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A SPECIAL MEETING REVIEW EDITION

Highlights in MASH From the AASLD 2025 Liver Meeting

A Review of Selected Presentations From the American Association for the Study of Liver Diseases 2025 Liver Meeting • November 7-11, 2025 • Washington, DC

Special Reporting on:

- Two-Year Time Course of Biomarker and Imaging Responses in Patients With Well-Compensated MASH Cirrhosis Treated With Resmetirom
- Once-Monthly Efimosfermin Alfa for Up to 48 Weeks in MASH With F2/F3 Fibrosis: Results From a Phase 2, Open-Label Extension Study
- Improvement in Health-Related Quality of Life After Treatment With Resmetirom in Cirrhotic and Noncirrhotic Patients With MASLD: Data From MAESTRO-NAFLD-1
- Weight-Dependent and -Independent Effects of Semaglutide in Participants With MASH: Secondary Analysis of the Phase 3 ESSENCE Trial
- Analysis of Baseline PRO-C3 and ELF Components in Patients With MASH/MASLD and MASH Cirrhosis and Correlations Between Change in PRO-C3 and ELF in Resmetirom-Treated Patients From the MAESTRO-NASH Trial
- Top-Line Phase 2 Results of DD01, a Dual GLP-1/Glucagon Agonist, Lead to Rapid Improvements in Liver and Metabolic Endpoints in Patients With MASLD/MASH
- Comparison of MAESTRO-NASH and ESSENCE: Effects of Resmetirom and Semaglutide Relative to Placebo on Primary and Secondary Liver Biopsy Endpoints Using Aligned Endpoints and Statistical Methods

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.

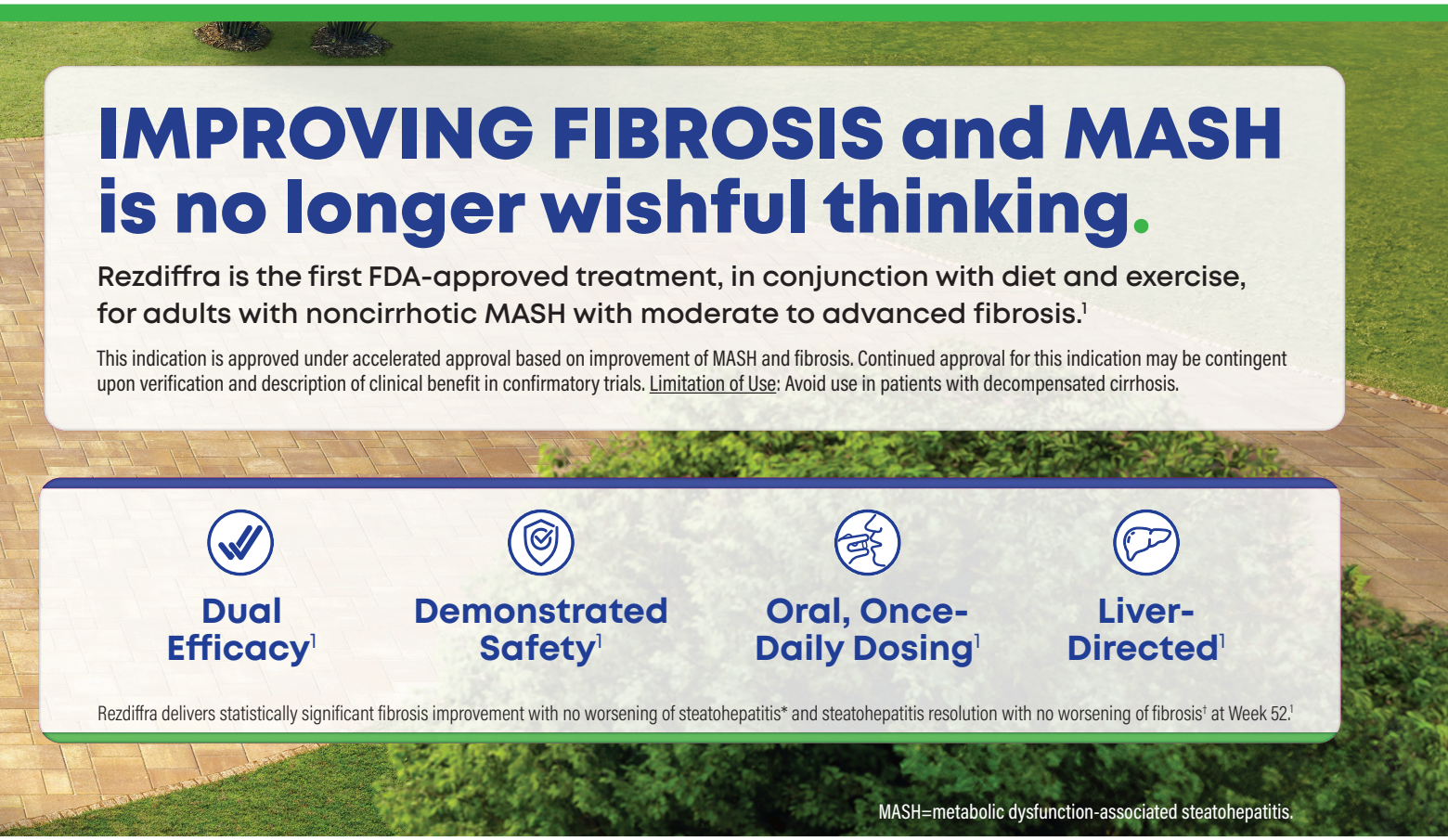
DRUG INTERACTIONS

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

Two-Year Time Course of Biomarker and Imaging Responses in Patients With Well-Compensated MASH Cirrhosis Treated With Resmetirom

The thyroid hormone receptor β (THR-β) agonist resmetirom has been approved by the US Food and Drug Administration (FDA) for adults with metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver scarring without cirrhosis. There are currently no FDA-approved therapies for MASH with compensated cirrhosis, and stage F4 fibrosis is associated with an increased risk of adverse outcomes, including liver-related complications, need for transplantation, and death.[1]

Through its binding to THR-β, resmetirom may affect multiple biologic processes in the liver, regulating gene expression, reducing inflammation, indirectly blocking stellate cell activation, and reducing fibrosis production.[2] 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 well compensated MASH cirrhosis (Child-Pugh A).[3] Patients were required to have at least 3 metabolic risk factors and a platelet count of 70,000/μL or higher.

Patients in the cohort received resmetirom 80 mg for 52 weeks. After a variable gap off treatment ranging from 1 month to 1 year (median treatment gap, 77 days), patients could enter a 1-year open-label extension (OLE). Of the 161 patients who completed 52 weeks of treatment, 122 enrolled in the OLE and 113 completed the 2-year study.

