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A SPECIAL MEETING REVIEW EDITION

Highlights in MASH From the AASLD 2024 Liver Meeting

A Review of Selected Presentations From the American Association for the Study of Liver Diseases 2024 Liver Meeting • November 15-19, 2024 • San Diego, California

Special Reporting on:

- Phase 3 ESSENCE Trial: Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis
- Effect of Resmetirom or Placebo in NASH Fibrosis Patients With <5% or ≥5% Weight Loss and/or on Baseline GLP-1 Therapy in the MAESTRO-NASH 52-Week Serial Liver Biopsy Study
- Use of Glucagon-Like Peptide-1 Receptor Agonists in Patients With MASLD in a Real-World Setting Is Associated With Slower Disease Progression and Lower All-Cause Mortality
- Assessment of Resmetirom Efficacy (80 mg vs. 100 mg) Stratified by Baseline Body Mass Index and Weight in Patients From the MAESTRO-NASH Trial
- Results From the 52-Week Phase 2b VOYAGE Trial of VK2809 in Patients With Biopsy-Confirmed Non-Alcoholic Steatohepatitis and Fibrosis: A Randomized, Placebo-Controlled Trial
- Liver Enzymes Reductions From Baseline Over Time in Resmetirom-Treated Patients in a Phase 3 Study, MAESTRO-NASH
- Once-Monthly Efimosfermin Alfa (BOS-580) in Metabolic Dysfunction-Associated Steatohepatitis With F2/F3 Fibrosis: Results From a 24-Week, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial
- Resmetirom Effects on NASH With Liver Fibrosis in Patients With NASH Genetic Risk Alleles
- Aerobic Exercise Training Leads to MASH Resolution as Defined by the MASH Resolution Index Without Body Weight Loss

PLUS Meeting Abstract Summaries

With Expert Comments by:

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NOW APPROVED

Rezdiffra™

resmetirom tablets

60 mg · 80 mg · 100 mg

In conjunction with diet and exercise

The first and only FDA-approved treatment for adults with noncirrhotic NASH with moderate to advanced fibrosis

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

NASH=nonalcoholic steatohepatitis.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

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. 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 in one patient. *Please see full Prescribing Information for more details on this specific case of Hepatotoxicity [see Warnings and Precautions (5.1)].*

Monitor patients during treatment 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-Related Adverse Reactions (cont.)

gallbladder event is suspected, interrupt Rezdiffra treatment until the event is resolved.

Drug Interaction with Certain Statins

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 Interaction *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.

Hypersensitivity Reactions

Reactions such as urticaria and rash, which may reflect drug hypersensitivity, were observed in patients receiving Rezdiffra.

Laboratory Abnormalities

Increases in mean ALT and AST levels were observed in the first 4 weeks after initiating treatment with Rezdiffra. 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.

DRUG INTERACTIONS

Clinically Significant Interactions Affecting Rezdiffra

- **Strong or Moderate CYP2C8 Inhibitors:** Resmetirom is a CYP2C8 substrate. Concomitant use with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. Reduce dosage if used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel).
- **Organic Anion-Transporting Polypeptides (OATP) 1B1 and OATP1B3 Inhibitors:** Resmetirom is an OATP1B1 and OATP1B3 substrate. Concomitant use with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.

Clinically Significant Interactions Affecting Other Drugs

- **Statins**
  - Limit daily rosuvastatin and simvastatin dosage to 20 mg
  - Limit daily pravastatin and atorvastatin dosage to 40 mg
- **CYP2C8 Substrates:** Resmetirom is a weak CYP2C8 inhibitor. 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. There are risks to the mother and fetus

Pregnancy (cont.)

related to underlying NASH with liver fibrosis, such as increased risks of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage. 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.

Pediatric Use

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

Geriatric Use

No overall differences in effectiveness but 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 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.

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) increases resmetirom C_{max} and AUC, which may increase the risk of adverse reactions.

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A).

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

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.

Madrigal Pharmaceuticals

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, arrythmia, 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, 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, West Conshohocken, PA

REZDIFFRA™ (resmetirom)

Phase 3 ESSENCE Trial: Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that has been extensively studied in a wide spectrum of cardiometabolic diseases.[1,2] As cardiovascular disease is the leading cause of mortality in metabolic dysfunction-associated steatotic liver disease (MASLD), it has been surmised that agents that result in improvements in cardiometabolic risk factors would also result in improved MASLD outcomes, including an improved liver condition.[3,4] Indeed, a randomized placebo-controlled phase 2 trial demonstrated that among 320 patients with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis stage 1 to 3, semaglutide 0.4 mg once daily was associated with a significantly higher percentage of patients who achieved MASH resolution with no worsening of fibrosis compared with placebo (59% vs 17%; *P*<.001).[5] These data led to the design of the ESSENCE trial, an ongoing phase 3, randomized, controlled trial comparing once-weekly subcutaneous semaglutide 2.4 mg vs placebo in patients with biopsy-defined MASH and fibrosis stage 2 or 3.[4] Patients were randomized in a 2 to 1 ratio to treatment with semaglutide, which was initiated at a dose of 0.25 mg and titrated up over 16 weeks to a final dose of 2.4 mg once-weekly, or placebo. The ESSENCE study plans to treat patients for up to 240 weeks.

In a late-breaking abstract, Newsome and colleagues presented efficacy data from the first 800 participants who completed 72 weeks of treatment alongside a more up-to-date safety dataset.[6] This 72-week phase 1 of the ESSENCE study was evaluated against 2 primary endpoints—resolution of steatohepatitis with no worsening of liver fibrosis, and improvement in liver fibrosis with no worsening of steatohepatitis. Resolution of steatohepatitis was defined as a Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis. An improvement in fibrosis was defined as a 1 grade or higher improvement. No worsening of steatohepatitis was defined as no increase from baseline in NAS for ballooning, inflammation, or steatosis. The 2 primary endpoints were analyzed using a Cochran-Mantel-Haenszel test, stratified by both baseline diabetes status as well as fibrosis stage.

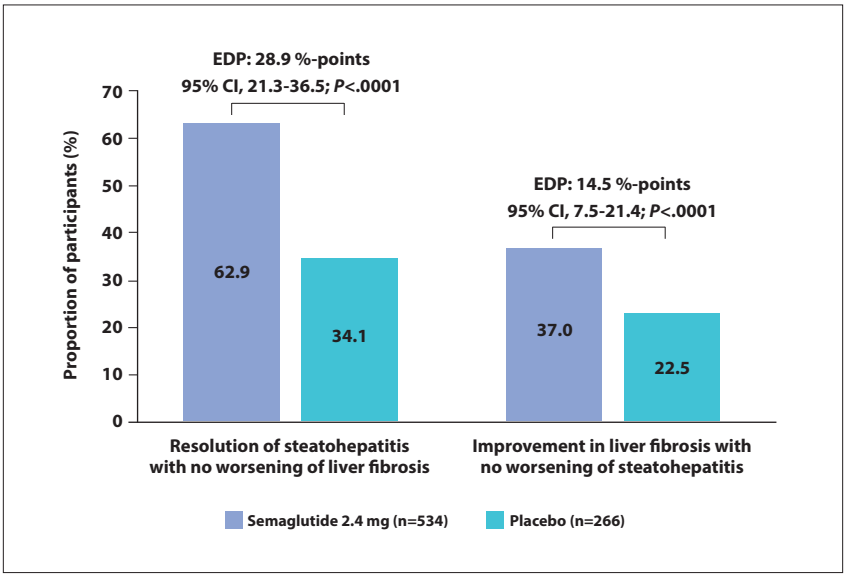

Figure 1. Intention-to-treat population with metabolic dysfunction-associated steatohepatitis meeting the primary endpoints in the ESSENCE trial. EDP, estimated difference in responder proportions. Adapted from Newsome PN, et al. AASLD abstract 5018. Presented at: The Liver Meeting; November 15-19, 2024; San Diego, CA.[6]

Among the first 800 randomized patients, 534 were randomized to treatment with semaglutide; at week 72, 88% remained on treatment and 87% had a biopsy. Baseline characteristics were well balanced across the semaglutide and placebo arms. The mean age was 56.3 years in the semaglutide arm and 55.4 years in the placebo arm; 58.6% and 54.1%, respectively, were female. At baseline, 55.4% of semaglutide-treated patients and 56.8% of placebo-treated patients had type 2 diabetes, and the mean body mass index (BMI) was 34.3 and 35.0, respectively. Approximately two-thirds of patients in each arm had fibrosis stage 3 (68.4% in the semaglutide arm and 69.5% in the placebo arm).

