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## A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

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### ABSTRACT

#### BACKGROUND

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with no approved treatment. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta-selective agonist in development for the treatment of NASH with liver fibrosis.

#### METHODS

We are conducting an ongoing phase 3 trial involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by  $\geq 2$  points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

#### RESULTS

Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group). NASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group ( $P < 0.001$  for both comparisons with placebo). Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group ( $P < 0.001$  for both comparisons with placebo). The change in low-density lipoprotein cholesterol levels from baseline to week 24 was  $-13.6\%$  in the 80-mg resmetirom group and  $-16.3\%$  in the 100-mg resmetirom group, as compared with  $0.1\%$  in the placebo group ( $P < 0.001$  for both comparisons with placebo). Diarrhea and nausea were more frequent with resmetirom than with placebo. The incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group.

#### CONCLUSIONS

Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage. (Funded by Madrigal Pharmaceuticals; MAESTRO-NASH ClinicalTrials.gov number, NCT03900429.)

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\*A complete list of the investigators in the MAESTRO-NASH trial is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**N**ONALCOHOLIC STEATOHEPATITIS (NASH), also known as metabolic dysfunction–associated steatohepatitis (MASH),<sup>1</sup> is a progressive liver disease characterized by the presence of 5% or greater hepatic steatosis with hepatocellular damage and inflammation.<sup>2–4</sup> Once NASH progresses to clinically meaningful fibrosis (stages F2 and F3, on a scale from F0 [no fibrosis] to F4 [cirrhosis]), the risk of adverse clinical outcomes markedly increases, especially among patients with type 2 diabetes.<sup>5–8</sup> A prospective study of clinical outcomes in adult patients with nonalcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction–associated steatotic liver disease,<sup>1</sup> indicated that only fibrosis of stages F3 and F4 is associated with death due to liver disease.<sup>9</sup> The estimated global prevalence of NASH is approximately 4 to 6%, and the associated socioeconomic costs are high.<sup>10–12</sup>

Currently, there is no approved pharmacologic treatment for NASH. Owing to the unmet need for a treatment for NASH, the Food and Drug Administration (FDA) has outlined an accelerated approval pathway allowing for conditional approval based on achievement of either of two histologic end points (improvement in liver fibrosis stage or resolution of NASH) considered to be reasonably likely to predict clinical benefit and for full approval based on reduction in clinical outcomes (death from any cause, liver transplantation, or hepatic decompensation events).<sup>13,14</sup>

Resmetirom is an oral, liver-directed, thyroid hormone receptor beta (THR- $\beta$ )–selective agonist in clinical development for the treatment of NASH.<sup>15,16</sup> In NASH, THR- $\beta$  function in the liver is impaired, which leads to a reduction in mitochondrial function and  $\beta$ -oxidation of fatty acids in association with an increase in fibrosis. Data from phase 2 and 3 trials have supported the potential efficacy and safety of resmetirom in adults with NASH.<sup>17–20</sup> MAESTRO-NASH is an ongoing phase 3 trial evaluating the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH. Here, we report week 52 results, including serial liver biopsies in 966 patients with NASH and liver fibrosis.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

We are conducting this phase 3, double-blind, randomized, placebo-controlled trial at 245 sites in

15 countries. The trial is ongoing and remains blinded to individual patient identification and trial-group assignments. The planned duration of the trial is 54 months; the two liver-biopsy primary end points were assessed at 52 weeks in the first 1050 patients who had undergone randomization, and the clinical-outcome primary end point is prespecified to be assessed at month 54. The protocol, which is available with the full text of this article at NEJM.org, was approved by the institutional review board and ethics committee at each participating site. The trial was and continues to be conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all relevant regulations. All the patients provided written informed consent.

The sponsor (Madrigal Pharmaceuticals) designed the trial and, in conjunction with contract research organizations, performed site monitoring, data collection, and data analysis. The first author and two authors employed by Madrigal Pharmaceuticals interpreted the data, wrote the first draft of the manuscript, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors had access to the data, critically reviewed the manuscript, and approved the manuscript for submission.

### PATIENTS

Eligible patients were 18 years of age or older who had at least three of five metabolic risk factors, according to a modified version of the International Diabetes Foundation criteria for the metabolic syndrome,<sup>21</sup> and who had undergone prescreening vibration-controlled transient elastography (VCTE; FibroScan) within the past 3 months that showed a controlled attenuation parameter (CAP) of 280 dB per meter or more and a liver-stiffness measurement of 8.5 kPa or more (alternatively, a liver biopsy that was performed within 6 months before randomization could be confirmed to be eligible as a baseline biopsy by the central pathologist of the trial). Additional key inclusion criteria were histologic evidence of NASH and an NAFLD activity score of 4 or more (on a scale of 0 to 8, with higher scores indicating more severe disease), with a score of 1 or more for each component (steatosis [on a scale from 0 to 3], lobular inflammation [on a scale from 0 to 3], and hepatocellular ballooning [on a scale from