Outcomes were presented based on baseline platelet count of 100,000/μL or higher (n=92; high-platelet group) or less than 100,000/μL (n=30; low-platelet group). Median spleen volume was substantially higher in the low-platelet group than the high-platelet group (906.5 mL vs 424.7 mL), which the investigators noted was attributed to advanced portal hypertension. Conversely, multiple measures of fibrosis and liver stiffness were higher in the low-platelet group, including median Agile-4 (0.85 vs 0.56), magnetic resonance elastography (MRE) (5.9 vs 5.1 kPa), vibration-controlled transient elastography (VCTE) (26.4 vs 19.3 kPa), and Fibrosis-4 (3.9 vs 2.0).

In the efficacy analysis, resmetirom was associated with significant reductions in liver stiffness measurement (LSM) as assessed by VCTE after 1 year and 2 years in both groups. In the low-platelet group, the mean change from baseline was -6.2 kPa at year 1 and -7.9 kPa at year 2; in the high-platelet group, the mean changes were -6.5 kPa and -6.4 kPa, respectively (Figure 1). After 2 years, 59% of patients in the low-platelet group and 49% of patients in the high-platelet group were considered LSM responders, with a 25% change in LSM.

At baseline, clinically significant portal hypertension (CSPH) or probable CSPH as assessed by the Baveno CSPH risk score was present in 93% of patients with a platelet count less than

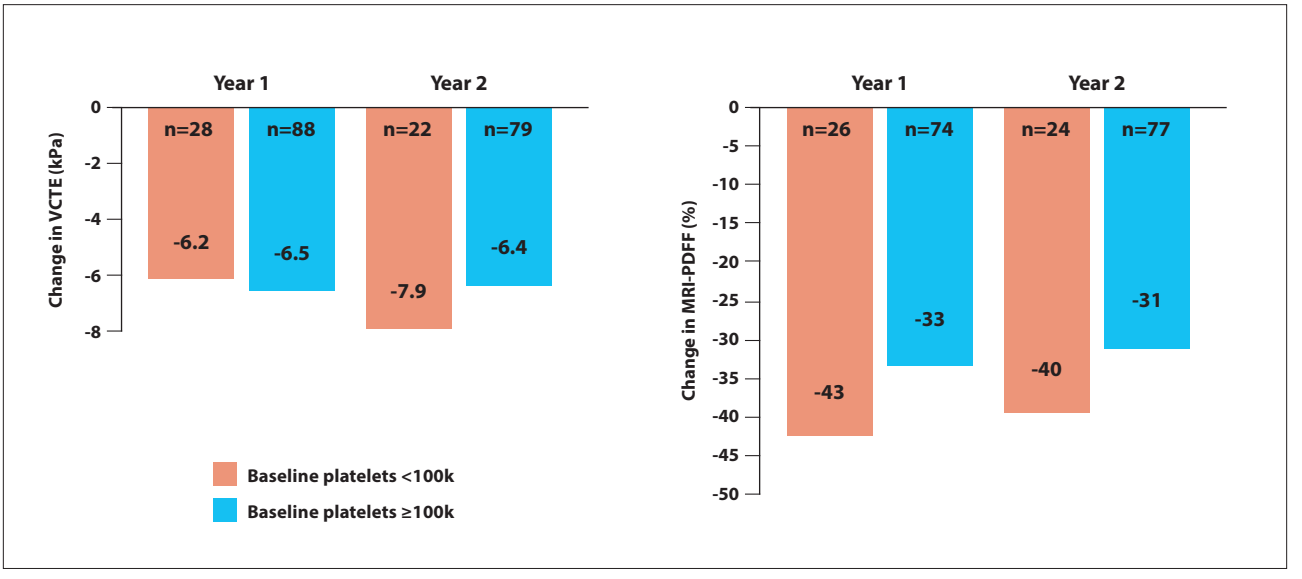


Figure 1. Change from baseline in liver stiffness measurement by VCTE (FibroScan) (kPa) and in MRI-PDFF in the open-label 52-week cirrhosis arm of MAESTRO-NAFLD-1 followed by a 52-week extension trial.

kPa, kilopascal; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; VCTE, vibration-controlled transient elastography.

Adapted from Alkhouri N, et al. AASLD abstract 0167. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[3]

It was striking that resmetirom treatment shifted two-thirds of individuals with CSPH to a lower Baveno risk score. This shift is important when it comes to treating a higher risk population, and therapy was safe. A concern in patients with more advanced disease, like those with portal hypertension, is always that side effects may limit treatment. Irrespective of how fibrosis was measured, there was an improvement with resmetirom in patients with compensated cirrhosis, especially in patients at high risk for CSPH, which is exciting news for individuals with more advanced MASLD.

—Nancy S. Reau, MD

100,000/μL and 36% of patients with a platelet count 100,000/μL or higher. Resmetirom was associated with a shift to a lower CSPH risk score in approximately two-thirds of patients and to a lower Agile-4 score, indicating a lower risk of cirrhosis. During the median 77-day treatment gap between years 1 and 2, there were transient increases in magnetic resonance imaging–proton density fat fraction (MRI-PDFF), apolipoprotein B, and VCTE; however, the reintroduction of resmetirom resulted in restoration of these values to the levels observed at the end of year 1.

Spleen volume decreased at year 1 of resmetirom in both the low-platelet group (median change, -2.4%) and in the high-platelet group (median change, -7.7%) and increased during the treatment gap. The increase was particularly notable in the low-platelet group. During year 2, spleen volume stabilized in the low-platelet group and decreased in the high-platelet group.

There were significant improvements in multiple imaging measures after 2 years, including in MRI-PDFF, controlled attenuation parameter, and MRE, and these improvements occurred across baseline platelet count groups. Liver enzyme levels also reduced significantly with resmetirom treatment, particularly in patients with a high baseline platelet count, as did biomarkers associated with fibrosis, liver injury, and atherogenic lipids.

In the safety analysis, no serious adverse events (AEs) were study drug–related. The most common AEs were diarrhea (37.7%), COVID-19 (31.1%), nausea (31.1%), and urinary tract infection (25.4%). Over 2 years of treatment, no changes in bone mineral density or fracture risk were noted; there were 6 hepatic decompensation events, 5 of which occurred in patients with a baseline platelet count less than 100,000/μL.

References

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Once-Monthly Efimosfermin Alfa for Up to 48 Weeks in MASH With F2/F3 Fibrosis: Results From a Phase 2, Open-Label Extension Study

Efimosfermin is a novel engineered fibroblast growth factor 21 analog that was designed to have an extended half-life to allow for once-monthly dosing.[1] Clinical trials are evaluating efimosfermina alfa in patients with MASH. The randomized, double-blind, placebo-controlled, phase 2 trial of patients with MASH with biopsy-confirmed F2/F3 fibrosis reported that, among 65 evaluable patients, efimosfermin alfa 300 mg every 4 weeks was significantly more effective than placebo after 24 weeks of treatment.[2] This was assessed by the proportion of patients attaining a fibrosis improvement of 1 stage or higher without worsening of MASH (45% vs 21%; *P*=.038) and the proportion of patients attaining MASH resolution without worsening of fibrosis (68% vs 29%; *P*=.002). In the prior safety analysis, the most frequent treatment-emergent AEs were gastrointestinal (GI), including nausea (33% vs 13% with placebo), diarrhea (23% vs 8%), and vomiting (16% vs 3%), and were mostly mild to moderate. The rate of discontinuations owing to AEs in the efimosfermin alfa arm was 4.7%.

