MD

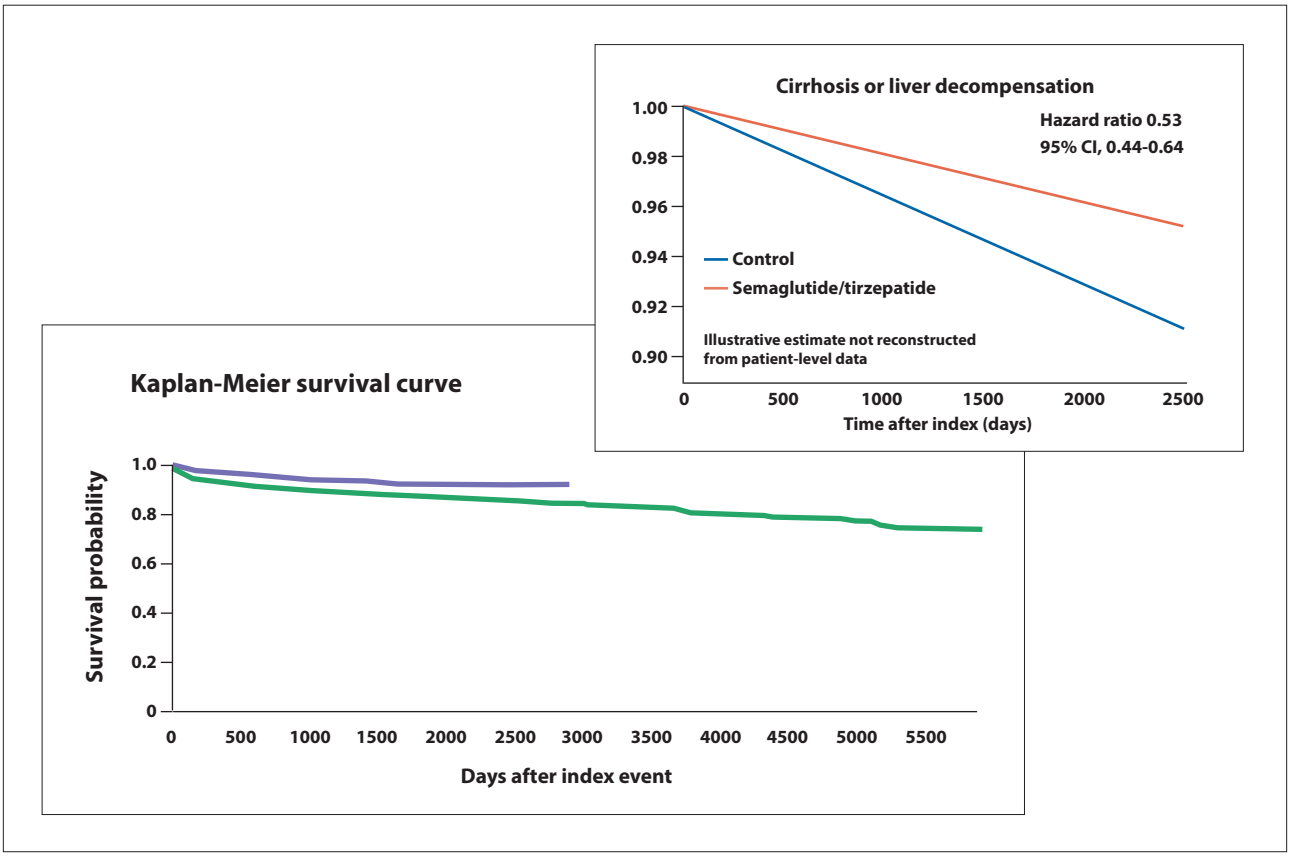


Figure 4. Incretin-based therapy with semaglutide or tirzepatide (green line) was associated with substantially lower observed rates of cirrhosis and liver decompensation compared with no prescription for either therapy (blue line) in a retrospective propensity-matched analysis using a large electronic health record database of patients with metabolic dysfunction-associated steatohepatitis. Adapted from Nyancho D, et al. Abstract P6080. Presented at: ACG 2026; October 9-14, 2026; Nashville, Tennessee.[3]

there are limitations to this study, including its retrospective, observational design, residual confounding factors, an incomplete data capture, adherence bias considerations, and the presence of duplicate patients. However, they concluded these real-world findings do provide further support to the role of incretin-based therapies in the management of MASH.

