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A Review of the Phase 3 MAESTRO Trials for Resmetirom in Metabolic Function Associated Fatty Liver Disease

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1. Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD), is the leading cause of chronic liver disease in the United States. It encompasses liver conditions characterized by fat accumulation without excessive alcohol consumption. Early symptoms such as fatigue and abdominal pain are nonspecific, leading to delayed diagnosis until severe complications arise. Diagnosis often relies on the NAFLD activity score (NAS) and the NASH Clinical Research Network (CRN) fibrosis score. The treatment focus lies on non-cirrhotic NASH with fibrosis scores between 1 and 4, with lifestyle changes being essential. Recent therapeutic advances include drugs targeting insulin sensitivity, lipid metabolism, and inflammation, such as saroglitazar and resmetirom. Resmetirom, a selective agonist of Thyroid Hormone Receptor (THR)-β, has been approved by the FDA for early to moderate NASH hepatitis. Phase 3 trials, including MAESTRO-NASH and MAESTRO-NAFLD, have demonstrated its potential efficacy and safety, advancing the treatment landscape for NAFLD.

2. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as the leading cause of chronic liver disease in the United States, encompassing a range of liver conditions characterized by fat accumulation without excessive alcohol consumption or other typical causes of liver disease. Recently, it has been renamed Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD). Symptoms in early stages like fatigue or abdominal pain are nonspecific, leading to delayed diagnosis until more severe complications arise. While early diagnosis remains controversial due to limited treatment options, lifestyle changes such as weight loss are essential in the management of this condition.

Diagnosis and assessment often rely on tools like the NAFLD activity score (NAS) and the NASH Clinical Research Network (CRN) fibrosis score. The treatment focus lies on non-cirrhotic NASH with liver fibrosis scores between 1 and 4. Various drugs targeting different aspects of the disease process such as insulin sensitivity, lipid metabolism, and inflammation, are being explored in clinical trials [1].

Recent successes include saroglitazar and resmetirom, targeting PPAR receptors and thyroid hormone receptors respectively. Molecular targets like TGF-beta1, PPAR activators, and transcription factors like KLF15 are under investigation. Current treatment options include lifestyle changes, bariatric surgery, and medications such as SGLT-2 inhibitors and GLP-1 agonists. FXR activation and vitamin E supplementation also show promise in certain patient populations [1].

Resmetirom, a liver-targeted selective agonist of Thyroid Hormone Receptor (THR)-β, holds promise for treating NASH (nonalcoholic steatohepatitis) by addressing impaired thyroid hormone activity in the liver. Hepatic THR-β activity is crucial for normal liver cell function. It plays a role in increasing lipophagy and β- oxidation, enhancing mitophagy and mitochondrial biogenesis, reducing reactive oxidative stress by limiting reactive oxygen species, and regulating cholesterol clearance. The reduction of hepatic fat observed in clinical trials suggests its potential efficacy [2]. In a

phase 2 trial, resmetirom-treated patients experienced a substantial reduction in hepatic fat compared to the placebo group. Moreover, higher doses of resmetirom in the open-label extension showed even more significant reductions in hepatic fat. These findings supported the advancement of resmetirom into phase 3 trials at doses of 80 and 100 mg once daily.

MAESTRO-NASH, MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE and MAESTRO-NASH-OUTCOMES were four phase 3 trials that studied resmetirom. MAESTRO-NASH was a treatment focused trial with endpoints at 52 weeks which has been completed and 52 months which is ongoing. It required biopsies to be taken before and after the trial to look for endpoints. MAESTRO-NAFLD 1 focused on the adverse reactions. OLE had an open labeled arm structure, focusing on patients from both trials for a longer term whereas NASH outcomes work with people with proven cirrhosis, to reduce decompensation with Resmetirom use [3].

3. Methods

MAESTRO-NASH, MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE and MAESTRO-NASH-OUTCOMES are 4 phase 3 trials for the use of Resmetirom. To look for findings of MAESTRO-NASH, various electronic databases including PubMed, Cochrane, Google Scholar and Clinicaltrials.gov were searched from January 2017 to May 2024 for randomized controlled trials and clinical trials. In this review, we summarize the demographics, primary outcomes and secondary outcomes of the MAESTRO-NASH trial.

4. Results and Discussion

Thyroid Hormone Receptors (THR)-β plays a crucial role in controlling the liver's handling of metabolic processes, which are often disrupted in NASH. People with NASH typically have lower activity levels of thyroid hormones in their livers, leading liver dysfunction. Resmetirom is a pill taken once a day that specifically targets and activates THR-β in the liver. It's was studied as a potential treatment for NASH [2].