Noureddin and colleagues presented additional findings from the trial, including efficacy and safety outcomes through the 24-week OLE in 15 patients originally assigned to efimosfermin alfa and in 18 patients crossing over from the placebo arm.[3] Results were reported for the full analysis set, which included patients who received at least 1 dose of study treatment in the OLE, and the biopsy analysis set, which included 11 patients initially

assigned to efimosfermin alfa and 17 patients initially assigned to placebo.

Among patients initially assigned to efimosfermin alfa, who had received up to 48 weeks of treatment, 5 of 11 patients (45.5%) had fibrosis improvement of 1 stage or more without worsening of MASH, including 2 patients (18.2%) with new fibrosis improvement. MASH resolution without worsening of fibrosis occurred in 7 patients (63.6%) and was new in 2 patients (18.2%), and 5 patients (45.5%) had fibrosis improvement of 1 stage or more and MASH resolution (Figure 2). Improvements in noninvasive markers of fibrosis included a mean change from baseline in PRO-C3 of -20.1% (n=13), in Enhanced Liver Fibrosis (ELF) score of -0.7 (n=13), and in VCTE LSM of -12.8 kPa. The mean change from baseline in alanine aminotransferase (ALT) was -31.1U/L, and in aspartate aminotransferase (AST) was -29.2 U/L.

There were sustained reductions in liver fat over 48 weeks as assessed by hepatic fat fraction, with a mean change of -50.0% at the end of study (relative reductions of ≥30% and ≥50% were attained by 53.8% and 46.2% of patients, respectively). Nearly 40% of patients (38.5%) attained liver fat normalization (≤5%). Improvements in cardiometabolic profile with efimosfermin alfa at 48 weeks included a mean change from baseline in the following levels: triglycerides, -0.3 mmol/L; high-density lipoprotein cholesterol, 0.1 mmol/L; low-density lipoprotein (LDL-C), 0.1 mmol/L; total cholesterol, 0.1 mmol/L; adiponectin, 79.2% change; and glycated hemoglobin (A1c), -0.5% units in all patients (n=13) and -0.6% units in patients with type 2 diabetes mellitus (T2DM, n=11). Treatment responses in patients initially assigned to placebo who crossed over to efimosfermin alfa

With this small study, results must be interpreted carefully; however, having another class of agents in late-stage development is encouraging. This once-a-month therapy shows not only sustained improvement in MASH and fibrosis, but also favorable cardiometabolic effects, which is important in this population enriched in cardiometabolic risk factors. Notably, during the period of treatment disruption, there was a slip in that improvement, which was regained when treatment resumed. This emphasizes that the improvement is an agent effect, not just natural history.

—Nancy S. Reau, MD

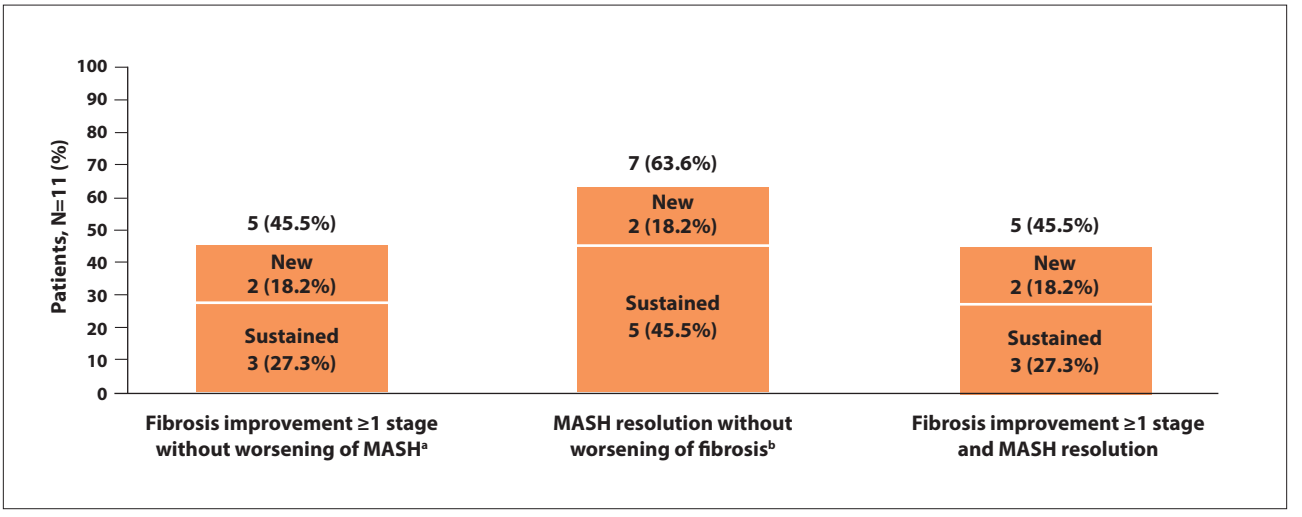

Figure 2. Proportion of patients with sustained or new response during up to 48 weeks of continued treatment with efimosfermin alfa 300 mg every 4 weeks in a phase 2, open-label extension study.

[a]Improvement in liver fibrosis ≥1 stage and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

[b]NAS score of 0 for ballooning and 0-1 for inflammation.

MASH, metabolic dysfunction-associated steatohepatitis; NAS, nonalcoholic fatty liver disease activity score.

Adapted from Noureddin M, et al. AASLD abstract 5011. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[3]

were consistent with those observed in patients originally assigned to the study drug.

In the safety analysis, the only serious AE was a case of appendicitis in the OLE that was considered not treatment-related. No patients discontinued treatment during the OLE period owing to AEs, and no antidrug antibodies were detected. Most GI AEs occurred in the first 24 weeks of treatment. Nausea was reported in 20% of patients in the original efimosfermin alfa group and 22% of patients in the crossover group; diarrhea occurred in 13% and 22% of patients, respectively, and vomiting occurred in 13% and 17% of patients, respectively. Two cases of hepatic calcification in the crossover group were considered not treatment-related.

Investigators concluded that once-monthly efimosfermin alfa was associated with fibrosis improvement and MASH resolution after up to 48 weeks in patients with F2/F3 MASH and improvements in noninvasive markers of fibrosis, liver injury, and liver fat through the end of the OLE. The ongoing phase 3 ZENITH-1 (NCT07221227) and ZENITH-2 (NCT07221188) trials are evaluating efimosfermin alfa in patients with biopsy-confirmed F2/F3 MASH.