The primary endpoint of resolution of steatohepatitis with no worsening of fibrosis was achieved in semaglutide- vs placebo-treated patients, respectively (62.9% vs 34.1%) (Figure 1). These results were considered to be highly significant, with an estimated difference in respondent proportions (EDP) of 28.9 percentage points (*P*<.0001). A similarly significant improvement in the other primary endpoint of improvement in liver fibrosis with no worsening of steatohepatitis was also observed in the semaglutide vs placebo arms (37.0% vs 22.5%; an EDP of 14.5 percentage points; *P*<.0001).

Results from several confirmatory secondary endpoints were also reported. One of these, patients who achieved both resolution of steatohepatitis and a 1-stage improvement in liver fibrosis, was significantly improved in the semaglutide arm compared with the placebo arm (32.8% vs 16.2%; *P*<.0001). Not unexpectedly, the

Semaglutide was significantly associated with improvement in both MASH resolution and fibrosis regression compared with placebo. These results were the most anticipated trial readout at The Liver Meeting and were met with great enthusiasm. Semaglutide has positive effects on each component of the metabolic syndrome, and now, its potential as a treatment for MASH with fibrosis can be seen. However, the modest estimated difference in responder proportions in fibrosis of 14.5% compared with placebo definitely leaves room for newer drugs and combination therapy.

— Naim Alkhouri, MD

mean change from baseline in body weight was significantly improved among semaglutide-treated patients vs placebo-treated patients (–10.5 vs –2.0, respectively; *P*<.0001). In contrast, the confirmatory secondary endpoint of mean change from baseline in bodily pain, chosen because it was significantly impacted in the phase 2 trial, did not achieve statistical significance in this study (0.9 vs –0.5 in the semaglutide vs placebo arms; *P*=.0488; a higher score represents an improvement in bodily pain).

A consistent effect of semaglutide on liver enzyme levels was observed, with a 30% to 40% placebo-adjusted reduction with semaglutide compared with placebo. These included a 40% decrease in alanine aminotransferase (ALT), 30% decrease in aspartate aminotransferase (AST), and 40% decrease in gamma-glutamyl transferase (GGT); *P*<.0001 vs placebo for all comparisons. The same was true for the noninvasive measurements of fibrosis, including changes in liver stiffness values assessed by vibration-controlled transient elastography (FibroScan), which was improved by a decrease of 20%; change in Enhanced Liver Fibrosis score, which was improved by a decrease of 0.6 units; and change in Pro-C3 level, which was improved by a decrease of 20%. An evaluation of cardiometabolic risk parameters showed significant improvements with semaglutide vs placebo across nearly all measures, including systolic and diastolic blood pressures, dyslipidemia (except low-density lipoprotein cholesterol), and highly sensitive C-reactive protein.

Between the semaglutide and placebo arms, there was no increase in serious nor fatal adverse events (AEs). Discontinuations owing to AEs were also not significantly increased with semaglutide vs placebo. In accordance with previous safety findings with semaglutide, gastrointestinal side effects were more commonly found in patients receiving semaglutide vs placebo, including nausea (36.3% vs 13.2%), diarrhea (26.9% vs 12.2%), and constipation (22.3% vs 8.4%). With regard to a specific AE, an increase in gallbladder-related disorders was noted (2.5% vs 1.5%).

These data led the study authors to conclude that semaglutide was associated with superior MASH-related outcomes compared with placebo.

References

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ABSTRACT SUMMARY Performance of Noninvasive Tests in Identifying Appropriate Patients for Resmetirom Treatment: Real-World Data From Four Tertiary Care Centers

In an attempt to find an alternative method for identifying patients eligible for treatment with resmetirom, an algorithm was proposed that included controlled attenuation parameter (≥80 dB/m), liver stiffness measurement (10-20 kPa), and platelet count (≥150 × 103/μL). This algorithm was applied to a cohort of 1006 patients with biopsy-proven patients with MASLD (Abstract 2041). The combination of these criteria was associated with a poor sensitivity of 39.3% and specificity of 67.7% to identify patients with accurate histologic features. This was associated with a positive predictive value of 0.390 and a negative predictive value of 0.680. These criteria showed a similarly poor performance in the prediction of the presence of F2/F3 disease on biopsy.

Effect of Resmetirom or Placebo in NASH Fibrosis Patients With <5% or ≥5% Weight Loss and/or on Baseline GLP-1 Therapy in the MAESTRO-NASH 52-Week Serial Liver Biopsy Study

In MASH, the function of the thyroid hormone receptor beta (THR-β) is reduced, causing a reduction in mitochondrial function and β-oxidation of fatty acids, resulting in an increase in fibrosis. The oral agent resmetirom, a liver-directed THR-β–selective agonist, was approved by the US Food and Drug Administration (FDA) in March 2024 for the treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stage F2 or F3 fibrosis), based on the results of the MAESTRO-NASH phase 3 trial.[1-3] Noureddin and colleagues summarized the results from the MAESTRO-NASH study on the effect of resmetirom in patients with biopsy-confirmed MASH and fibrosis with weight loss or GLP-1 therapy.[4] (Note: the term MASH replaces NASH throughout except when used in a trial name).

The aim of the ongoing 54-month, randomized, double-blind, placebo-controlled MAESTRO-NASH trial is 2-fold: to determine the effects of resmetirom compared with placebo on GLP-1 therapy at baseline, and to determine the effect of at least 5% weight loss on liver biopsy endpoints with or without GLP-1 baseline therapy. At baseline, 13% to 17% of patients in the treatment groups were receiving stable GLP-1 therapy for at least 6 months prior to randomization. All of the patients receiving GLP-1 therapy in the MAESTRO-NASH study had type 2 diabetes, with multiple GLP-1 therapies used. Other diabetic therapies associated with weight loss included sodium-glucose cotransporter 2 (SGLT2) inhibitors.

To be eligible for study enrollment, patients were required to have the presence of 3 or more metabolic risk factors, as well as diagnosed MASH on biopsy with a NAS of 4 or greater (with ≥1 in each component), fibrosis stage F1, F2, or F3, and 8% or more hepatic fat by magnetic resonance imaging proton density fat fraction (MRI-PDFF). A total of 966 patients with biopsy-confirmed MASH were randomized in a 1:1:1 ratio to treatment with either resmetirom 80 mg, resmetirom 100 mg, or placebo, each administered orally once daily. Additionally, patients were counseled on moderate diet and exercise at each study visit. Dual histologic primary endpoints were both assessed at week 52—MASH resolution and fibrosis improvement. MASH resolution was defined as a ballooning score equal to 0, an inflammation score equal to 0 or 1, and a reduction in NAS of at least 2 points, with no worsening of fibrosis. Fibrosis improvement was defined as at least a 1 stage improvement in fibrosis, with no worsening of NAS.