0 to 2]). At least 50% of the total enrollment was required to have a fibrosis stage of F3. No more than 15% of the total enrollment could have a fibrosis stage of F1, primarily F1B (moderate fibrosis stage, pericentral area only), and no more than 3% of the total enrollment could have a fibrosis stage of F1A or F1C (only if the N-terminal type III collagen propeptide level was  $\geq 14$  ng per milliliter). Weight was required to be stable ( $< 5\%$  change in 3 months), and doses of glucagon-like peptide-1 agonists were required to be stable for at least 6 months before biopsy. Key exclusion criteria were alcohol consumption of more than 20 g per day for women and more than 30 g per day for men, a glycated hemoglobin level of more than 9.0% at screening, and causes of chronic liver disease other than noncirrhotic NASH. Full eligibility criteria are listed in the Supplementary Appendix, available at NEJM.org.

#### PROCEDURES

Patients were randomly assigned in a 1:1:1 ratio to receive resmetirom at a dose of 80 mg or 100 mg or placebo, administered orally once daily (Fig. S1 in the Supplementary Appendix). Randomization was performed with the use of an interactive Web-response system. Patients were stratified according to status with respect to type 2 diabetes (presence or absence) and fibrosis stage (F1, F2, or F3). Throughout the trial, patients received nutrition and exercise counseling according to current recommendations.<sup>3,22</sup> Patients were unaware of the trial-group assignments, as were site personnel, personnel of contract research organizations, and sponsor personnel who were conducting the trial, administering the investigational product, and performing clinical assessments. Selected persons were aware of the trial-group assignments to facilitate dispensation of resmetirom or placebo. All trial personnel were unaware of the results of postbaseline tests that could reveal the trial-group assignments, including levels of total and free thyroxine (T4), sex hormone-binding globulin, and lipids as well as magnetic resonance imaging proton density fat fraction (MRI-PDFF).

Screening biopsy results were used as baseline values for histologic variables, and a second biopsy was performed at week 52. Biopsy specimens on glass slides were assessed centrally by two independent expert pathologists (the second and third authors) to determine the NAFLD activity score

and fibrosis stage (according to NASH Clinical Research Network criteria<sup>23</sup>). For the primary analysis, all screening or baseline biopsy specimens and week 52 biopsy specimens on glass slides were reread independently by both pathologists in large unpaired groups of screening or baseline biopsy specimens (50 to 100 slides per group, spiked with biopsy specimens obtained from patients who had screening failure) or a separate matched set of week 52 biopsy specimens (50 to 100 slides per group). The pathologists were unaware of the trial-group assignments, patient characteristics, and each other's assessments. A consensus review was conducted as a supportive analysis wherein the two pathologists read blinded (to time of biopsy and identification code) digitized images for cases in which there was disagreement on the primary read with respect to response status for the two primary end points or a reduction in fibrosis by at least two stages. Only the NAFLD activity scores or fibrosis components that determined the response for which there was disagreement between the pathologists were reread. Details are provided in the Supplementary Appendix.

#### END POINTS

The two primary end points at week 52 were NASH resolution (achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by  $\geq 2$  points) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score. The key secondary end point was the percent change from baseline in the low-density lipoprotein (LDL) cholesterol level at week 24. Safety end points included adverse events, biochemical assessments, and clinical assessments. Selected serious adverse events (including deaths, cardiovascular events, and potential drug-induced liver injury) were adjudicated by independent, external event-adjudication committees whose members were unaware of the trial-group assignments. A complete list of primary and secondary end points is provided in Table S1.

#### STATISTICAL ANALYSIS

On the basis of a sample size of at least 780 patients, the trial had more than 90% power to detect a difference between each dose of resmetirom and placebo with the use of a stratified

Cochran–Mantel–Haenszel test, under the assumption that NASH resolution with no worsening of fibrosis would occur in 7.2% of the patients receiving placebo and 19.8% of those receiving resmetirom and that fibrosis improvement by at least one stage with no worsening of the NAFLD activity score would occur in 14% of the patients receiving placebo and 26% of those receiving resmetirom.<sup>19</sup> No comparisons were planned between the two resmetirom dose groups. The trial recruited additional patients to further expand the safety profile of resmetirom, support more robust subgroup analyses, and allow for uncertainty

in the assumed treatment effects relative to placebo. Multiplicity was controlled with the use of a weighted Bonferroni approach ( $\alpha=0.04$  at week 52 and  $\alpha=0.01$  at month 54) (Fig. S2). In addition, a two-stage gatekeeping procedure was used to control alpha at 0.04 for the week 52 family of end points. Recycling of alpha to the month 54 analysis, as appropriate, is planned.