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Improvement in Health-Related Quality of Life After Treatment With Resmetirom in Cirrhotic and Noncirrhotic Patients With MASLD: Data From MAESTRO-NAFLD-1

Metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH are associated with significant impairments in health-related quality of life (HRQL), particularly in patients with advanced fibrosis.[1] The MAESTRO-NAFLD-1 trial evaluated resmetirom in patients with MASLD cirrhosis (MASH cirrhosis) or MASLD without cirrhosis (early MASH).[2] In the early MASH cohort (VCTE 5.5 up to 8.5 kPa or MRE 2.0 up to 4.0 kPa), 1143 patients were enrolled into a double-blind arm of resmetirom 100 mg (n=325), resmetirom 80 mg (n=327), or placebo (n=320), or an open-label arm of resmetirom 100 mg (n=171). The MASH cirrhosis cohort included 180 patients with well-compensated MASH cirrhosis with no history of decompensation who received open-label resmetirom 80 mg. The median age of patients in the early MASH cohort was 56 years; 43% were male, 53% had T2DM, and the median MRI-PDFF was 18%. The median age of patients in the MASH cirrhosis cohort was 61 years; 38% were male, 73% had T2DM, and the median MRI-PDFF was 9%.

> In this study, treatment of MASLD was associated with improved HRQL, especially in patients who had improvement with MRI-PDFF. This suggests that it is the treatment of disease that is improving how patients feel. Despite the GI side effects associated with resmetirom, abdominal symptoms significantly improved. When patients report feeling better, this could be from reducing hepatomegaly. Essentially, the results show how preventing disease progression is vital to this population, as this decreases the concern patients have about becoming ill from this progressive disease.
>
> —Nancy S. Reau, MD

Younossi and colleagues reported on the effects of resmetirom treatment on HRQL in patients with MASLD with and without cirrhosis enrolled in the MAESTRO-NAFLD-1 trial.[3] HRQL was assessed using the 17-domain Liver Disease Quality of Life (LDQOL) questionnaire and the 6-domain Chronic Liver Disease Questionnaire–non-alcoholic fatty liver disease (CLDQ-NAFLD). At baseline, HRQL scores in patients with MASH cirrhosis were significantly lower than those of patients with early MASH. In the early MASH cohort, after no differences were found between the double-blind resmetirom arm and the open-label resmetirom arm, the two groups were pooled for subsequent analyses.

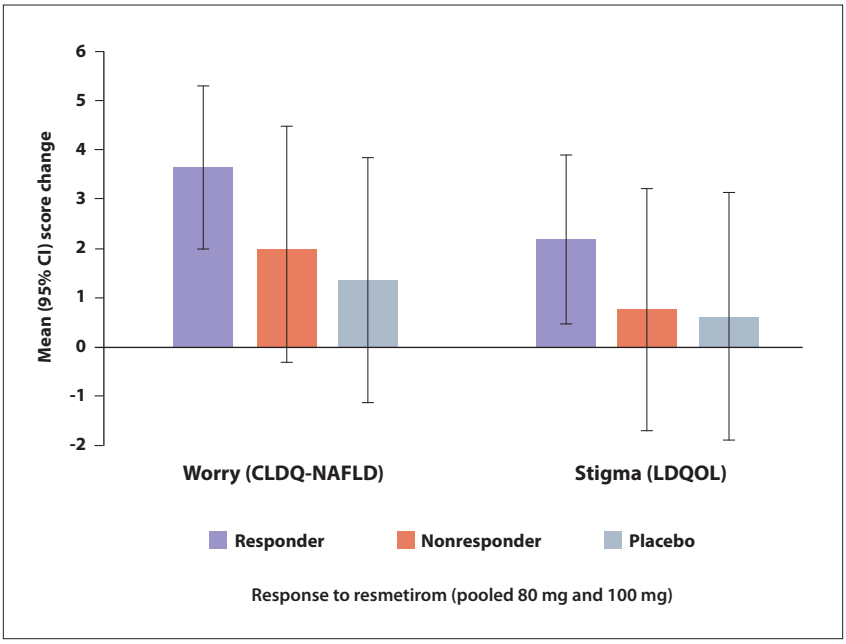

Figure 3. Selected health-related quality-of-life scores in patients with early metabolic dysfunction-associated steatohepatitis who achieved a 30% or more reduction in magnetic resonance imaging–proton density fat fraction (from baseline by week 52) with resmetirom treatment vs nonresponders and placebo in the MAESTRO-NAFLD-1 trial.

CLDQ-NAFLD, Chronic Liver Disease Questionnaire–Non-Alcoholic Fatty Liver Disease; LDQOL, Liver Disease Quality of Life instrument.

Adapted from Younossi ZM, et al. AASLD abstract 0181. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[3]

In patients with early MASH, 52 weeks of resmetirom was associated with significant improvements over placebo in abdominal symptoms, worry, and health distress scores, and appeared to reduce the extent of declines in physical and emotional role functioning. Patients who attained a 30% or greater reduction in MRI-PDFF after 52 weeks of resmetirom had greater improvements in the Worry and Abdominal Symptoms domains of CLDQ-NAFLD and the Stigma from liver disease domain of the LDQOL than patients in the placebo arm or nonresponders (Figure 3).

Across all domains, HRQL scores were lower in patients with cirrhosis than in patients with early MASH and in patients with biopsy-proven F2 to F3 MASH (per historic data in the MAESTRO-NASH trial).[4] The greatest impairments were observed in the Worry, Health Distress, Role Physical, Hopelessness, Physical Functioning, and General Health domains.

Among patients with MASH cirrhosis, resmetirom was associated with improvements in the Worry domain of the CLDQ-NAFLD and the Health Distress domain of the LDQOL by week 24, and these improvements were sustained out to year 2 ($P<.05$). Significant improvements in the Stigma score were observed in patients with MASH cirrhosis with a PDFF response at week 52 ($P<.05$).

Resmetirom was associated with improvements in selected HRQL scores in patients with MASH cirrhosis and those with early MASH, and these benefits were sustained long-term. The findings suggest that resmetirom addresses patient-reported outcomes in patients with MASLD.

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ABSTRACT SUMMARY A Phase 2, Multicenter, Randomized, Placebo-Controlled Trial of Pemvidutide in MASH

Pemvidutide is a 1:1 glucagon/GLP-1 dual receptor agonist that was designed with a pharmacokinetic profile to enhance tolerability. The efficacy of pemvidutide in patients with F2/F3 MASH was evaluated in the phase 2b multicenter, randomized, placebo-controlled IMPACT trial (Abstract 5001). A total of 212 patients were randomly assigned to pemvidutide 1.2 mg (n=41), 1.8 mg (n=85), or placebo (n=86) weekly. At week 24, MASH resolution without worsening of fibrosis was attained in 58% of patients at the 1.2-mg dose and 52% at the 1.8-mg dose, compared with 20% with placebo. Multiple fibrosis biomarkers were significantly improved with pemvidutide, including FAST score, ELF, LSM, and PRO-C3, as were the liver injury and inflammatory biomarkers ALT, AST, and corrected T1. Liver fat content was significantly reduced with pemvidutide at 24 weeks and weight loss of up to 5.8% occurred. GI toxicities were primarily mild or moderate and included nausea (up to 41.2%), diarrhea (up to 21.2%), constipation (up to 12.9%), and vomiting (up to 8.2%). One patient discontinued pemvidutide compared with 2 patients on placebo.