Among patients with diabetes, there were no meaningful differences in baseline characteristics between patients treated with either GLP-1 or SGLT2 therapy. The most common dose was 1 mg semaglutide or comparable (dulaglutide). At baseline, fibrosis stage 3 was more common in patients with diabetes (64.1%) and patients receiving GLP-1 therapy (67.9%) compared with patients without diabetes (52.7%). The same was true for hypertension (83.3%, 84.7%, and 67.4%, respectively) and dyslipidemia (79.8%, 85.4%, and 54.2%, respectively). More patients who were diabetic (58.1%) and diabetic receiving GLP-1 therapy (61.3%) were being treated with

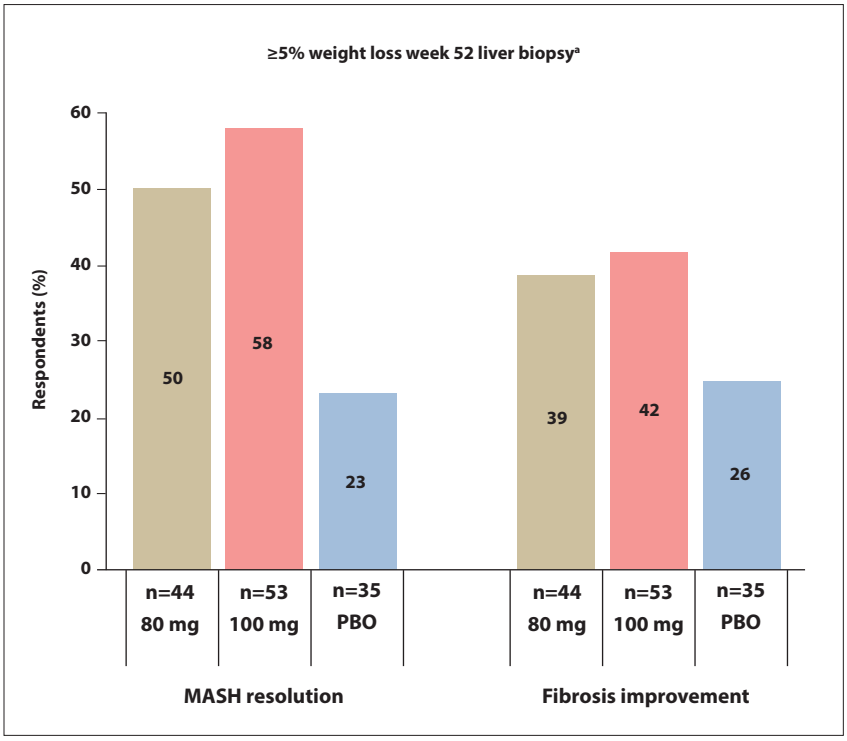

Figure 2. Impact of weight loss on biopsy endpoints, MASH resolution and fibrosis improvement, in patients treated with resmetirom in the MAESTRO-NASH study. MASH, metabolic dysfunction-associated steatohepatitis; PBO, placebo. [a]Patients with week 52 weight loss data and biopsy; consensus biopsy review. Adapted from Noureddin M, et al. AASLD abstract 132. *Hepatology.* 2024;80(suppl 1).[4]

The fact that a modest amount of weight loss (≥5% of total body weight) significantly enhanced the rates of both MASH resolution and fibrosis improvement in patients treated with resmetirom should emphasize to treating clinicians the importance of a comprehensive lifestyle intervention as part of any management plan for patients with MASH.

— Naim Alkhouri, MD

a statin at baseline compared with nondiabetic patients (30.4%). In contrast, this group of patients had lower liver enzymes (mean ALT: 52.1 U/L, 45.6 U/L, and 62.1 U/L; mean AST: 38.8 U/L, 34.3 U/L, and 45.7 U/L). Patients on GLP-1 therapy at baseline showed no difference in baseline MRI-PDFF or body weight.

Among patients with diabetes who were treated with either dose of resmetirom plus GLP-1 therapy, liver biopsy responses were equivalent to those in patients with diabetes who were not receiving these therapies. For patients on GLP-1 therapy, the coprimary endpoint of MASH resolution was achieved in 27% and 39% of patients treated with resmetirom 80 mg and resmetirom 100 mg, respectively, compared with 32% and 38% of patients not treated with GLP-1 therapy. Similarly, the other coprimary endpoint of fibrosis improvement was achieved in 29% and 20% of patients treated with resmetirom 80 mg and resmetirom 100 mg, respectively, compared with 29% and 32% of patients not receiving GLP-1 therapy.

A similar trend was observed in patients with diabetes who were treated with either dose of resmetirom plus SGLT2 therapy. In patients treated with SGLT2 therapy, MASH resolution was achieved in 36% and 43% of patients treated with resmetirom 80 mg and resmetirom 100 mg, respectively, compared with 29% and 37% of patients not treated with SGLT2 therapy. Similarly, fibrosis improvement was achieved in 22% and 28% of patients treated with resmetirom 80 mg and resmetirom 100 mg, respectively, compared with 31% and 30% of patients not receiving SGLT2 therapy.

Further, neither diabetes drug impacted MRI-PDFF reduction at week 52 by resmetirom. At week 52, the MRI-PDFF reduction overall (regardless of diabetes drug) was –44% and –50% among patients with no diabetes treated with resmetirom 80 mg and resmetirom 100 mg, respectively, and was –41% and –52% among patients with diabetes treated with resmetirom 80 mg and resmetirom 100 mg, respectively. When analyzing the MRI-PDFF reduction in patients with diabetes, there was no difference between patients with GLP-1 therapy (–36% in resmetirom 80 mg– and –52% in resmetirom 100 mg–treated patients) and without GLP-1 therapy (–41% in resmetirom 80 mg– and –52% in resmetirom 100 mg–treated patients). Similar outcomes were noted for patients with diabetes treated with either SGLT2 therapy or insulin.

Weight loss of 5% or more at week 52 was observed more frequently in resmetirom- as compared with placebo-treated patients (17% and 22% in the resmetirom 80 mg and 100 mg groups, respectively). Among patients who achieved a 5% or more weight loss, the median weight loss was 7%. Weight loss of 5% or more that was achieved by diet and exercise occurred in approximately 22% of patients treated with either dose of resmetirom, compared with 12% of patients treated with placebo. GLP-1 treatment was not associated with weight loss; rates of weight loss of 5% or more or less than 5% were 14% vs 15%, respectively, for patients on GLP-1 therapy.

Weight loss of 5% or more was associated with high rates of MASH resolution and fibrosis improvement among resmetirom-treated patients. Among patients treated with resmetirom 100 mg specifically, a 5% or more weight loss was associated with increased fibrosis improvement (42%) and MASH resolution (58%) on liver biopsy (Figure 2). Similar outcomes were also reported among patients treated with resmetirom 80 mg. Compared with placebo, 3-fold more patients who were treated with resmetirom and had achieved a 5% or more weight loss had also achieved the coprimary endpoints of MASH resolution or fibrosis improvement.

MRI-PDFF reduction in patients with 5% or more weight loss improved at week 52 relative to week 16; there was no change between week 16 and week 52 in patients with less than 5% weight loss. Among resmetirom-treated patients, 98% with 5% or more weight loss had a 30% or higher MRI-PDFF reduction. The study authors concluded that relatively small amounts of weight loss (≥5%) could enhance the effects of resmetirom on outcomes such as MASH resolution and liver fibrosis improvement.