Phase 1 and Phase 2 clinical data indicated that resmetirom could potentially be used in treating Non- Alcoholic Steatohepatitis (NASH), Non-Alcoholic Fatty Liver Disease (NAFLD), and associated dyslipidemias. Resmetirom did not show suppression of the central thyroid axis or effects on heart rate or bone, and it effectively reduces elevated liver enzymes in NASH patients. Madrigal Pharmaceuticals recently finished a Phase 3 multinational, double-blind, randomized, placebo-controlled clinical trial of Resmetirom in patients with NASH and liver fibrosis [4].

966 participants were involved in the MAESTRO-NASH trials with even distribution amongst placebo, 80mg, and 100 mg doses (Table 1) [5].

The average age was 56.6 +/- 10.9 years. Most patients were Caucasian (89.3%), with 21.1% of the patients Hispanic; and only 2.0% of the patients Black. The included population had a high incidence of risk factors (hypertension, 78.1%; dyslipidemia, 71.3%; and type 2 diabetes, 67.0%). The mean BMI across groups was 35.7±6.8. The predominant sex was female with 56.1% involvement. Adherence was >90% [5].

For MAESTRO-NAFLD-1, the average age was 56. Most patients were Caucasian (88%), with 34% of the patients Hispanic. The included population had a high incidence of risk factors (hypertension, 75%; dyslipidemia, 88%; and type 2 diabetes, 49%). The mean BMI across groups was 35. The predominant sex was female with 57% involvement. Compliance was 81.2% in the OL arm and 76.4% across the three DB arms [6].

Table 1:

	NAFLD-1	NASH
Placebo	318	321
Resmetirom 80 mg	327	322
Resmetirom100 mg	324	323
Resmetirom100 mg	171	

The study faced challenges due to the closure of study sites and the limited availability of the drug during the COVID-19 pandemic. Overall, 77.4% of patients (750 out of 969) across the three arms of the double-blind study successfully finished the trial, while 22.6% (219 out of 969) had to drop out. Among the 171 patients who were assigned to receive 100 mg of resmetirom in the open-label arm, 89.0% completed the full 52- week treatment period [6].

Co-morbid conditions such as obesity, hyperlipidemia and diabetes predispose the patient to develop steatosis, further steatohepatitis and ultimately cirrhosis. The MAESTRO-NASH and NAFLD-1 had greater than 60 and 50 percent of people with diabetes (Table 2). Mean BMI was >35 across both trials and across all groups. This population is indicative of risk factors actually present in the pathophysiology of NASH [4]. This stratification allows prevention of confounding variables.

Across the four arms, the most frequently used medications included antidiabetic medications like glucagon- like peptide-1 (GLP-1) receptor agonists, metformin, pioglitazone, and sodium/glucose cotransporter-2 inhibitors at stable doses. Additionally, drugs used to treat dyslipidemia, such as statins, were also commonly used (46%).

The predominant study population was Caucasians. This prevents generalizability of the study to populations other than Caucasians. Nearly 90% of the population was white whereas as per the national average in 2019, NASH prevalence was highest in Hispanics (45.4%), followed by Whites (32.2%), and lowest in Blacks (20.3%) [7]. The overall 55% involvement of women in the studies reflects national averages with the proportion of patients with NASH by gender was 54.1% female *vs* 45.9% male in a recent study. The increased risk of NAFLD in postmenopausal women is attributed to decreased estrogen levels, which alter visceral fat distribution and promote a dyslipidemic milieu. There have been studies in Japan and south China supporting the estrogen hypothesis but a single race being studied might not be reflective of the entire population [8].

To be eligible, patients needed to have confirmed NAFLD and meet specific criteria, including FibroScan VCTE LSM and FibroScan CAP measurements, standard blood chemistry, hematology screening laboratory results, and at least 8% hepatic fat measured by MRI-PDFF. Additionally, patients had to have failed the screening for MAESTRO-NASH or meet specific FibroScan VCTE/LSM and FibroScan CAP criteria at sites not involved in MAESTRO-NASH. Distribution of Fibroscan and MRI parameters amongst the treatment groups are as below in Table 3[6].

For the NASH trial, biopsies at the beginning of the trial showed 83.5% of patients with NAS(NAFLD Activity Score) of 5 or more. With regards to fibrosis, F1B fibrosis was prevalent in 5.1%, F2 fibrosis in 33%, and F3 fibrosis in 61.9% of the patients as mentioned in Table 4 [5].