Weight-Dependent and -Independent Effects of Semaglutide in Participants With MASH: Secondary Analysis of the Phase 3 ESSENCE Trial

The phase 3 ESSENCE trial is evaluating the efficacy of semaglutide in patients with biopsy-defined MASH and stage 2 or 3 fibrosis.[1] In part 1 of the study, 800 patients were randomly assigned to once weekly semaglutide at 2.4 mg following a 16-week dose escalation (n=534) or to placebo (n=266).[1] The mean age of enrolled patients was 56 years; 57% were female, the mean body weight was 24.5 kg, and 55.9% had T2DM. Semaglutide demonstrated significant improvements in liver-related parameters compared with placebo, including a greater proportion of patients attaining resolution of steatohepatitis without worsening of fibrosis (62.9% vs 34.3%; *P*<.001) and a greater proportion of patients attaining reductions in liver fibrosis without worsening of steatohepatitis (36.8% vs 22.4%; *P*<.001). Mean changes in body weight were -10.5% and -2.0%, respectively (*P*<.001).

> With GLP-1 receptor agonists, some speculate it is loss of weight that leads to improvement, not the agents' direct effects in the liver. However, in this study, patients with MASH who received semaglutide had improvements in liver health–related parameters, even at low levels of weight reduction. They also had greater improvements on their liver parameters, compared with those who received placebo. This suggests a potential effect of the agent itself not driven solely by weight reduction, although weight loss does improve features of MASLD.
>
> —Nancy S. Reau, MD

Newsome and colleagues presented post-hoc analyses investigating the association between body weight reduction and liver outcomes in the ESSENCE trial.[2] At week 72, improvements in MASH-related and fibrosis-related endpoints were observed across body weight reduction thresholds. Rates of steatohepatitis resolution without worsening of liver fibrosis among patients receiving semaglutide

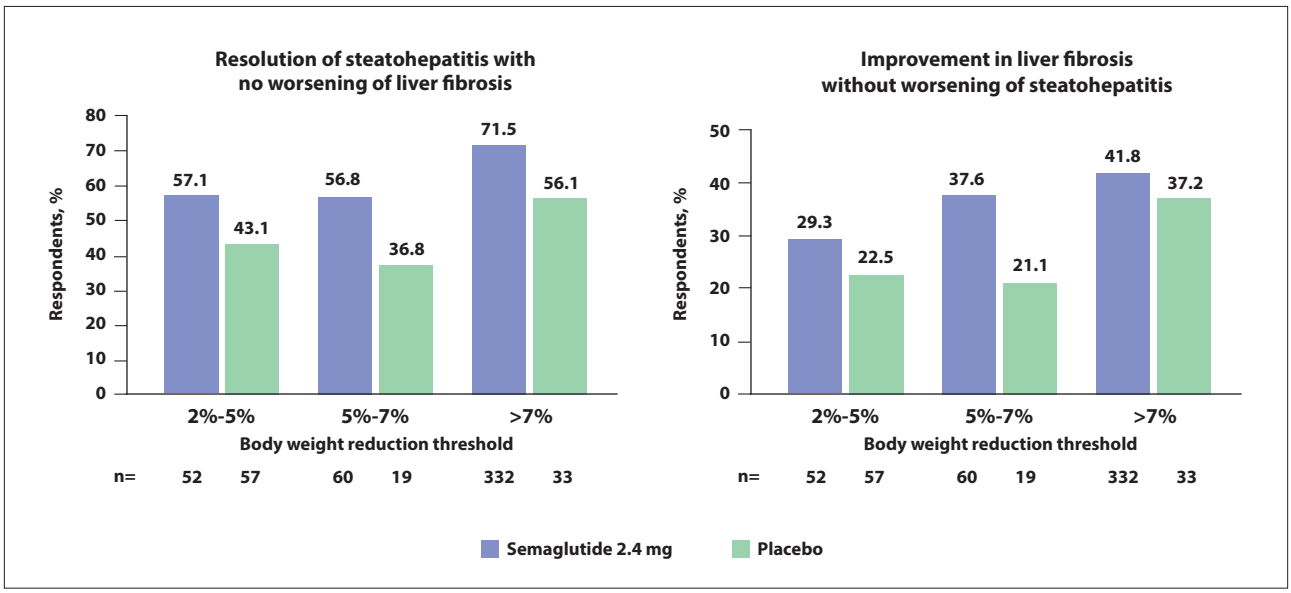

Figure 4. Improvements in metabolic dysfunction-associated steatohepatitis–related histologic and noninvasive test responses were observed across all body weight reduction thresholds in patients treated with semaglutide in the ESSENCE trial.

Adapted from Newsome PN, et al. AASLD abstract 0010. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[2]

ranged from 57.1% (43.1% for placebo) in patients with 2% to 5% body weight reduction to 71.5% (56.1% for placebo) in patients with greater than 7% body weight reduction. Rates of improvement in liver fibrosis without worsening of steatohepatitis ranged from 29.3% (22.5% for placebo) in patients with 2% to 5% body weight reduction to 41.8% (37.2% for placebo) in patients with greater than 7% body weight reduction (Figure 4).

Improvements in MASH-related noninvasive test parameters were also observed across body weight reduction thresholds in patients receiving semaglutide, as were improvements in fibrosis-related histologic and noninvasive test responses, including change in ELF scores and VCTE.

The investigators used exploratory mediation analyses to attempt to measure the extent to which the effects of semaglutide on liver parameters were indirect effects (resulting from body weight reduction) or direct effects (not attributed to body weight reduction). They found that MASH-related histologic changes and noninvasive test responses (including histologic resolution of MASH without worsening of liver fibrosis, ALT responses, and FibroScan AST [FAST] responses), as well as fibrosis-related histologic improvement and noninvasive test responses (including improvement in fibrosis without worsening of MASH, VCTE responses, and ELF score responses), were greater in patients receiving semaglutide than in patients receiving placebo, even at a similar amount of weight reduction.

These exploratory findings suggest that factors other than weight reduction may contribute to the liver health benefits observed with semaglutide. However, investigators cautioned that interaction and confounding effects can influence outcomes and may complicate the analysis. They added that a few people on the placebo arm had large amounts of weight loss, which may also complicate the analysis. Moreover, the model requires assumptions that are not always testable. Despite these limitations, the investigators concluded that the benefits of semaglutide on liver health are not driven by weight reduction alone.