The primary statistical analysis model used the Cochran–Mantel–Haenszel test to determine response with respect to the biopsy end points. Patients with missing biopsies were considered to have not had a response. Disagreement was

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Primary Population).\***

Characteristic	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
Age — yr	55.9±11.5	57.0±10.8	57.1±10.5
Male sex — no. (%)†	140 (43.5)	141 (43.7)	143 (44.5)
Race or ethnic group — no. (%)†			
White	291 (90.4)	291 (90.1)	281 (87.5)
Black	5 (1.6)	5 (1.5)	9 (2.8)
Asian	10 (3.1)	9 (2.8)	9 (2.8)
Other‡	12 (3.7)	11 (3.4)	18 (5.6)
Missing data	4 (1.2)	7 (2.2)	4 (1.2)
Hispanic or Latino ethnic group — no. (%)†	71 (22.0)	81 (25.1)	52 (16.2)
Body weight — kg	100.1±22.3	101.9±22.9	100.2±23.1
Body-mass index	35.5±6.4	36.2±7.4	35.3±6.5
Type 2 diabetes — no. (%)	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension — no. (%)	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidemia — no. (%)	229 (71.1)	236 (73.1)	224 (69.8)
Hypothyroidism — no. (%)§	39 (12.1)	46 (14.2)	45 (14.0)
History of ASCVD — no. (%)	20 (6.2)	23 (7.1)	14 (4.4)
Estimated 10-yr risk of ASCVD — %¶	14.7±12.0	14.5±12.1	15.4±11.6
FibroScan liver-stiffness measurement — kPa			
Mean	13.3±6.8	13.6±7.1	12.9±5.5
Median (IQR)	11.5 (9.5–14.9)	11.9 (9.5–15.9)	11.7 (9.4–14.8)
FibroScan controlled attenuation parameter — dB/m**	346.1±37.2	349.4±38.7	347.2±37.0
MRI-PDFF — %††	18.2±6.8	17.2±6.6	17.8±6.8
Liver stiffness on MRE — kPa	3.5±0.9	3.7±1.1	3.5±1.0
Fibrosis-4 index score‡‡	1.4±0.7	1.5±0.7	1.4±0.7
LDL cholesterol level — mg/dl	106.6±37.4	103.0±36.8	106.8±41.1
Alanine aminotransferase level — U/liter	52.8±27.3	56.3±34.0	54.7±34.8
Aspartate aminotransferase level — U/liter	38.2±19.3	42.5±25.2	40.7±24.6
γ-Glutamyltransferase level — U/liter	84.3±111.3	84.6±99.0	75.7±85.0

Table 1. (Continued.)

Characteristic	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
Liver-biopsy findings — no. (%)			
NAFLD activity score $\geq 5$ <sup>§§</sup>	266 (82.6)	288 (89.2)	253 (78.8)
Fibrosis stage <sup>¶¶</sup>			
F1B	16 (5.0)	15 (4.6)	18 (5.6)
F2	107 (33.2)	100 (31.0)	112 (34.9)
F3	199 (61.8)	208 (64.4)	191 (59.5)

\* Plus-minus values are means  $\pm$ SD. Percentages may not total 100 because of rounding. ASCVD denotes atherosclerotic cardiovascular disease, IQR interquartile range, LDL low-density lipoprotein, and MRE magnetic resonance elastography.

† Data on sex, race, and ethnic group were reported by the patient.

‡ “Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and all other nonspecified race or ethnic group categories.

§ Shown are patients who were receiving thyroxine-replacement therapy at screening.

¶ The risk of cardiovascular events was derived from multiple risk factors, including age, sex, race, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, LDL cholesterol, history of diabetes, smoking status, hypertension treatment, statin treatment, and aspirin therapy. Persons are preliminarily classified on the basis of estimated risk: a 10-year risk of ASCVD of less than 5% is low risk; 5 to 7.4% is borderline risk; 7.5 to 19.9% is intermediate risk; and 20% or more is high risk.<sup>25</sup>

|| Liver stiffness was measured by means of vibration-controlled transient elastography. Values of more than 8.5 are considered to be indicative of fibrosis of stage F2 or higher.<sup>3</sup>

\*\* Controlled attenuation parameter is a method for the noninvasive assessment of steatosis, which measures the increased attenuation of ultrasound waves when traveling through steatotic hepatic tissue, as compared with normal liver tissue. The maximum value is 360 dB per meter; for this trial, a reading of more than 280 dB per meter was considered to be high.<sup>3</sup>

†† Magnetic resonance imaging proton density fat fraction (MRI-PDFF) is a magnetic resonance imaging–derived noninvasive, quantitative biomarker to assess liver fat content. A reading of more than 5% is considered to be high.<sup>26</sup>

‡‡ The Fibrosis-4 index score is derived from platelet count, aspartate aminotransferase level, age, and alanine aminotransferase level. Scores of more than 2.67 are considered to be indicative of advanced fibrosis and an elevated risk of liver-related events.<sup>3</sup>

§§ The nonalcoholic fatty liver disease (NAFLD) activity score is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2). NAFLD activity scores of 4 or more are considered to indicate at-risk nonalcoholic steatohepatitis (NASH).<sup>23</sup>

¶¶ Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis). A stage of F1B indicates moderate fibrosis, pericentral area only. Five patients in each group who were scored as having F3 fibrosis at eligibility and who were rescored as having F4 fibrosis at baseline by one or both central pathologists were evaluated in the F3 group.