The inclusion criterion for NASH trial included consenting adults greater than 18 years of age with recent fibroscan with CAP of >280 and 8.5kPa or more stiffness. Due to the lack of knowledge on teratogenicity, breast feeding was prohibited. Weight and drug regimens had to be stable for at least 3 months with less than 5% variance. More than 50% of the subjects were to have F3 and less than 15% F1 fibrosis. Patients had to have had 3/5 risk factors for metabolic syndrome including central obesity, raised triglycerides, reduced HDL, raised fasting plasma glucose and elevated arterial blood pressure. Histologic evidence of NASH and an NAFLD activity score of 4 or more was a key point separating it from NAFLD trial given it lacked histological requirements [5].

People with pre-existing other liver diseases, regular alcohol consumption for 3 months over the past 1 year equal to or greater than approximately 2 alcoholic drinks per day for males, and approximately 1.5 alcoholic drinks per day for females, considered as regular alcohol consumption, were excluded. One alcoholic drink is equal to 12 ounces (355 mL) of 5% Alcohol by Volume (ABV) beer, 5 ounces (148 mL) of 12% ABV wine, or 1.5 ounces (44.4 mL) of 40% ABV distilled spirits [5,6].

Endpoints at the end of 52 weeks form the basis of these 2 studies

Table 2:

MAESTRO-NASH	Age	Sex(male)	Race(White)	BMI	Diabetes mellitus
Placebo	57.1±10.5	143 (44.5)	281 (87.5)	36.2±7.4	210 (65.4)
80	55.9±11.5	140 (43.5)	291 (90.4)	35.5±6.4	224 (69.6)
100	57.0±10.8	141 (43.7)	291 (90.1)	36.2±7.4	213 (65.9)
MAESTRO-NAFLD 1					
Placebo	55.7±12.2	146 (47.2)	276 (89.3)	35.2±5.8	156 (50.5)
80	56.2±11.7	141 (44.1)	284 (88.8)	35.4±6.0	156 (48.8)
100	56.2±11.5	142 (45.2)	278 (88.5)	35.4±6.4	152 (48.4)
OL 100	55.6±11.5	54.3 (41.8)	150 (88.2)	36.1±6.3	83 (48.2)

Table 3:

	Fibroscan VCTE/LSM	Fibroscan CAP	MRI-PDFF	MRE	FIB-4
Placebo DB	7.5±5.5	344.1±34	17.8±6.9	2.6±0.5(n=205)	1.0±0.5
Resmetirom 80 mg DB	7.4±4.4	339.5±32.9	17.7±6.7	2.6±0.5(n=219)	1.0±0.5
Resmetirom 100 mg DB	7.3±4.1	341.3±34	18.1±7.3	2.6±0.5(n=232)	1.0±0.4
Resmetirom 100 mg OL	7.84±3.4	342.3±35.6	17.9±7.1	2.8±0.9(n=114)	1.0±0.6

Table 4:

	F1	F2	F3
Placebo	18 (5.6)	112 (34.9)	191 (59.5)
80 mg	16 (5.0)	107 (33.2)	199 (61.8)
100 mg	15 (4.6)	100 (31.0)	208 (64.4)

Table 5:

Primary end point, At week 52-	Secondary End point
A. 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 ≥2 points) with no worsening of fibrosis	A. ≥2-Point improvement in NAFLD activity score, including ≥1- point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis
B. An improvement in fibrosis by at least one stage with no worsening of the NAS	B. ≥2-Point improvement in NAS including ≥1- point imp. in fibrosis
	C. Improvement in each component of NAFLD activity score
	D. Improvement in fibrosis by ≥2 stages
	E.Both NASH resolution and fibrosis improvement by ≥1 stage

with treatment including the resolution of steatohepatitis including ballooning score of zero and, lobular inflammation score of 0 or 1 being focus of MAESTRO-NASH trial. The other primary endpoint is improvement in fibrosis. Secondary endpoints include different levels of improvement in inflammation or fibrosis, all of which were achieved at 52 weeks of Resmetirom (Table 5) [5].

For MAESTRO-NAFLD 1, the trial focuses more on safety with adverse reactions being the primary focus (Table 6).

Both trials met with success with MAESTRO-NASH proving efficacy with treatment groups having statistically significant achievement of both primary and secondary endpoints with respect to treatment (Table 7) whereas MAESTRO-NAFLD 1 showing no statistical increase in adverse effects (Table 8).