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Analysis of Baseline PRO-C3 and ELF Components in Patients With MASH/MASLD and MASH Cirrhosis and Correlations Between Change in PRO-C3 and ELF in Resmetirom-Treated Patients From the MAESTRO-NASH Trial

Noninvasive methods, such as ELF and PRO-C3, are used for assessing extent of fibrosis and predicting liver outcomes in patients with MASH. The FDA-approved prognostic biomarker ELF incorporates 3 serum biomarkers—tissue inhibitor of metalloproteinase 1 (TIMP-1), N-terminal propeptide of type III procollagen (P3NP), and hyaluronic acid (HA)—to provide a more reliable marker compared with individual markers.[1] PRO-C3 is a clinically validated marker of fibrosis that is independently associated with fibrotic stage. In the MAESTRO-NASH trial in patients with biopsy-confirmed MASH and fibrosis, resmetirom was associated with a reduction in ELF and in 2 of its components—P3NP and TIMP-1—but not HA.[2]

Bansal and colleagues presented results of an analysis further investigating changes in biomarkers in two trials of resmetirom.[3] Baseline ELF scores and ELF components were assessed according to biopsy fibrosis stage in a pooled cohort of patients from the MAESTRO-NASH and MAESTRO-NAFLD-1 trials. Correlations between

> This study demonstrated that the components within the ELF score may vary depending on treatment. This is important for a clinical trial because researchers need to understand how an agent is working, especially when evaluating multiple classes of drugs and suggesting that if one improves one area and another improves a different area, that might be a nice combination of options. However, in clinical practice, where separating out these components is not possible, it is reassuring to know that the ELF score will be useful for evaluating treatment efficacy and that it correlates to improvement of disease.
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> —Nancy S. Reau, MD

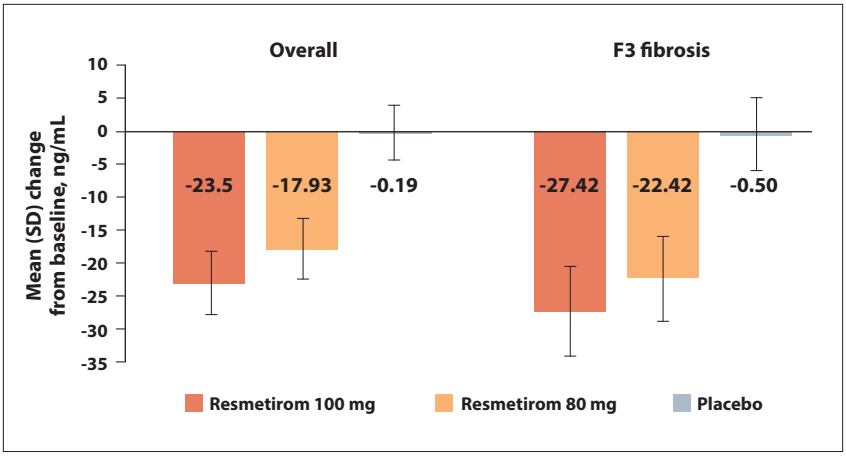

Figure 5. Change from baseline to week 52 in PRO-C3 observed in patients with F3 fibrosis in the resmetirom arms of the MAESTRO-NASH trial, and the correlation between change from baseline to week 52 in P3NP/ELF and PRO-C3.

ELF, Enhanced Liver Fibrosis; P3NP, Procollagen III aminoterminal peptide; PRO-C3, N-terminal pro-peptide of type-III collagen.

Adapted from Bansal M, et al. AASLD abstract 4074. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[3]

Test	Correlation coefficient (ρ)		
	Resmetirom 100 mg	Resmetirom 80 mg	Placebo
P3NP	0.557	0.548	0.524
ELF	0.483	0.484	0.487

ELF/P3NP and PRO-C3 at baseline and week 52, and the effect of resmetirom vs placebo on PRO-C3 and P3NP/ELF scores, were evaluated in patients from the MAESTRO-NASH trial who received resmetirom 80 mg, resmetirom 100 mg, or placebo.

In the assessment of ELF components and total scores at baseline, levels of TIMP-1 and P3NP did not increase from stage F0 to F2 but did increase by 20% moving from stage F2 to F3/F4. HA levels in patients with fibrosis stages F0 to F2 were higher in patients with diabetes than in patients without diabetes. Moreover, HA levels nearly doubled (1.9-fold increase) moving from stage F3 to F4, which is the likely reason for the increase in ELF score in patients with F4 fibrosis.

In the analysis of baseline ELF/P3NP and PRO-C3 levels in patients in the MAESTRO-NASH trial, correlations were found between P3NP and PRO-C3 (correlation coefficient, ρ=0.563) and between ELF and PRO-C3 (correlation coefficient, ρ=0.458).

In the assessment of changes in PRO-C3 from baseline to week 52 in patients receiving resmetirom or placebo, both resmetirom dose levels were associated with greater reductions in PRO-C3 over time than placebo, with a mean change of -23.05 ng/mL with resmetirom 100 mg and -17.93 ng/mL with resmetirom 80 mg, compared with -0.19 ng/mL with placebo. Greater PRO-C3 reductions were observed in the subset of patients with F3 fibrosis, with mean changes from baseline to week 52 of -27.42 ng/mL with resmetirom 100 mg, -22.24 ng/mL with resmetirom 80 mg, and -0.50 ng/mL with placebo (Figure 5).

Positive correlations of similar strength were reported in changes from baseline to week 52 in P3NP and ELF, and in changes from baseline to week 52 in PRO-C3 across treatment groups. The findings support including assessments of the individual ELF components when using the ELF test in patients treated for MASH.

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Top-Line Phase 2 Results of DD01, a Dual GLP-1/Glucagon Agonist, Lead to Rapid Improvements in Liver and Metabolic Endpoints in Patients With MASLD/MASH

DD01 is a pegylated glucagon-like peptide-1 (GLP-1)/glucagon dual receptor agonist with a biodistribution preferentially targeting the liver and a half-life of approximately 8 days, allowing for once-weekly dosing. Clinical trials are evaluating DD01 for the treatment of MASLD/MASH and other metabolic disorders.

Noureddin and colleagues presented results from up to 24 weeks of a randomized, placebo-controlled phase 2 study of DD01 in patients with MASLD/MASH.[1] The trial enrolled 67 patients with an MRI-PDFF of at least 10% steatosis and metabolic syndrome or with biopsy-confirmed F1

to F3 MASH. Patients were randomly assigned to subcutaneous DD01 40 mg once weekly following a 2-week titration period (n=33) or placebo (n=34). The primary endpoint was the proportion of patients achieving 30% or greater liver fat reduction by MRI-PDFF after 12 weeks of treatment.

The mean age of enrolled patients was 48 to 49 years (59%-67% were female, 61%-65% were Hispanic/Latino), and the mean body mass index (BMI) was 35.7 to 36.6 kg/m^2. The majority of patients (79.4%-75.8%) had biopsy-confirmed MASH and F2/3 fibrosis (42.4%-52.9%).