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Use of Glucagon-Like Peptide-1 Receptor Agonists in Patients With MASLD in a Real-World Setting Is Associated With Slower Disease Progression and Lower All-Cause Mortality

GLP-1 RAs, currently used in the treatment of type 2 diabetes and obesity, are also under investigation for their potential to reduce the risk for cirrhosis and other complications in patients with MASLD.[1,2] Barritt and colleagues presented a study in which they evaluated the association between the use of GLP-1 RAs and MASLD outcomes.[3]

TARGET-NASH, a real-world longitudinal observational cohort study, included patients with MASLD who were receiving usual care at academic and community sites across the United States. Once enrolled, participants consented to provide access to their prior 3 years of medical records and were then prospectively followed. A detailed curation of these data was conducted using human in-the-loop and automated methodologies, encompassing electronic health records, clinician narratives, laboratory results, imaging, and pathology reports.

A set of real-world definitions was used to define the disease states for this study.[4] If a patient had a biopsy, this would be used to define their disease as either metabolic dysfunction-associated steatotic liver (MASL), MASH, or MASH cirrhosis. Without a biopsy, MASH was defined as the presence of hepatic steatosis on imaging (computed tomography, ultrasound, or MRI), presence of at least one cardiometabolic risk factor, and elevated ALT. MASH cirrhosis was defined as the presence of one or more cardiovascular risk factors and hepatic steatosis with one of the following: fibrosis stage 4 on liver biopsy; fibrosis stage 3 on liver biopsy and one or more secondary indicators (evidence of ascites, portal hypertension, varices or portal gastropathy, platelet count <140,000, or cirrhosis or splenomegaly on imaging or scans); the presence of 2 or more secondary indicators; FibroScan stiffness result of 12.5 to 15.9 kPa together with one or more secondary indicators; or transient elastography stiffness results (≥16 kPa). Decompensation events were defined either as any ascites, any complications of ascites, hepatic encephalopathy, or variceal bleeding.

The analysis reported here aimed to describe the demographics and clinical characteristics, disease progression, and all-cause mortality among patients with MASLD who were prescribed

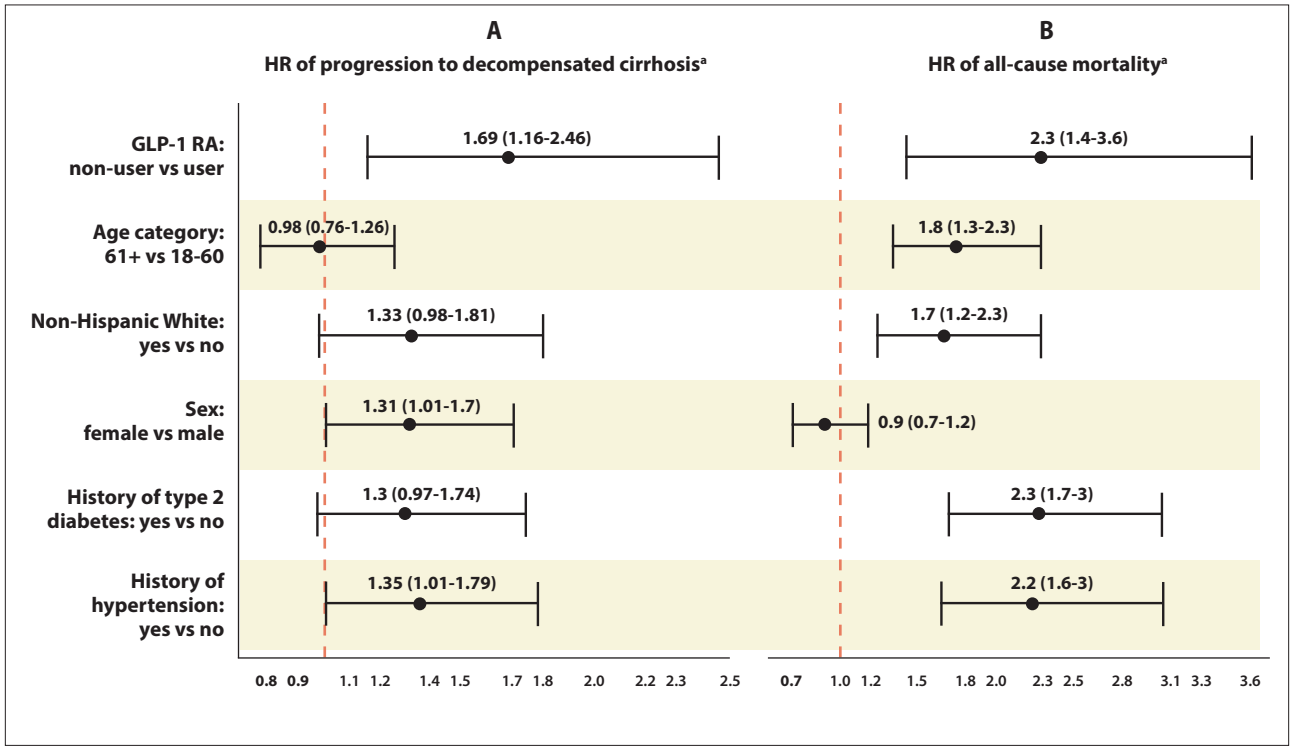

Figure 3. Liver disease progression and all-cause mortality in diabetic patients with metabolic dysfunction-associated steatotic liver disease who were GLP-1 RA users vs non-users. GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio. [a]HR estimates (95% CI) are rounded. Adapted from Barritt AS, et al. AASLD abstract 772. *Hepatology.* 2024;80(suppl 1).[3]

GLP-1 RAs in real-world clinical practice through the TARGET-NASH study. To be included in the analysis, patients were required to be adults who had been diagnosed with MASL, MASH, or MASH cirrhosis in the 3 years prior to enrollment. Patients were grouped into cohorts defined by their use of GLP-1 treatments; GLP-1 RA users were defined as patients who had received either a GLP-1 RA or GLP-1 RA/glucose-dependent insulinotropic polypeptide for at least 1 year. Exclusion criteria included having 6 months or less of follow-up data, either prevalent liver cancer or liver transplant, or having received a GLP-1 RA for less than 1 year.

After excluding patients, a total of 4219 remained for analysis. These patients were relatively evenly distributed among disease definitions (1311 with MASL, 1331 with MASH, and 1577 with MASH cirrhosis). About 10% of patients met the definition for GLP-1 RA users (375 GLP-1 RA users and 3844 nonusers). Across the disease definitions, 86, 74, and 215 patients in the MASL, MASH, and MASH cirrhosis cohorts were GLP-1 RA users.

According to the patient demographics, as the disease progressed, the age increased. However, within each group, median age was similar between GLP-1 RA users and nonusers. More females accounted for the GLP-1 RA users vs nonusers in both the MASH (74.3% vs 59.6%; *P*<.05) and the MASH with cirrhosis (65.6% vs 56.8%; *P*<.05) cohorts. Within the MASH cohort, there were more prevalent cardiovascular events in GLP-1 RA users vs nonusers (21.6% vs 12.6%; *P*<.05), but not in the MASH with cirrhosis cohort (34.9% vs 32.2%). Hypertension was also more frequent in GLP-1 RA users compared with nonusers in the MASH (67.6% vs 52.4%; *P*<.05) and MASH with cirrhosis (78.1% vs 71.3%; *P*<.05) cohorts. Type 2 diabetes mellitus was more common among the GLP-1 RA users vs nonusers in all 3 cohorts (MASL: 80.2% vs 28.0%; MASH: 81.1% vs 33.3%; and MASH with cirrhosis: 93.5% vs 63.4%; *P*<.05 for all comparisons).