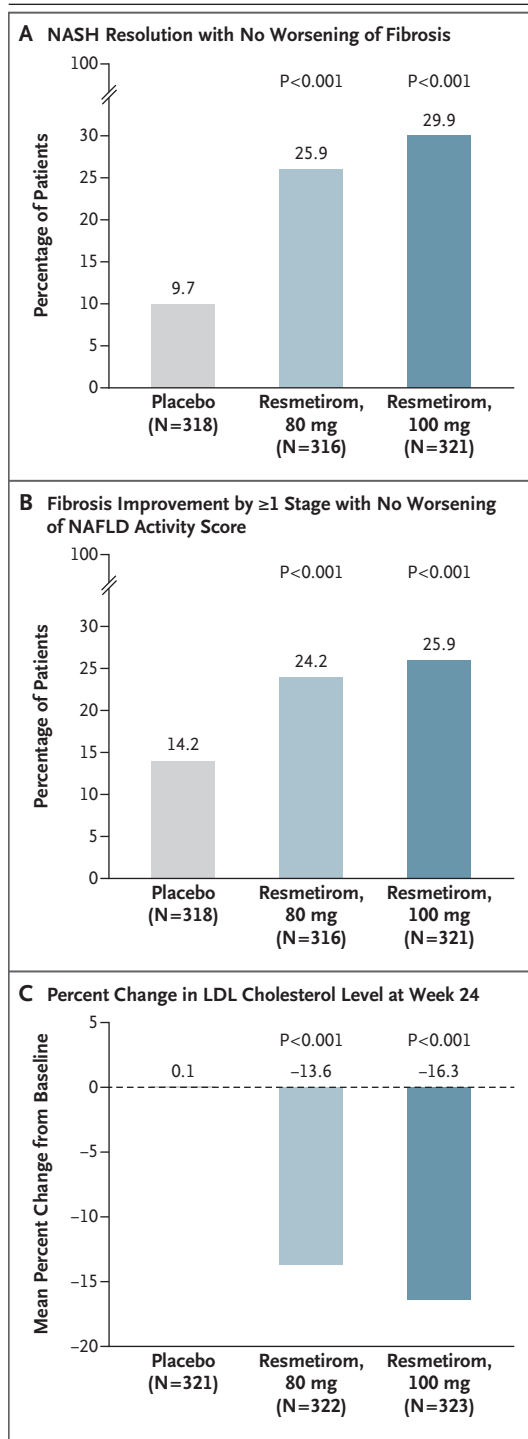
incorporated into a statistical Cochran–Mantel–Haenszel model that provided partial credit for cases in which pathologists disagreed on response status for any biopsy end point. Multiple sensitivity analyses were conducted, including multiple imputation and tipping-point analysis. Details of secondary, exploratory, and safety analyses were specified in the statistical analysis plan (available with the protocol). All reported P values are two-sided. For end points not included in the hierarchical plan to adjust for multiple testing, 95% confidence intervals are reported without P values; 95% confidence intervals should not be used in place of hypothesis tests.

## RESULTS

### PATIENTS

From March 2019 through July 2021, a total of 1050 patients underwent randomization; 966 patients who had a fibrosis stage of F1B, F2, or F3 at baseline (primary population for safety and efficacy) were randomly assigned to receive 80 mg of resmetirom (322 patients), 100 mg of resmetirom (323 patients), or placebo (321 patients) (Fig. S3). A total of 84 patients who had a fibrosis stage of F1A or F1C at baseline were randomly assigned to receive 80 mg of resmetirom (30 patients), 100 mg of resmetirom (26 patients),



**Figure 1. Primary and Key Secondary End Points.**

The two primary end points at week 52 were resolution of nonalcoholic steatohepatitis (NASH) with no worsening of fibrosis (Panel A), and an improvement (reduction) in fibrosis by at least one stage with no worsening of the nonalcoholic fatty liver disease (NAFLD) activity score (Panel B). The key secondary end point was the percent change from baseline in the low-density lipoprotein (LDL) cholesterol level at week 24 (Panel C). The NAFLD activity score is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2). NASH resolution was defined as achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by at least 2 points. Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis). A total of 11 patients had a delay in their week 52 biopsy due to coronavirus disease 2019–related closure of the biopsy site or related reasons and were removed from the primary analysis population for liver-biopsy analyses.

from the primary biopsy analysis population, a decision consistent with regulatory guidance regarding Covid-19.<sup>24</sup> As such, the primary biopsy analysis population consisted of 955 patients: 316 in the 80-mg resmetirom group, 321 in the 100-mg resmetirom group, and 318 in the placebo group.