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ABSTRACT SUMMARY Resmetirom vs GLP-1 RAs in the Prevention of Cirrhosis in MASH: Insights From a Large Global Database

A retrospective propensity-matched cohort study compared resmetirom vs GLP-1 RAs for the prevention of cirrhosis in patients with MASH (Abstract P3978). The cohort, from the US TriNetX electronic health records database, included 1080 patients receiving resmetirom alone and 21,319 patients receiving a GLP-1 RA alone. Patients were matched 1:1 for 28 variables to yield an evaluable population of 1067 patients per group. Overall, resmetirom was associated with a significant reduction over GLP-1 RA in the likelihood of developing cirrhosis in the matched analysis (OR, 0.38; 95% CI, 0.25-0.58; *P*<.001) and in the unmatched analysis (OR, 0.51; 95% CI, 0.36-0.73; *P*<.001). In the matched analysis, the incidence of cirrhosis was 3.0% in the resmetirom group and 7.5% in the GLP-1 RA group. The investigators concluded that resmetirom was associated with a significantly lower reduction in cirrhosis risk than GLP-RAs in this multicenter real-world MASH cohort but added that randomized controlled trials are needed to confirm these associations, and there is a need to study long-term clinical outcomes.

Efruxifermin in MASH With F2/F3 Fibrosis: Post Hoc Analysis Indicated Early Histologic Features of Regression Were Associated With Week 96 Fibrosis Improvement

The randomized, double-blind, phase 2b HARMONY trial evaluated the efficacy and safety of efruxifermin compared with placebo in 747 patients with MASH and F2/F3 fibrosis.[1] The trial met its primary endpoint, showing improvement in liver fibrosis (decrease in ≥1 fibrosis stage) without worsening of MASH at Week 24 in a significant proportion of patients in the efruxifermin 28-mg group (39%; risk ratio, 2.3; *P*=.025) and efruxifermin 50-mg group (41%; risk ratio, 2.2; *P*=.036) over patients in the placebo group (20%).

Additional follow-up continued to show efficacy improvements with efruxifermin over placebo at 96 weeks. Among 88 patients with biopsies at Week 96, the proportion of patients with fibrosis improvement (≥1-stage) without MASH worsening was 46% in the efruxifermin 28-mg group (n=26), 75% in the efruxifermin 50-mg group (n=28), and 24% in the placebo group (n=34).[2] Mild to moderate gastrointestinal adverse events, including diarrhea and nausea, were reported with efruxifermin more than placebo.

> In this post hoc analysis, the authors identified early histologic features on liver biopsy that was done after treating patients with efruxifermin for 24 weeks. The histologic features were associated with response after completing 96 weeks of treatment. These findings could have great implications for the design of future trials with other antifibrotic drugs, which may help expedite regulatory approval.
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Behling and colleagues performed a post hoc analysis of the HARMONY trial to identify detailed histologic features of fibrosis regression.[3] Included in the analysis were patients with liver biopsies at baseline and at Week 24. For the analysis, 2 pathologists independently reassessed biopsy images and generated a combined score for 6 predetermined features of regression at baseline and Week 24. Features of regression included: regenerative changes, interrupted septa, isolated thick collagen fibers, thick and thin collagen, large lipogranulomas, and isolated arteries. A change in combined score from baseline to Week 24