The primary statistical analysis model used was 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. 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 [5].

Table 9 demonstrating adverse effects seen in MAESTRO-NASH, yielding comparable results to MAESTRO- NAFLD 1 [5].

The primary endpoint, which assessed the incidence of Treatment-Emergent Adverse Events (TEAEs) over a duration of up to 52 weeks of treatment and 4 weeks of follow-up, showed no significant differences between the treatment arms. Across the trial, 86.1-88.4% of patients treated with resmetirom and 81.8% of those on placebo reported experiencing a TEAE. There were no notable increases in specific serious TEAEs in the resmetirom arms compared to placebo. TEAEs occurring more frequently than placebo included mild to moderate diarrhea (23.5-31.2% in the resmetirom arms *versus* 13.8% in the placebo arm) and nausea (11.9-18.2% *versus* 7.9%, respectively). The occurrence of diarrhea (or nausea) was higher in the resmetirom arms compared to placebo within the initial 12 weeks of treatment but did not show increased incidence in the resmetirom arms beyond 12 weeks. The median duration of diarrhea was 15-20 days in the double-blind resmetirom arms, irrespective of dosage. Discontinuation from the study due to TEAEs was observed in 1.2- 3.1% of patients in the resmetirom arms compared to 1.3% in the placebo arm [6].

Finally, key secondary end points were achieved for both the DB 100 mg and 80 mg resmetirom arms. At week 24, resmetirom treatment resulted in significant reductions in atherogenic lipid levels from baseline compared to placebo treatment.

The resmetirom arms demonstrated a lower incidence of ALT increases of ≥3 × ULN compared to the placebo arm, suggesting a potential improvement in liver function with resmetirom treatment. Specifically, there was a reduction in the percentage Change from Baseline (CFB) in liver enzymes over time in the resmetirom arms compared to placebo, indicating a positive influence on liver health. Concerning safety, there were no indications of increased signs or symptoms of thyroid hormone disturbances in the resmetirom arms [6].

Moreover, treatment with resmetirom resulted in reductions in liver volume, with mean reductions of 21% and 23% following 16 and 52 weeks of treatment, respectively. After adjusting for reduced liver volume, there was an average reduction of 61% in hepatic fat observed in the treatment arm, suggesting a beneficial effect on liver fat content.

Table 6:

Primary end point	Secondary End point
At week 52, incidence of treatment emergent adverse effects between the resmetirom-treated patients and the placebo-treated patients.	LDL-C ApoB Triglycerides (over 24 weeks), Hepatic fat (over 16 and 52 weeks) Liver stiffness (over 52 weeks)

Table 7:

Primary Outcome	Secondary biopsy outcome	Secondary lab outcome
a. NASH resolution with no worsening of fibrosis [% and [%; (CI)]	a. ≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis[% and [%;(CI)]	a. The change in low-density lipoprotein cholesterol levels from baseline to week 24[% and [%;(CI)] – -DFP-–16.4 (−20.1 to −12.6) -Placebo- 0.1±1.7% (P<0.001 for both comparisons with placebo)
Placebo -9.7%	Placebo- 21.2%	
80-mg resmetirom -25.9%	80 mg- 41.3%	80-mg- −13.6±1.7%
Difference from Placebo [DFP]- 16.4 (11.0–21.8)	DFP- 20.2 (13.8–26.5)	DFP-–13.7 (−17.5 to −10.0)
100-mg resmetirom -29.9%	100 mg- 44.9%	100-mg −16.3±1.7%
Difference from Placebo - 20.7 (15.3–26.2)	DFP- 23.8 (17.4–30.2)	DFP-–16.4 (−20.1 to −12.6)
DFP- 23.8 (17.4–30.2) DFP-–16.4 (−20.1 to −12.6)		
(P<0.001 for both comparisons with placebo)	(P<0.001 for both comparisons with placebo)	
b. Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score [% and [%;(CI)]	b. ≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with improvement in fibrosis [% and [%;(CI)]	b. Apolipoprotein B level at week 24[% and [%;(CI)] – -
Placebo- 14.2%	Placebo- 8.5%	Placebo- 0.39±1.3
80-mg resmetirom- 24.2%	80 mg- 18.8%	80-mg- −16.8±1.3%
DFP- 10.2 (4.8–15.7)	DFP- 10.5 (5.8–15.3)	DFP- -17.2(-20- -14.4)
100-mg resmetirom- 25.9%	100 mg- 21.2 %	100-mg - −19.8±1.3% -
DFP- 11.8 (6.4–17.2)	DFP- 13.0 (8.3–17.7)	DFP-–20.2 (−22.9 to −17.4)
(P<0.001 for both comparisons with placebo)	(P<0.001 for both comparisons with placebo)	
	c.Improvement in each component of NAFLD activity score[% and [%;(CI)] DFP- 20.9 (15.8–25.9)	c. Triglyceride level at wk 24[% and [%;(CI)]
	Placebo- 7.2%	Placebo- −2.6±4.1
	80 mg- 23.3%	80-mg- −22.7±4.0
	DFP- 16.1 (11.1–21.0)	DFP-–20.1 (−28.3 to −11.8)
	100 mg- 27.9%	100-mg - −21.7±4.3
	DFP- 20.9 (15.8–25.9)	DFP-–19.1 (−27.8 to −10.3)
	(P<0.001 for both comparisons with placebo)	
	d.Improvement in fibrosis by ≥2 stages[% and [%; (CI)]	d.MRI-PDF at 52W Significant
	Placebo- 2.8%	Placebo- -8.7%
	80 mg- 8.3%	80 mg- -35.4%(SD- 2.8)
	DFP- 5.6 (2.5–8.7)	DFP- -26.7(-32.9- -20.6)
	100 mg- 10.1%	100 mg- -46.6(SD- 2.8)
	DFP- 7.4 (3.9–10.8)	DFP- -37.9 (-44.2- -31.7)
	(P<0.001 for both comparisons with placebo)	