The demographic and clinical characteristics of the patients at baseline were similar across the trial groups (Table 1 and Table S2). Most patients were White (89.3%), with a high incidence of metabolic risk factors (hypertension, 78.1%; dyslipidemia, 71.3%; and type 2 diabetes, 67.0%). A total of 21.1% of the patients were Hispanic; only 2.0% of the patients were Black. (The representativeness of the trial population is described in Table S3.) The mean ( $\pm$ SD) age of the patients was  $56.6 \pm 10.9$  years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was  $35.7 \pm 6.8$ . Baseline biopsies indicated that 83.5% of the patients had an NAFLD activity score of 5 or more; 5.1% had F1B fibrosis, 33.0% had F2 fibrosis, and 60.4% had F3 fibrosis. The use of medications at baseline was generally balanced across the trial groups. The demographic and clinical characteristics of the patients at baseline according to fibrosis stage are reported in Table S4. At the time of database lock for the week 52 end

or placebo (28 patients) (exploratory population for safety and efficacy) (Tables S7 and S8). A total of 11 of 966 patients had a delay in their week 52 biopsy for reasons related to coronavirus disease 2019 (Covid-19), were considered to have missing data completely at random, and were removed

**Table 2. Biopsy End Points.\***

End Point	Resmetirom, 80 mg (N=316)	Resmetirom, 100 mg (N=321)	Placebo (N=318)	Difference between Resmetirom, 80 mg and Placebo (95% CI)†	P Value	Difference between Resmetirom, 100 mg and Placebo (95% CI)†	P Value
	<i>percent with response</i>			<i>percentage points</i>		<i>percentage points</i>	
<b>Primary end points</b>							
NASH resolution with no worsening of fibrosis	25.9	29.9	9.7	16.4 (11.0–21.8)	<0.001	20.7 (15.3–26.2)	<0.001
Fibrosis improvement by ≥1 stage with no worsening of NAFLD activity score	24.2	25.9	14.2	10.2 (4.8–15.7)	<0.001	11.8 (6.4–17.2)	<0.001
<b>Other end points</b>							
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis	41.3	44.9	21.2	20.2 (13.8–26.5)		23.8 (17.4–30.2)	
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with improvement in fibrosis	18.8	21.2	8.5	10.5 (5.8–15.3)		13.0 (8.3–17.7)	
Improvement in each component of NAFLD activity score	23.3	27.9	7.2	16.1 (11.1–21.0)		20.9 (15.8–25.9)	
Improvement in fibrosis by ≥2 stages	8.3	10.1	2.8	5.6 (2.5–8.7)		7.4 (3.9–10.8)	
Both NASH resolution and fibrosis improvement by ≥1 stage	14.2	16.0	4.9	9.5 (5.4–13.6)		11.6 (7.5–15.8)	

\* Of the 966 patients in the primary population, 11 patients (6 in the 80-mg resmetirom group, 3 in the 100-mg resmetirom group, and 2 in the placebo group) had a delay in their week 52 biopsy for reasons related to coronavirus disease 2019 (Covid-19), and were not evaluated for the end points shown here. NASH resolution was defined as a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by at least 2 points.  
 † The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

**Table 3. Key Secondary and Other Secondary End Points (Primary Population).\***

Measurement	Resmetirom, 80 mg (N = 322)	Resmetirom, 100 mg (N = 323)	Placebo (N = 321)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†
	<i>least-squares mean percent change from baseline</i>				
LDL cholesterol level at wk 24‡§	-13.6±1.7	-16.3±1.7	0.1±1.7	-13.7 (-17.5 to -10.0)¶	-16.4 (-20.1 to -12.6)¶
Apolipoprotein B level at wk 24§	-16.8±1.3	-19.8±1.3	0.39±1.3	-17.2 (-20.0 to -14.4)	-20.2 (-22.9 to -17.4)
Triglyceride level at wk 24	-22.7±4.0	-21.7±4.3	-2.6±4.1	-20.1 (-28.3 to -11.8)	-19.1 (-27.8 to -10.3)
Lipoprotein(a) level at wk 24§**	-30.4±3.8	-35.9±4.0	-0.84±3.5	-29.5 (-37.6 to -21.5)	-35.1 (-43.5 to -26.6)
MRI-PDFF at wk 52	-35.4±2.8	-46.6±2.8	-8.7±2.7	-26.7 (-32.9 to -20.6)	-37.9 (-44.2 to -31.7)
Alanine aminotransferase level at wk 48††	-26.6±3.7	-33.2±3.9	-6.9±3.8	-19.7 (-27.7 to -11.6)	-26.3 (-34.5 to -18.1)
Aspartate aminotransferase level at wk 48††	-22.1±3.9	-28.3±3.9	-2.9±3.8	-19.3 (-27.2 to -11.3)	-25.4 (-33.5 to -17.4)
γ-Glutamyltransferase level at wk 48††	-25.0±5.5	-31.9±6.3	3.3±5.2	-28.3 (-37.3 to -19.3)	-35.2 (-45.5 to -25.0)

\* Multiple imputation analyses were used for lipids and liver enzymes. Details on the change from baseline in levels of lipids, lipoproteins, and lipid particles at weeks 24 and 52 are provided in Table S11.