> This study used real-world data from a large cohort that included over 4000 patients with MASLD and showed a significant reduction in both overall mortality and progression to decompensated cirrhosis in diabetic patients who were receiving GLP-1 RAs compared with nonusers. These results highlight the need to prioritize the use of GLP-1 RAs in patients with diabetes and MASLD, given the beneficial effects of these medications on meaningful long-term outcomes.
>
> — Naim Alkhouri, MD

Disease progression events from compensated to decompensated cirrhosis occurred in 33 (20%) of the GLP-1 RA users compared with 217 (23%) of the nonusers. This was calculated to yield a hazard ratio (HR) of 1.69 (95% CI, 1.16-2.46) for the development of a decompensation event among GLP-1 RA users (Figure 3A). By comparison, other factors that increase the risk for disease progression were associated with less of a hazard risk, including non-Hispanic White race (HR, 1.331; 95% CI, 0.981-1.805), female sex (HR, 1.309; 95% CI, 1.008-1.700), the presence of type 2 diabetes (HR, 1.302; 95% CI, 0.972-1.744), and the presence of hypertension (HR, 1.347; 95% CI, 1.012-1.79). The median time of disease progression from compensated to decompensated cirrhosis was 24.2 months vs 21.2 months in the 2 groups.

The number of mortality events observed was 20 (5%) among GLP-1 RA users compared with 243 (6%) among nonusers, which was calculated as an increased risk of death (HR, 2.28; 95% CI, 1.43-3.60) in nonusers (Figure 3B). This was similar to the increased risk of death observed with type 2 diabetes (HR, 2.263; 95% CI, 1.689-3.032) and hypertension (HR, 2.229; 95% CI, 1.635-3.037). This HR was higher than the HR for other factors such as age (61+ years vs 18-60 years; HR, 1.746; 95% CI, 1.341-2.273) and non-Hispanic White race (HR, 1.671; 95% CI, 1.237-2.256).

According to the authors, the limitations for this analysis included the use of real-world data with nonstandardized follow-up, as well as the use of pragmatic disease definitions that were not based on histology. There is also a potential for a healthy user effect among patients who received treatment with GLP-1 RAs, particularly in this nonrandomized study.

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Assessment of Resmetirom Efficacy (80 mg vs. 100 mg) Stratified by Baseline Body Mass Index and Weight in Patients From the MAESTRO-NASH Trial

Noureddin and colleagues presented a second analysis of the MAESTRO-NASH trial, which focused on the efficacy of resmetirom according to baseline BMI and weight.[1] The recommended dosage of resmetirom is based on actual body weight; for patients weighing under 100 kg, the recommended dosage is 80 mg orally once daily, whereas for patients who weigh 100 kg or more, the recommended dosage is 100 mg orally once daily.[2]

The only variable found to determine exposure to resmetirom among patients with MASH was body weight. Pharmacokinetic modeling indicated that patients with a higher exposure to resmetirom showed a higher rate of sex hormone-binding globulin (SHBG) response (≥120% increase in SHBG) and also a higher rate of MRI-PDFF response (≥30% reduction in MRI-PDFF). More patients treated with resmetirom 100 mg vs resmetirom 80 mg achieved these targets for SHBG and PDFF, with differences between doses occurring primarily in patients with a body weight of 100 kg or more.

Further exposure modeling showed that higher exposure to resmetirom was also associated with higher rates of both MASH and fibrosis responses on biopsy (Figure 4). Among patients weighing less than 100 kg, the rate of MASH resolution was 32% and 36% among patients treated with resmetirom 80 mg and resmetirom 100 mg, respectively. In patients weighing 100 kg or more, the rate of MASH resolution was 27% and 36% in the resmetirom 80 mg and resmetirom 100 mg treatment groups, respectively. For the outcome of fibrosis improvement, among patients weighing less than 100 kg, 35% and 34% achieved fibrosis improvement with resmetirom 80 mg and resmetirom 100 mg, respectively. In patients weighing 100 kg or more, the rate of fibrosis improvement was 23% and 33% in the resmetirom 80 mg and resmetirom 100 mg treatment groups, respectively.

Among patients who had both a baseline and week 52 liver biopsy, equivalent biopsy responses for both MASH resolution (22% with resmetirom 80 mg and 21% with resmetirom 100 mg) and fibrosis improvement (13% with resmetirom 80 mg and 12% with resmetirom 100 mg) were achieved in patients with a BMI less than 35. However, among patients with a higher BMI (≥35), the rates of MASH resolution (10% with resmetirom 80 mg and 20% with resmetirom 100 mg) and fibrosis improvement (7% with resmetirom 80 mg and 11% with resmetirom 100 mg) were both

> These data provide reassurance that dosing resmetirom based on the prescribing information provided by the FDA (80 mg daily for those with weight <100 kg and 100 mg daily for those with weight ≥100 kg) is appropriate and will not be associated with lower response rates with the lower dose. Providers should strive to keep patients who weigh over 100 kg, or who have a BMI of 35 or more, on the higher dose.
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> — Naim Alkhouri, MD

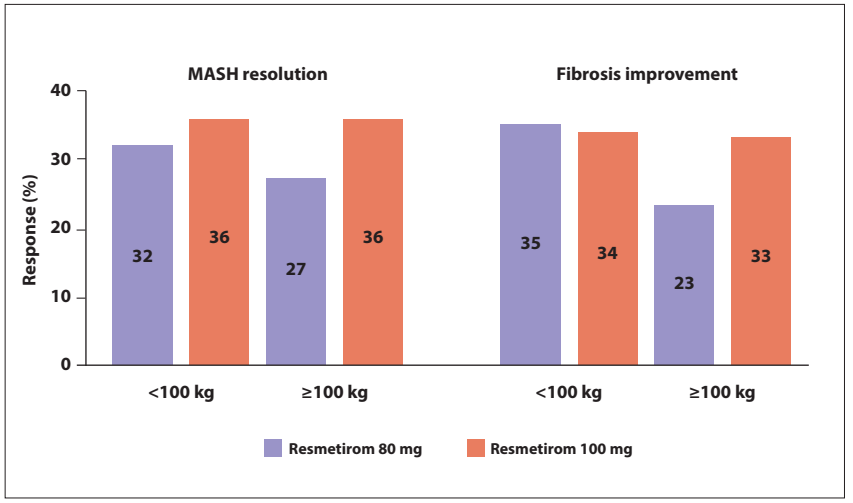

Figure 4. Liver biopsy responses to resmetirom doses of 80 mg and 100 mg in patients with MASH from the MAESTRO-NASH trial stratified by weight. Paired biopsy population (both baseline and week 52 not placebo corrected). MASH, metabolic dysfunction-associated steatohepatitis. Adapted from Noureddin M, et al. AASLD abstract 1644. *Hepatology.* 2024;80(suppl 1).[1]

higher with resmetirom 100 mg.

Other biomarkers, such as ALT, FibroScan, and controlled attenuation parameter, showed similar improvements relative to placebo at both resmetirom doses.

The frequency of diarrhea was higher with the resmetirom 100 mg dose compared with the resmetirom 80 mg dose (33.4% vs 27.0%) and was higher with both than with placebo (15.6%). The rate of discontinuation owing to an AE was higher with resmetirom 100 mg (6.8%) but was relatively similar between resmetirom 80 mg (1.9%) and placebo (2.2%). Further, the rate of overall discontinuations of the resmetirom 100 mg dose was highest in the lower body weight group (19% in the <100 kg group compared with 17% in the ≥100 kg group), but the opposite was true for the resmetirom 80 mg dose (10% in the <100 kg group compared with 15% in the ≥100 kg group).

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Results From the 52-Week Phase 2b VOYAGE Trial of VK2809 in Patients With Biopsy-Confirmed Non-Alcoholic Steatohepatitis and Fibrosis: A Randomized, Placebo-Controlled Trial

Lian and colleagues presented data from the 52-week phase 2b VOYAGE trial, which evaluated the investigational agent VK2809, a potent and selective THR-β agonist.[1,2] VK2809 has been demonstrated to have liver-targeting characteristics, including CYP3A4-mediated cleavage; because CYP3A4 is primarily expressed in the liver, this results in a largely targeted delivery of the drug to the liver tissue.