At week 12, the trial met its primary endpoint, with 75.8% of patients in the DD01 arm attaining at least a 30% reduction in liver fat by MRI-PDFF (P<.0001 vs placebo). Nearly half of patients (48.5%) attained normalization with at least 5% liver fat (P<.0001 vs placebo). The mean relative reduction in liver fat was 62.3% in the DD01 arm vs 8.3% in the placebo arm (P<.0001) (Figure 6).

Mean improvements in liver stiffness by MRE at week 12 were significantly greater with DD01 vs placebo in all patients (-19.7% vs -7.2%; P<.01 vs placebo) and in patients with F2/3 fibrosis (-20.1% vs -8.7%). In the overall population, the mean relative change in ALT at week 12 was -35.9% with DD01 and -9.9% with placebo; at week 24, relative changes were -38.15% and -11.7%, respectively. Among patients with F2/3 with MASH, the mean change in ALT at week 12 was -46.7% with DD01 and -15.8% with placebo; relative changes at week 24 were -54.7% and -10.5%, respectively.

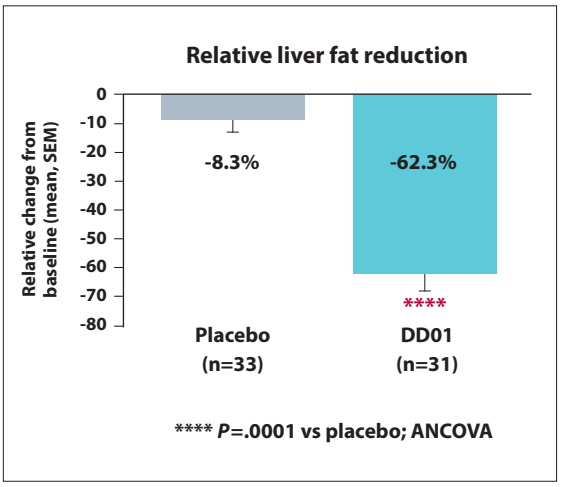

Figure 6. Relative change from baseline in liver fat reduction at week 12 in patients with metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis treated with DD01.

ANCOVA, analysis of covariance; SEM, standard error of the mean. Adapted from Noureddin M, et al. AASLD abstract 5004. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[1]

Improvements in lipid parameters, including total cholesterol, LDL-C, and triglycerides, were all significantly greater with DD01 compared with placebo at weeks 12 and/or 24, as were reductions in A1c at weeks 12 and 24. DD01 was also associated with significantly greater weight loss compared with placebo. At week 12, 42.4% of patients in the DD01 arm had attained at least 5% weight loss compared with 0% of patients in the placebo arm (P<.0001); by week 24, rates of at least 5% weight loss increased to 51.5% and 8.8%, respectively (P<.0001).

DD01 was well tolerated and GI toxicities were transient, nonsevere, and self-limiting, occurring sporadically over the first 12 weeks of treatment. Three patients discontinued DD01 owing to GI toxicities. The most frequent toxicities were nausea, reported in 54.5% of patients receiving DD01 and 17.6% of patients receiving placebo, diarrhea (27.3% vs 17.6%), constipation (30.3% vs 11.8%), decreased appetite (24.2% vs 5.9%), vomiting (18.2% vs 2.9%), and fatigue (18.2% vs 8.8%). The results support proceeding with phase 2b and 3 trials of DD01.

With multiple GLP-1 receptor agonists and GLP-1 combinations in development, competition has increased and improvements in new and currently available agents have led to more weight loss with variable side effect profiles. Treatment with DD01 also led to significant improvement in histology and significant loss of liver-related fat after just 12 weeks, which correlated to improvements in liver biochemical markers and liver stiffness scores. GI side effects were transient and generally self-limited. These exciting results support the potential of this agent to become another option for patients in whom GLP-1 therapy is an important part of their treatment armamentarium.

—Nancy S. Reau, MD

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Comparison of MAESTRO-NASH and ESSENCE: Effects of Resmetirom and Semaglutide Relative to Placebo on Primary and Secondary Liver Biopsy Endpoints Using Aligned Endpoints and Statistical Methods

The MAESTRO-NASH and ESSENCE trials are ongoing studies evaluating new therapies in patients with MASH.[1,2] The MAESTRO-NASH trial enrolled 966 patients including 917 with fibrosis stage 2/3, who were randomly assigned to resmetirom 100 mg (n=323), resmetirom 80 mg (n=322), or placebo (n=321). At week 52, the trial met its dual primary endpoints with both doses of resmetirom demonstrating significantly improvements over placebo in the proportion of patients attaining NASH resolution with no worsening of fibrosis with at least 2-point reduction in nonalcoholic fatty liver disease activity score (NAS) (P<.001 for both vs placebo), and at least 1-stage improvement in fibrosis with no worsening of NAS (P<.001 for both vs placebo).[1]

The ESSENCE trial enrolled 1197 patients with biopsy-defined MASH and fibrosis stage 2/3 who were randomly assigned to once weekly subcutaneous semaglutide at 2.4 mg (n=534) or placebo (n=266). In an analysis of the first 800 patients, the trial met its primary endpoint, with significantly higher proportions of patients in the semaglutide arm attaining resolution of steatohepatitis without worsening of liver fibrosis (P<.001 vs placebo) and attaining significantly greater reductions in liver fibrosis without worsening of steatohepatitis (P<.001 vs placebo).[2]

In an exploratory cross-trial analysis, Loomba and colleagues compared responses to drug treatment and placebo in the MAESTRO-NASH and ESSENCE trials using aligned biopsy endpoints and statistical tools. Baseline characteristics between patients with fibrosis stage 2/3 were similar across both trials; the mean age was 56 years in both trials; 57% of patients in both trials were female, and the mean BMI was 35.6 kg/m^2 in MAESTRO-NASH and 34.6 kg/m^2 in ESSENCE.

When placebo responses were imputed for missing data, the improvements with treatment over placebo in the likelihood of attaining at least 1-stage improvements in fibrosis with no worsening of NAS were similar with