† The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

‡ The key secondary end point was the percent change from baseline in the LDL cholesterol level at week 24. LDL cholesterol was directly measured.

§ Data were missing for one patient in the 80-mg resmetirom group.

¶ P<0.001.

|| Data are for patients with a baseline triglyceride level of more than 150 mg per deciliter.

\*\* Data are for patients with a baseline lipoprotein(a) level of more than 10 nmol per liter.

†† Data are for patients with a baseline alanine aminotransferase level of 30 U per liter or more.



points, adherence to the trial regimen was high (92% with >80% adherence).

#### EFFICACY

NASH resolution with no worsening of fibrosis was achieved in significantly more patients who received resmetirom than in those who received placebo (25.9% in the 80-mg group and 29.9% in the 100-mg group, vs. 9.7% in the placebo group;  $P < 0.001$  for both comparisons with placebo) (Fig. 1A and Table 2). An improvement in fibrosis by at least one stage with no worsening of the NAFLD activity score was also achieved in significantly more patients who received resmetirom than in those who received placebo (24.2% in the 80-mg group and 25.9% in the 100-mg group, vs. 14.2% in the placebo group;  $P < 0.001$  for both comparisons with placebo) (Fig. 1B and Table 2). A consensus read (sensitivity analysis) of digitized images of biopsy specimens for which there was disagreement between the pathologists as to whether there was a response with respect to either primary end point yielded results similar to those of the primary analysis (Table S5A). Similar results were obtained individually by each pathologist and in multiple sensitivity analyses (Tables S5B, S5C, and S6).

Subgroup analyses of the primary end points showed generally consistent results across the subgroups (defined according to baseline fibrosis stage, baseline NAFLD activity score, status with respect to type 2 diabetes, age, and sex), with more patients who received resmetirom having either NASH resolution or fibrosis improvement than those who received placebo (Fig. S4A through S4D). The results of additional biopsy end points and sensitivity analyses were generally supportive of the results of the primary analyses of the two primary end points (Table 2 and Tables S9 and S10).

LDL cholesterol levels were reduced from baseline at week 24 among patients who received resmetirom (−13.6% in the 80-mg group and −16.3% in the 100-mg group) and not in those who received placebo (0.1%) ( $P < 0.001$  for both comparisons with placebo) (Table 3 and Fig. 1C); these effects seemed to be maintained at week 52 (Table S11 and Fig. S7). At week 24 and week 52, levels of triglycerides (in patients with baseline triglyceride levels of >150 mg per deciliter), non-high-density lipoprotein (HDL) cholesterol, apolipoprotein B, apolipoprotein C-III, and lipo-

protein(a) appeared to decrease more from baseline in the resmetirom groups than in the placebo group. Levels of additional lipids and lipoproteins appeared to decrease more from baseline in the resmetirom groups than in the placebo group at week 52 (Table S12).

In addition, levels of liver enzymes — including alanine aminotransferase, aspartate aminotransferase, and  $\gamma$ -glutamyltransferase — seemed to decrease more in the resmetirom groups than in the placebo group (Table 3). Results of multiple noninvasive tests, including the MRI-PDFF at weeks 16 and 52 and Fibroscan CAP at week 52, suggested improvements associated with resmetirom treatment (Table 3 and Fig. S8). Liver stiffness (as assessed by VCTE or magnetic resonance elastography) appeared to decrease more from baseline with resmetirom treatment than with placebo (Figs. S9 and S10). By week 16, both liver volume and spleen volume appeared to decrease more from baseline with resmetirom treatment; this effect was maintained at week 52 (Fig. S11).

The Enhanced Liver Fibrosis test score and components of the score appeared to be improved by resmetirom treatment relative to placebo (Fig. S12). In addition, there seemed to be improvements in levels of cytokeratin 18, adiponectin, and reverse triiodothyronine among patients who received resmetirom as compared with those who received placebo.