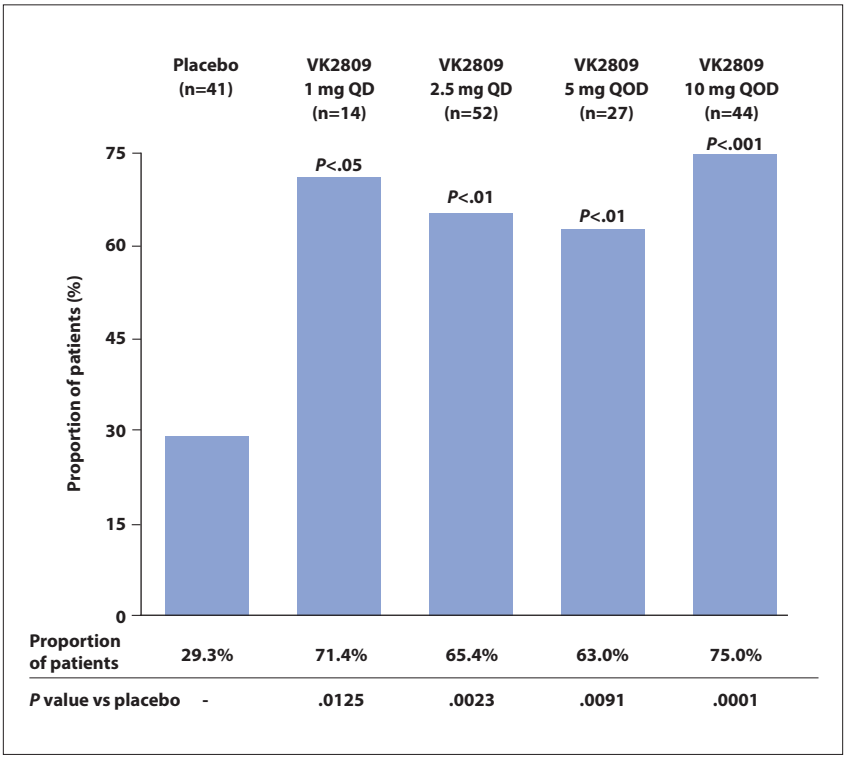

Figure 5. Proportion of patients (all with baseline magnetic imaging and week 52 biopsy) treated with VK2809 in the phase 2b VOYAGE trial demonstrating resolution of metabolic dysfunction-associated steatohepatitis with no worsening of fibrosis. QD, every day; QOD, every other day. Adapted from Lian B, et al. AASLD abstract 5016. Presented at: The Liver Meeting; November 15-19, 2024; San Diego, CA.[1]

The VOYAGE study was designed as a 12-month, double-blind, placebo-controlled, phase 2b trial. In this study, patients with biopsy-confirmed MASH were randomized to treatment with either placebo or VK2809 at 1 of 4 doses (1.0 mg once daily, 2.5 mg once daily, 5 mg every other day, or 10 mg every other day). At baseline, patient characteristics were well balanced, with females more prevalent than males across all arms, and age, weight, and BMI consistent across all arms.

The primary endpoint of the VOYAGE study was the change in MRI-PDFF at 3 months. A significant reduction in liver fat was observed at this time point at all doses of VK2809, except 1.0 mg once daily, compared with placebo. Patients experienced up to a 57% median reduction in MRI-PDFF from baseline. Importantly, these reductions in liver fat were sustained or improved through week 52, which showed up to a 56% median reduction in MRI-PDFF from baseline. Up to 85% of patients treated with VK2809 achieved a 30% or more decrease in liver fat at 12 weeks; this was increased to 88% at the week 52 time point. A reduction in liver fat was found to correlate with improved odds of long-term histology benefit.

Resolution of MASH without worsening of fibrosis was observed in

These promising results with VK2809 provide further validation for targeting thyroid hormone receptor beta as an effective treatment for patients with MASH and significant fibrosis. The high rates of MASH resolution, fibrosis improvement, and reduction in liver fat fraction lend support to developing VK2809 in phase 3 trials. The beneficial effects on lipid levels seen in this trial may also lead to improved cardiovascular outcomes with long-term use; however, these beneficial effects need to be proven in prospective trials.

— Naim Alkhouri, MD

up to 75% of patients (Figure 5). At the highest 2 doses of VK2809 (5 mg or 10 mg every other day), a significant proportion of patients achieved a 1-stage or higher improvement in fibrosis, without worsening of MASH. Among this group, similar fibrosis improvement rates were observed among patients with F2 or F3 stages.

The majority (94%) of treatment-emergent AEs reported were mild or moderate, and the rates of discontinuations due to an AE were balanced across the VK2809 doses and in comparison to placebo. The rates of gastrointestinal-related AEs in VK2809-treated patients were similar to placebo-treated patients.

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Liver Enzymes Reductions From Baseline Over Time in Resmetirom-Treated Patients in a Phase 3 Study, MAESTRO-NASH

Many patients treated with resmetirom may also receive treatment with statins, the latter of which are known to have potentially harmful effects on the liver.[1,2] Therefore, Baum and colleagues reported on an analysis of the phase 3 MAESTRO-NASH trial, which aimed to evaluate the effects of resmetirom and statins, alone and in combination, on liver function as assessed by changes in the levels of the liver enzymes ALT, AST, and GGT over time.[3]

As part of the eligibility criteria for enrollment in MAESTRO-NASH, patients were required to have an AST level of greater than 17 U/L (women) or greater than 20 U/L (men), and were excluded if serum ALT was greater than 250 U/L. At baseline, 49% of the 966 patients were receiving treatment with a statin. These included atorvastatin (23.1%), rosuvastatin (11.8%), simvastatin (6.6%), pravastatin (6.5%), lovastatin (0.7%), and pitavastatin (0.3%). Among the 49% of patients receiving a statin, 13% were receiving treatment with high-intensity statin therapy (rosuvastatin 20 mg; atorvastatin 40 mg) and the remaining 36% were receiving treatment with moderate-to-low-intensity statin therapy (36%).

Among the 473 patients who were receiving statins at baseline, a total of 149 patients were randomized to receive resmetirom 80 mg, 166 received resmetirom 100 mg, and 158 received placebo. At baseline, patients

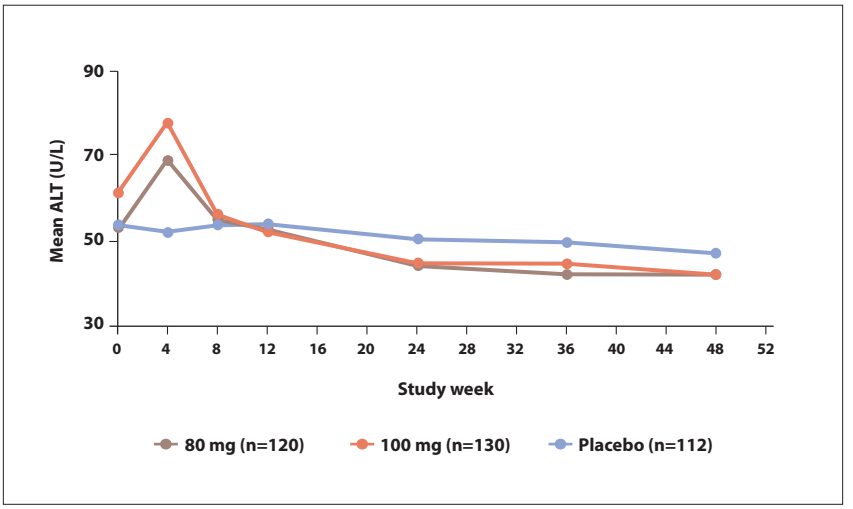

Figure 6. ALT levels at baseline and post randomization in patients receiving resmetirom 80 mg or 100 mg and a statin vs placebo in the MAESTRO-NASH trial. ALT, alanine aminotransferase. Adapted from Baum S, et al. AASLD abstract 1652. *Hepatology.* 2024;80(suppl 1).[3]

This study provides reassurance that the mild increases in ALT and AST seen in patients on baseline statin therapy treated with resmetirom were mild and transient. The ALT and AST levels slightly increased by week 4 (<1.5 the baseline values), with the levels returning to baseline by week 8, then improving by week 12.