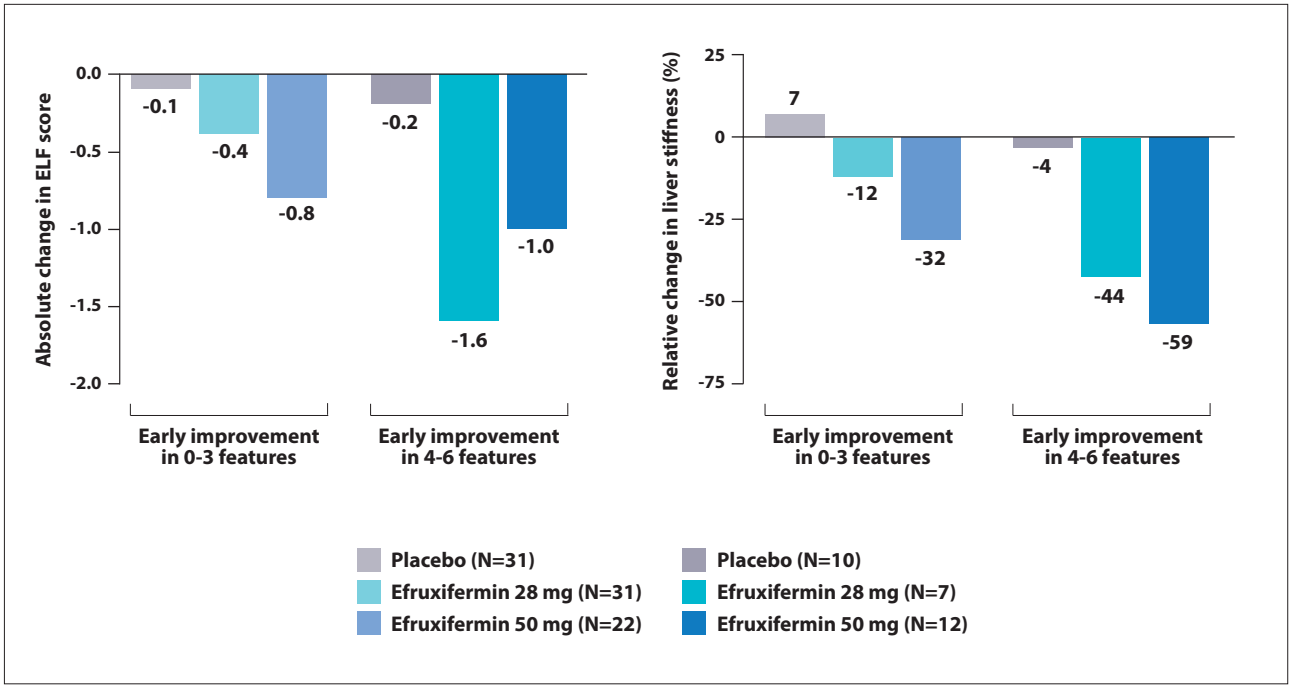


Figure 5. Greater improvements in noninvasive markers of fibrosis at Week 96 were observed in efruxifermin-treated participants in the phase 2b HARMONY trial who showed early improvement in more histologic features. ELF, Enhanced Liver Fibrosis. Adapted from Behling C, et al. Abstract P1675. Presented at: ACG 2026; October 9-14, 2026; Nashville, Tennessee.[3]

was calculated for each patient. An increase in combined score indicated early improvement for that feature at Week 24. Subsequently, this score was analyzed in patients with histologic responses at Week 96. In this subset of patients, the number of features with early improvement was numerically higher in patients receiving efruxifermin 28 mg or 50 mg, with a median of 3 features with early improvement, than in patients receiving placebo, with a median of 1 feature with early improvement. The most frequently observed changes at Week 24 among patients with a Week 96 histologic response were changes related to collagen morphology.

In a combined analysis of 33 patients receiving either dose of efruxifermin with a Week 96 histology response, there was a strong correlation between improvements in interrupted septa and improvements in thick/thin collagen at Week 24. In contrast, improvement in large lipogranulomas was not associated with improvements in other features assessed.

Investigators also reported an association between the number of early features with improvement at Week 24 and Week 96 response in all patients. In all measurements, greater improvements at Week 96 were noted in the patients receiving efruxifermin

ABSTRACT SUMMARY Resmetirom Plus GLP-1 RA vs GLP-1 Alone in MASH: A 6-Month Real-World Comparative Effectiveness Study

The effectiveness of resmetirom plus a GLP-1 RA was compared with a GLP-1 RA alone for reducing triglycerides and improving hemoglobin A1c (HbA1c) levels in patients with MASH in a retrospective propensity-matched cohort study (Abstract P1710). The authors used data from the TriNetX US Collaborative Network and included 228 patients with MASH receiving resmetirom + GLP-1 RA and 228 matched patients receiving a GLP-1 RA alone. Patients with cirrhosis and other liver diseases were excluded. Investigators noted that laboratory availability ranged from 34% to 69%. At 180 days, resmetirom + GLP-1 RA was associated with significant improvements over GLP-1 RA alone in HbA1c level (6.31% vs 6.70%; *P*=.022) and triglyceride level (136 vs 173 mg/dL; *P*=.027). The total bilirubin level was increased significantly with resmetirom + GLP-1 RA vs GLP-1 RA alone (0.63 vs 0.54; *P*=.038), and there were nonsignificant increases in ALT (53 vs 43 U/L; *P*=.057) and AST (41 vs 35 U/L). Investigators concluded that the lower levels of triglycerides and HbA1c with combination therapy suggest complementary metabolic effects, although the study has several limitations, including its observational design and lack of fibrosis endpoints. They added that the significance of the transaminase and bilirubin differences is unknown.

(28 mg or 50 mg) who showed early improvement in more features than in patients receiving placebo. Greater improvement was noted in those with more features (4-6 features vs 0-3 features). Measurements included change in NAS at Week 24 and at Week 96 and change in markers of fibrosis, such as ELF, liver stiffness (Figure 5), and Pro-C3, and markers of liver injury (alanine transaminase [ALT] and aspartate transaminase [AST]) at Week 96 in patients receiving efruxifermin vs placebo.

Clinical trials are continuing to evaluate efruxifermin in different patient populations, including the SYNCHRONY Histology trial[4] in patients with MASH and F2/F3 fibrosis and the SYNCHRONY Outcomes trial[5] in patients with compensated cirrhosis.

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