#### SAFETY

Overall, 91.6 to 91.9% of the patients who received resmetirom and 92.8% of those who received placebo reported an adverse event (Table 4). Most adverse events were mild or moderate in severity. The most frequent adverse events were gastrointestinal (diarrhea and nausea) (Table S13) and Covid-19. Diarrhea and nausea occurred more frequently in the resmetirom group than in the placebo group. The onset of diarrhea and nausea occurred at the initiation of resmetirom (Fig. S13). Approximately 50% of the cases of diarrhea were described as “worsening of preexisting diarrhea” or “intermittent/loose stool(s)”; no episodes of severe diarrhea were reported. The median duration of diarrhea was approximately 15 to 20 days, independent of resmetirom dose (Fig. S14).

The incidence of serious adverse events was similar across the trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg

**Table 4. Safety Summary (Primary Population).**

Event	Resmetirom, 80 mg (N = 322)	Resmetirom, 100 mg (N = 323)	Placebo (N = 321)
	<i>number of patients (percent)</i>		
≥1 Adverse event	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1: mild	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2: moderate	180 (55.9)	183 (56.7)	169 (52.6)
Grade 3 or higher: severe	43 (13.4)	47 (14.6)	52 (16.2)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)
Adverse event leading to trial discontinuation before wk 52†	6 (1.9)	22 (6.8)	7 (2.2)
Adverse event leading to trial discontinuation during entire treatment period†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal adverse event	1 (0.3)	2 (0.6)	1 (0.3)
Major adverse cardiovascular event‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event‡	0	1 (0.3)	3 (0.9)
Adverse events affecting >10% of patients in any group			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)

\* Shown are events that were considered by investigators to be related to resmetirom or placebo.

† Data are for events that emerged after the first dose of resmetirom or placebo and within 30 days after the last dose.

‡ Major adverse cardiovascular events were defined as nonfatal stroke, nonfatal myocardial infarction, and death from cardiovascular causes. All cardiovascular events were adjudicated.

group, and 11.5% in the placebo group (Table 4 and Table S14). Serious adverse events that were considered by investigators to be related to the trial regimen occurred in two patients in the 80-mg resmetirom group and one in the placebo group (Table 4). Cancer was reported in 1.2% of the patients in the 80-mg group, 3.4% of those in the 100-mg group, and 3.7% of those in the placebo group (Table S15). There was no incidence of drug-induced liver injury. At week 52, trial discontinuations due to adverse events were more common in the 100-mg resmetirom group than in the other two trial groups (6.8% in the 100-mg resmetirom group, 1.9% in the 80-mg

resmetirom group, and 2.2% in the placebo groups). Thereafter, trial discontinuations were similar across the trial groups.

Resmetirom treatment had no effect on heart rate or body weight and was not associated with arrhythmias (Table S16). Blood pressure appeared slightly reduced among patients who received resmetirom. Levels of sex hormones were little changed from baseline (Table S17). Independent of thyroxine-replacement status, resmetirom treatment reduced levels of prohormone free T4 (FT4) by approximately 16 to 19%, with no effect on levels of thyrotropin or the active thyroid hormone, free triiodothyronine (FT3) (Table S18).

There were no increases in fractures or substantial changes in bone mineral density T scores (Table S19).

## DISCUSSION

Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to the two primary histologic end points (NASH resolution with no worsening of fibrosis, and an improvement in fibrosis by  $\geq 1$  stage with no worsening of the NAFLD activity score) at week 52. These are consistent with the end points proposed by the FDA as reasonably likely to predict clinical benefit in a phase 3 trial involving adults with NASH and liver fibrosis.<sup>13,14</sup> The primary analyses were supported by multiple sensitivity analyses. The effects that were observed with resmetirom treatment were consistent across key subgroups. Multiple noninvasive tests for NASH, steatosis, and fibrosis (including blood biomarkers and imaging) showed a similar direction of effects favoring resmetirom treatment, which supports the findings for the primary end points.

Among patients with NASH (the majority of whom have diabetes), cardiovascular risk and mortality are high.<sup>6,27</sup> Levels of a broad range of atherogenic lipids and lipoproteins, including LDL cholesterol, non-HDL cholesterol, triglycerides, apolipoprotein B, and lipoprotein(a), appeared to be reduced by resmetirom relative to placebo, findings consistent with those of earlier studies.<sup>18,19</sup> Although not yet shown for resmetirom, reductions in apolipoprotein B and LDL cholesterol levels of this magnitude have been associated with improvement in cardiovascular outcomes.<sup>28,29</sup>

More patients in the 100-mg resmetirom group than in the other two trial groups discontinued the trial because of adverse events (6.8% in the 100-mg resmetirom group, 1.8% in the 80-mg resmetirom group, and 2.2% in the placebo group). Diarrhea and nausea occurred more frequently in the resmetirom groups than in the placebo group. The safety profile of resmetir-

om in the MAESTRO-NASH trial is consistent with that in previous phase 2 or 3 trials in which the most common adverse events were generally self-limited diarrhea and nausea at treatment initiation.<sup>18,19</sup> The incidence of serious adverse events was similar in the three trial groups (10.9% to 12.7%).