— Naim Alkhouri, MD

receiving statins had lower liver enzyme levels than patients not receiving statins (median ALT level, 43 U/L vs 54 U/L; median AST level, 33 U/L vs 38 U/L; and median GGT level, 55 U/L vs 51 U/L).

Mild increases in both ALT and AST levels (<1.5-fold over baseline) were apparent at week 4 among statin-treated patients compared with patients not receiving statins, as shown in Figure 6 for ALT. These increases were transient and resolved by week 8, declining thereafter. GGT levels declined from the time resmetirom treatment was initiated.

In patients with ALT levels of 30 U/L or higher at baseline who were receiving a statin, at week 48 the ALT level had declined from baseline by 20% in the resmetirom 80 mg arm and 24% in the resmetirom 100 mg arm (P<.001 vs placebo for both comparisons). Among patients who were not receiving a statin, the week 48 ALT levels had declined from baseline by 37% and 43% in the resmetirom 80 mg and 100 mg arms, respectively (P<.001 vs placebo for both comparisons).

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Once-Monthly Efimosfermin Alfa (BOS-580) in Metabolic Dysfunction-Associated Steatohepatitis With F2/F3 Fibrosis: Results From a 24-Week, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial

Efimosfermin alfa is a long-acting, once-monthly fibroblast growth factor 21 (FGF21) analogue with an extended half-life of 21 days. In a phase 2a multiple dose/regimen study, efimosfermin alfa led to significant improvements in liver steatosis, markers of liver injury, and fibrosis among patients with MASH.[1] Noureddin and colleagues presented results of the histologic assessment of a randomized, double-blind phase 2b study comparing efimosfermin alfa 300 mg once monthly vs placebo.[2]

To be eligible for the study, patients were required to have biopsy-confirmed MASH with F2 and F3 fibrotic stage. The primary endpoint was safety and tolerability; histologic endpoints were also evaluated, including fibrosis improvement of 1 or more stages without worsening of MASH, MASH resolution without worsening of fibrosis, and fibrosis improvement together with MASH resolution. A total of 84 patients were randomized, with 67 completing study treatment. Baseline characteristics were well balanced between the efimosfermin alfa and placebo arms, with the exception

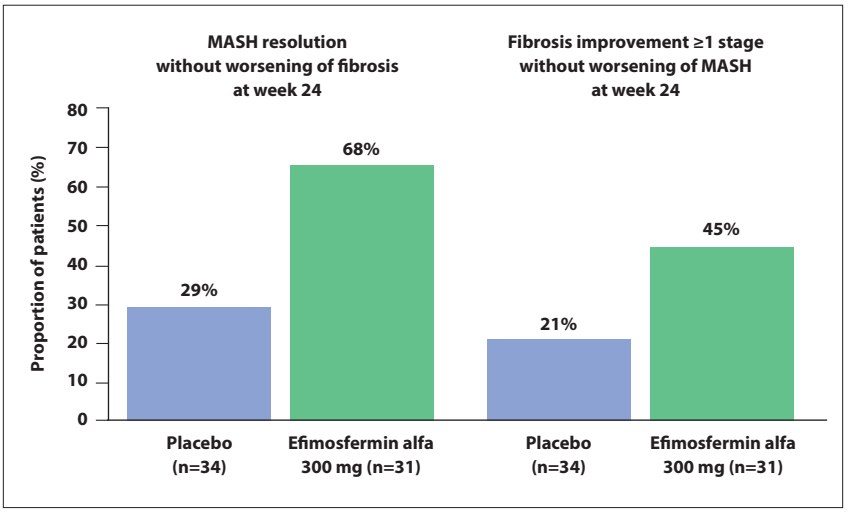

Figure 7. Effects of once-monthly efimosfermin alfa treatment at 24 weeks in patients with biopsy-confirmed MASH and F2/F3 fibrosis. MASH, metabolic dysfunction-associated steatohepatitis. Adapted from Noureddin M, et al. AASLD abstract 5017. Presented at: The Liver Meeting; November 15-19, 2024; San Diego, CA.[2]

Efimosfermin alfa represents an attractive new therapeutic target for MASH with fibrosis, given its mechanism of action as an FGF21 agonist, and the fact that it can be dosed monthly. The results of this phase 2 trial demonstrated high efficacy on fibrosis regression and MASH resolution after a relatively short duration of treatment, providing confidence for taking this drug into phase 3 development.

— Naim Alkhouri, MD

of a higher proportion of patients with diabetes in the efimosfermin alfa group.

Efimosfermin alfa, compared with placebo, achieved statistically significant improvements at week 24 in MASH resolution without worsening of fibrosis (68% vs 29%; *P*<.01) and fibrosis improvement without worsening of MASH (45% vs 21%; *P*<.01), as shown in Figure 7. Several biomarkers were also improved with efimosfermin alfa, including MRI-PDFF reduction as well as clinically meaningful glycemic control markers such as glycated hemoglobin.

Efimosfermin alfa was associated with a favorable safety profile; one grade 3 treatment-related AE was reported. Low rates (<5%) of changes in appetite were reported with efimosfermin alfa, and no weight gain was apparent. Few (<5%) injection site reactions occurred.

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Resmetirom Effects on NASH With Liver Fibrosis in Patients With NASH Genetic Risk Alleles

Another analysis of the MAESTRO-NASH study was presented by Chalasani and colleagues.[1] This analysis focused on the impact of particular genotypes (*PNPLA3*, *HSD17B13*, *TM6SF2*, *SERPIN* [*AAT*], and *MBOAT7*) on baseline characteristics and the response to resmetirom. In MAESTRO-NASH, single nucleotide polymorphisms were genotyped in 740 patients across the 3 arms consenting to DNA collection and genetic testing.

A significant proportion of patients in the MAESTRO-NASH study were positive for genetic risk markers, particularly *PNPLA3* (22.5% homozygous vs 10.5% in the non-MASH population) and *HSD17B13* (65% wild-type vs 52% to 58% in the non-MASH population), as well