Table 8:

	One TEAE	One serious TEAE	Mild TEAE	Moderate TEAE	Severe to fatal TEAE	AE leading to discontinuation	Diarrhea	Nausea
Placebo	260 (81.8)	20 (6.3)	92 (28.9)	139 (43.7)	29 (9.1)	All treatments combined, n=21; (2.17%)	44 (13.8)	25 (7.9)
80	289 (88.4)	20 (6.1)	99 (30.3)	164 (50.2)	26 (8.0)	All treatments combined, n=21; (2.17%)	76 (23.2)	38 (11.6)
100	279 (86.1)	24 (7.4)	99 (30.6)	151 (46.6)	29 (9.0)	All treatments combined, n=21; (2.17%)	101 (31.2)	59 (18.2)

Table 9:

Adverse effects
Diarrhea and nausea
Placebo- 11.5%
80mg resmetirom: 10.9%
100-mg resmetirom: 12.7%
≥1 Adverse event attributed to resmetirom or placebo
Placebo-27.4%
80mg- 38.5%
100mg- 41.5%
≥1 Serious adverse event
Placebo- 11.5%
80mg- 10.9%
100mg- 12.7%
Adverse event leading to trial discontinuation before wk 52
Placebo- 2.2%
80mg- 1.9%
100mg- 6.8%

5. Conclusions

The Phase 3 MAESTRO trials for Resmetirom, targeting patients with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), demonstrated significant promise in addressing the challenges posed by Nonalcoholic Steatohepatitis (NASH). Resmetirom, a selective Thyroid Hormone Receptor (THR)-β agonist, has shown substantial efficacy in reducing hepatic fat and improving liver histology, crucial endpoints in the treatment of NASH.

MAESTRO-NASH trial results indicate that Resmetirom significantly enhances NASH resolution and reduces fibrosis without worsening the NAFLD activity score. The success of the MAESTRO-NAFLD-1 trial, focused on safety, corroborates that resmetirom does not significantly increase adverse effects compared to placebo, highlighting its potential as a safe treatment option.

These findings underscore the potential of Resmetirom to fill a significant therapeutic gap in the management of NASH and related metabolic dysfunctions. Further research, particularly from ongoing arms of the MAESTRO trials, will be essential in confirming long-term efficacy and safety, ultimately paving the way for Resmetirom's clinical use in broader patient populations. There is particular interest in MAESTRO NASH OUTCOMES trial which focuses on patients who have already progressed to cirrhosis. The trial (involving approximately 700 adults with well-compensated NASH cirrhosis (Child-Pugh A 5-6) aims to evaluate all-cause mortality, liver transplant, liver-related events (such as hepatic decompensation events including ascites, hepatic encephalopathy, and gastroesophageal variceal hemorrhage), HCC, and a confirmed increase in MELD score from <12 to ≥15. Additionally, the trial will assess the long-term safety of resmetirom 80 mg compared to placebo. The study is expected to last 2-3 years (3).

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