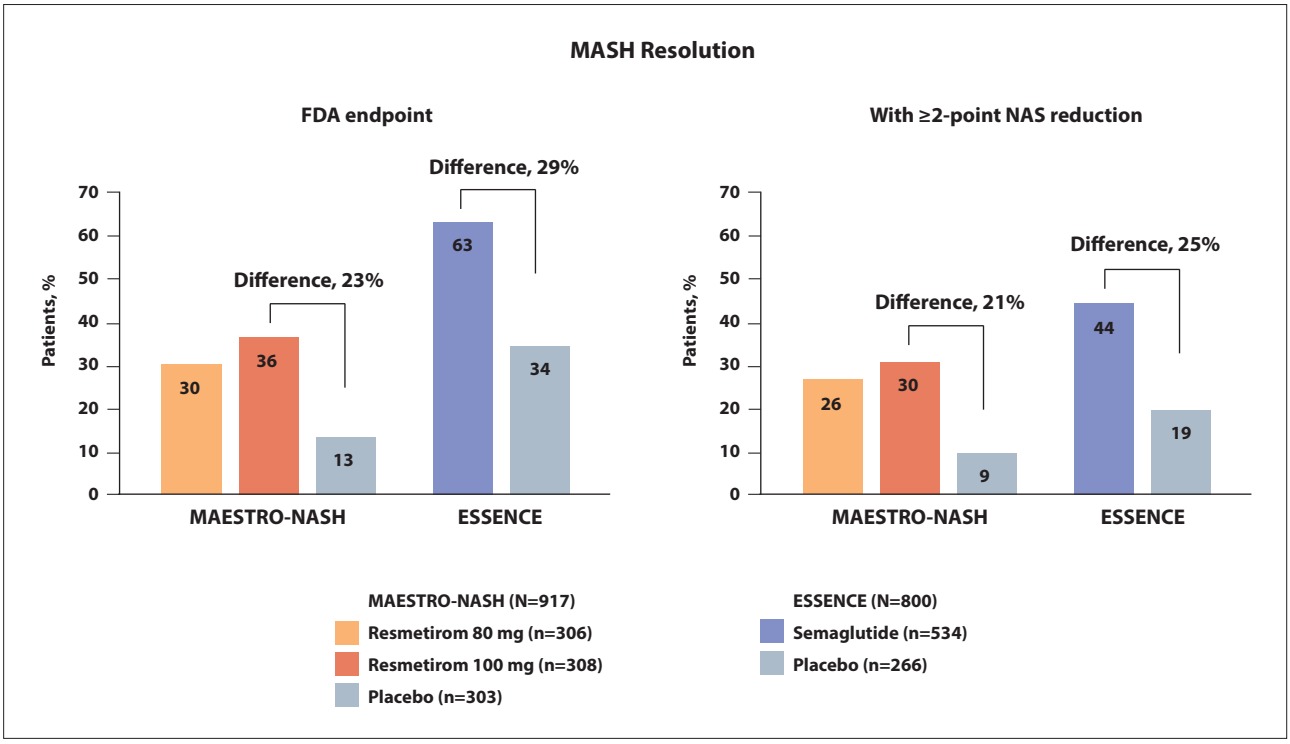

Figure 7. Achievement of biopsy endpoint MASH resolution in patients with fibrosis stages 2 to 3 treated with resmetirom or placebo in the MAESTRO-NASH trial vs semaglutide or placebo in the ESSENCE trial.

FDA, US Food and Drug Administration; MASH, metabolic dysfunction-associated steatohepatitis; NAS, nonalcoholic fatty liver disease activity score.

Adapted from Loomba R, et al. AASLD abstract 4093. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.[3]

resmetirom 100 mg in MAESTRO-NASH (15% difference over placebo, approximate 2.4-fold improvement) as with semaglutide in ESSENCE (14% difference over placebo, approximate 2-fold improvement).

In MAESTRO-NASH, 36% of patients receiving resmetirom 100 mg attained the FDA endpoint of NASH resolution, compared with 13% in the placebo arm (23% difference), whereas in the ESSENCE trial, rates of NASH resolution were 63% with semaglutide and 34% with placebo (29% difference). However, using the more stringent endpoint of NASH resolution with at least 2-point NAS reduction, rates of resolution in the MAESTRO-NASH trial were 30% with resmetirom and 9% with placebo (21% difference) and in the ESSENCE trial were 44% with semaglutide and 19% with placebo (25% difference) (Figure 7).

The proportion of patients attaining a 2-point NAS reduction was 51% with resmetirom 100 mg in MAESTRO-NASH and 50% with semaglutide in ESSENCE, compared with 25% in both placebo arms. Investigators concluded that the similar rates of 2-point NAS reduction in the placebo arms suggest that the high rate of MASH resolution of 34% reported in the ESSENCE trial can be attributed to low NAS in the reassessed baseline biopsies.

> When considering outcomes for MASLD studies, one of the most challenging findings has been that the placebo arms also get better over time. That response can blunt the perceived efficacy in the study. This study nicely demonstrated that both resmetirom and semaglutide led to around a 15% improvement over placebo when looking at the baseline characteristics of the liver biopsies in the intervention as well as placebo arms. When the authors evaluated for this 2-point change in NAS, the placebo groups did have a similar response in both studies, showing that both of these agents worked.
>
> —Nancy S. Reau, MD

The proportion of patients attaining ballooning reduction was numerically higher for patients in the resmetirom 100 mg arm in the MAESTRO-NASH trial than for patients in the semaglutide arm in the ESSENCE trial (66% vs 61%); rates in the placebo arms in both trials were 31% and 40%, respectively, indicating a greater difference from placebo in the resmetirom trial.

Regarding safety, resmetirom was associated with higher rates of diarrhea and nausea vs placebo, and semaglutide was associated with higher rates of nausea, diarrhea, constipation, and vomiting vs placebo. In both trials, the incidence of serious AEs was similar between treatment and placebo arms.

ABSTRACT SUMMARY A Randomized, Placebo-Controlled, Phase 2 Study of the Safety and Efficacy of Combination Treatment With Semaglutide, Cilofexor, and Firsocostat in Patients With Compensated Cirrhosis Due to MASH (WAYFIND)

The WAYFIND trial evaluated the combination of semaglutide plus the fixed-dose combination of cilofexor (cilo), a nonsteroidal gut-restricted selective farnesoid X receptor agonist, and firsocostat (fir), a liver-targeted acetyl-coenzyme A carboxylase inhibitor, in patients with compensated cirrhosis (F4c) due to MASH (Abstract 0148). The trial enrolled 453 patients with a mean age of 62 years; 64.5% were female and 68.2% had diabetes mellitus. The study did not meet its primary endpoint, showing no significant difference in rates of fibrosis improvement without MASH worsening at week 72 with semaglutide plus cilo/fir compared with placebo as assessed by central pathologists (13.7% vs 8.3%; P=.2289). When liver biopsies were assessed by PathAI, rates of fibrosis improvement without MASH were significantly higher with semaglutide plus cilo/fir compared with placebo (16.0% vs 6.0%; nominal P=.0011) and were also higher with semaglutide vs placebo (12.4% vs 6.0%; P=.0093) and with cilo/fir alone vs placebo (12.9% vs 6.0%; P=.0066). Noninvasive fibrosis tests were also superior with semaglutide, cilo/fir, and the combination compared with placebo. Investigators noted that the combination regimen was well tolerated; no treatment-related serious AEs were reported.

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3. Loomba R, Taub R, Labriola D, Alkhouri N, Noureddin M. Comparison of MAESTRO-NASH and ESSENCE: effects of resmetirom and semaglutide relative to placebo on primary and secondary liver biopsy endpoints using aligned endpoints and statistical methods. AASLD abstract 4093. Presented at: The Liver Meeting; November 7-11, 2025; Washington, DC.


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