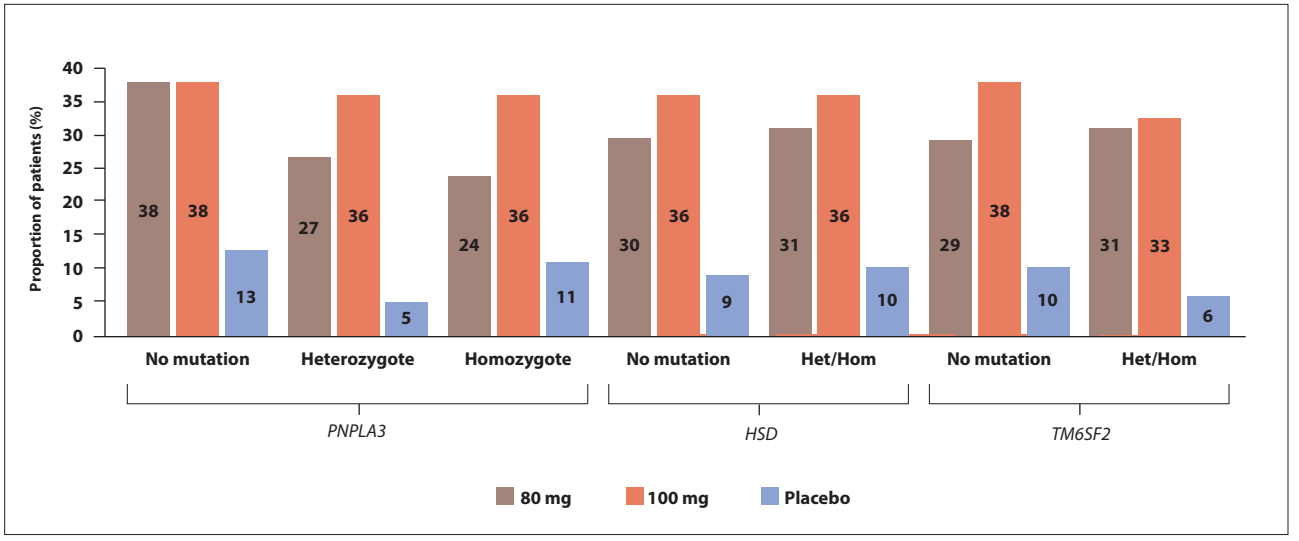

Figure 8. Resolution of metabolic dysfunction-associated steatohepatitis (week 52 liver biopsy) in resmetirom-treated patients in the MAESTRO-NASH population who had genetic risk markers. Het/Hom, heterozygote/homozygote. Adapted from Chalasani N, et al. AASLD abstract 2070. *Hepatology.* 2024;80(suppl 1).[1]

This study demonstrated that although certain genetic risk alleles were common in patients with MASH, such as the *PNPLA3* variants, they did not have an impact on response to resmetirom therapy in a large phase 3 trial. *PNPLA3* variants have been associated with higher rates of MASLD and risk for progression in certain populations, especially in Hispanic patients. The study results are reassuring in terms of the treatment efficacy of resmetirom in this population.

— Naim Alkhouri, MD

as *TM6SF2*. These markers impacted several baseline features, including ethnicity, metabolic features, baseline liver enzyme levels, and lipids.

Higher genetic risk was associated with fewer metabolic risk factors (eg, dyslipidemia, hypertension, and type 2 diabetes) in the noncirrhotic MASH population of MAESTRO-NASH, suggesting that compared with patients without genetic risk factors, patients with higher genetic risk may require less metabolic risk to progress to an equivalent MASH fibrosis stage. However, the presence of MASH risk alleles did not influence the treatment response to resmetirom on liver biopsy, imaging, or other markers of response. In resmetirom-treated patients, the percentage achieving MASH resolution was not impacted by any MASH genetic risk markers (Figure 8), nor was the percentage with fibrosis improvement on liver biopsy.

Reference

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Aerobic Exercise Training Leads to MASH Resolution as Defined by the MASH Resolution Index Without Body Weight Loss

Lifestyle intervention, including dietary changes and increased physical activity, is recommended for all patients with MASLD with a goal of achieving 7% to 10% in weight loss.[1] However, the vast majority of patients struggle to achieve this goal. Exercise training specifically has many benefits, several of which occur without significant body weight loss.[2] Although these benefits can occur outside the liver, many also impact the liver itself. For example, exercise training can lead to clinically significant reductions in MRI-measured liver fat, and a higher likelihood of achieving a 30% or more reduction in MRI-PDFF, considered a surrogate for histologic improvement.[3] Likewise, exercise training lessens MASH activity, even in the context of no body weight loss.[4]

ABSTRACT SUMMARY Optimal Treatment Duration of Resmetirom for Metabolic Dysfunction-Associated Steatotic Liver Disease: A Cost-Effectiveness Analysis

A cost-effectiveness analysis was reported which calculated the optimal treatment duration for resmetirom in patients with MASLD (Abstract 3329). This study determined that the medical costs per patient for patients with no treatment were approximately twice those of patients receiving treatment ($96,822 vs $49,026), whereas the drug costs were $283,326. This led to total costs of $96,822 and $332,353, respectively. The quality-adjusted life years (QALY) were higher with resmetirom treatment vs no treatment (11.57 years vs 10.80 years). These results led the study authors to conclude that lifetime treatment with resmetirom was not cost-effective at a willingness to pay of $150,000 per QALY, and that the optimal treatment duration was 6 years.

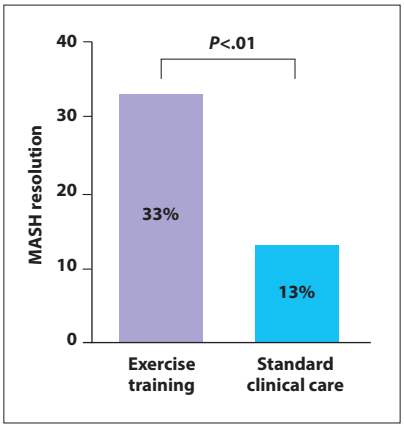

Figure 9. Exercise training achieved MASH resolution without body weight loss in patients in the NASHFit study. MASH, metabolic dysfunction-associated steatohepatitis. Adapted from Channapragrada T, et al. AASLD abstract 1428. *Hepatology.* 2024;80(suppl 1).[5]

This post hoc analysis of the NASHFit trial provides more evidence for the role of aerobic exercise alone regardless of weight loss as an effective intervention for patients with MASH. Gastroenterologists should learn how to prescribe an exercise program for their patients with MASLD, given the proven benefits of aerobic exercise on multiple comorbidities.

— Naim Alkhouri, MD

Channapragrada and colleagues provided an overview of a study which investigated the impact of lifestyle intervention, in the form of aerobic exercise training, on MASH resolution.[5] The MASH Resolution Index (MASH-RI)[6] was applied in a post hoc analysis of data from the NASHFit trial[7] to assess if exercise training can lead to MASH resolution without body weight loss. This NASHFit cohort was comprised mainly of non-Hispanic White women with early-stage MASH. A total of 15 patients received an aerobic exercise intervention, while 8 received standard of care.

This analysis found that exercise training achieved MASH resolution about 3-fold more often and without significant body weight loss (33% vs 13%; $P<.01$), as shown in Figure 9. Additionally, patients who participated in exercise training showed a greater reduction in MRI-PDFF (–4.3% vs +1.2%) and greater reduction in ALT levels (–14 U/L vs –6 U/L).

According to the study authors, the data demonstrate that sustained exercise training can result in MASH resolution, even without weight loss, and that future work should focus on whether exercise training can lead to liver fibrosis regression and resolution.

ABSTRACT SUMMARY Resmetirom Therapy of MASH-Associated Child Pugh A Cirrhosis Reduces Estimated Risk for Clinical Outcome Based on HepQuant RISK ACE Model

The HepQuant DuO Test, a quantitative liver function test, was used to quantify changes in liver function and portal-systemic shunting among patients in the MAESTRO-NAFLD-1 study. These data were then analyzed to estimate the risk for an adverse clinical event (Abstract 2027). At week 48, 39% of patients treated with resmetirom showed an improvement from baseline (compared with 13% at week 28; $P=.046$). Further, 44% of patients showed stable hepatic function (Disease Severity Index [DSI] change of ±2), whereas 17% showed worsening (increase in DSI >2). During the same time frame, the 1-year risk of adverse clinical events decreased in 19 of the 23 patients assessed, showing a significant reduction in average risk from baseline to week 48 with resmetirom (–8.1%; $P=.0474$).

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Notes


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