Noninvasive testing to identify patients with NASH for treatment and to monitor treatment response will be important in clinical practice in which liver biopsy is infrequently used. The MAESTRO-NASH trial used a screening paradigm consistent with guidelines that identified a high-risk NASH population (metabolic risk factors, FibroScan thresholds, additional imaging, and biomarkers).<sup>3,16</sup> In this trial, achievement of a 30% reduction in hepatic fat (MRI-PDFF) or a 120% increase in the sex hormone-binding globulin level appeared to be associated with biopsy responses (Fig. S4C and S4D).

A current limitation in the data from the MAESTRO-NASH trial is the lack of clinical-outcomes data to correlate with histologic data. The safety of long-term use of resmetirom has not yet been assessed. The trial is planned to continue to 54 months in order to accrue and evaluate liver-related outcomes, including progression to cirrhosis.

Data for the first 1050 patients from the MAESTRO-NASH trial, together with data from completed resmetirom trials, support the potential for resmetirom to provide benefit to patients with NASH and liver fibrosis. Both the 80-mg dose and the 100-mg dose of resmetirom were shown to be efficacious with respect to the two primary histologic end points in patients with NASH and liver fibrosis.

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## APPENDIX

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## REFERENCES

- Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78:1966-86.
- Chalasanani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328-57.
- Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797-835.
- Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell* 2021;184:2537-64.
- Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology* 2017;65:1557-65.
- Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, associates with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015;149(2):389-97.e10.
- Huang DQ, Wilson LA, Behling C, et al. Fibrosis progression rate in biopsy-proven nonalcoholic fatty liver disease among people with diabetes versus people without diabetes: a multicenter study. *Gastroenterology* 2023;165(2):463-472.e5.
- Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. *Lancet Gastroenterol Hepatol* 2021;6:578-88.
- Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med* 2021;385:1559-69.
- Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;67:123-33.
- Schattenberg JM, Lazarus JV, Newsome PN, et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: a cost-of-illness analysis. *Liver Int* 2021;41:1227-42.
- Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology* 2016;64:1577-86.
- Omokaro SO. FDA regulatory considerations for NASH clinical trial endpoints. Silver Spring, MD: Food and Drug Administration, February 26, 2018 (<http://www.globalengage.co.uk/nash/Omokaro.pdf>).
- Department of Health and Human Services. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment: guidance for industry. Silver Spring, MD: Food and Drug Administration, December 2018 (<https://www.fda.gov/media/119044/download>).
- Kelly MJ, Pietranico-Cole S, Larigan JD, et al. Discovery of 2-[3,5-dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yloxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile (MGL-3196), a highly selective thyroid hormone receptor  $\beta$  agonist in clinical trials for the treatment of dyslipidemia. *J Med Chem* 2014;57:3912-23.
- Harrison SA, Ratziu V, Anstee QM, et al. Design of the phase 3 MAESTRO clinical program to evaluate resmetirom for the treatment of nonalcoholic steatohepatitis. *Aliment Pharmacol Ther* 2024;59:51-63.
- Taub R, Chiang E, Chabot-Blanchet M, et al. Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor- $\beta$  agonist. *Atherosclerosis* 2013;230:373-80.
- Harrison SA, Taub R, Neff GW, et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med* 2023;29:2919-28 (<https://www.nature.com/articles/s41591-023-02603-1>).
- Harrison SA, Bashir MR, Guy CD, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2019;394:2012-24.
- Harrison SA, Bashir M, Moussa SE, et al. Effects of resmetirom on noninvasive endpoints in a 36-week phase 2 active treatment extension study in patients with NASH. *Hepatol Commun* 2021;5:573-88.
- Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome — a new world-wide definition: a consensus statement from the International Diabetes Federation. *Diabet Med* 2006;23:469-80.
- Pais R, Cariou B, Noureddin M, et al. A proposal from the liver forum for the management of comorbidities in non-alcoholic steatohepatitis therapeutic trials. *J Hepatol* 2023;79:829-41.
- Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological



scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;41:1313-21.

24. Conduct of clinical trials of medical products during the COVID-19 public health emergency: guidance for industry, investigators, and institutional review boards. Silver Spring, MD: Food and Drug Administration, August 30, 2021 (<https://www.fda.gov/media/136238/download/>).

25. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiol-

ogy/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935-59.

26. Anastasiou J, Alisa A, Virtue S, Portmann B, Murray-Lyon I, Williams R. Non-invasive markers of fibrosis and inflammation in clinical practice: prospective comparison with liver biopsy. *Eur J Gastroenterol Hepatol* 2010;22:474-80.

27. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;363:1341-50.

28. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88.

29. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions. *JAMA* 2016;316:1289-97.

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## Double Take Video: A Treacherous Course



This video reviews the differential diagnosis for a man with acute nausea, vomiting, abdominal pain, fever, and hemoptysis and reviews how the diagnosis evolves as new clinical findings are presented.

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