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Original Research Article

# CLINICAL OUTCOMES OF RESMETIROM IN NASH: A FOCUSED THERAPEUTIC ANALYSIS

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**ABSTRACT**

MASH has emerged as a major public health concern, as it is closely linked to metabolic syndrome, which includes obesity, T2DM, hypertension, and dyslipidemia. Fatty liver disease with a higher prevalence of cirrhosis is seen in around 75% of people with insulin resistance and T2DM. In the United States, the prevalence of MASH in adults ranges from 3% to 12%, with ethnic variance in prevalence. Thyroid hormones and their analogues manage and regulate cholesterol homeostasis via multiple pathways. Thyroid hormone is an activator for de novo lipogenesis and a regulator for beta-oxidation of fatty acids. Resmetirom (MGL-3196) is an FDA-approved drug for metabolic dysfunction-associated steatohepatitis. It is a highly selective THR-β agonist that primarily targets hepatic tissues, where THR-β is predominantly expressed, hence minimizing off-target effects such as cardiac stimulation, in contrast to non-selective thyroid hormone analogs, thus having a favorable safety profile. The safety and clinical efficacy of resmetirom in treating MASH have been thoroughly assessed through different clinical trials. The studies have shown a 37% liver fat reduction with improvement in liver enzymes. Resmetirom is well tolerated in all the clinical trials, which proves the safety profile of the drug. The study analyzed the efficacy of various drugs for the resolution of MASH and regression of hepatic fibrosis and showed that although resmetirom was found to be an effective option, FGF21 analogues (pegozafermin), dual agonists (tirzepatide), and GLP1 Ras (semaglutide) were found to be much better options for fibrosis regression and MASH resolution. Even though the use of Resmetirom for nonalcoholic steatosis is novel and promising, large-scale clinical trials can help in the progression of personalized therapy for patients.

**Keywords:** RESMETIROM, NASH.

## INTRODUCTION

Non-alcoholic steatohepatitis, now known as metabolic-associated steatohepatitis (MASH), is the progression of metabolic-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD). It is characterized by hepatic steatosis, inflammation, and hepatocellular injury, which may or may not lead to fibrosis.

MASH due to MASLD has emerged as a major public health concern, as 32.4% of the population is affected, and there is a rise in metabolic syndrome, including obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia. Fatty liver disease with a higher prevalence of cirrhosis is seen in around 75% of people with insulin resistance and T2DM. Polycystic ovarian disease (PCOS), lipodystrophies, mitochondrial illnesses, Weber-Christian disease, and Wilson disease are additional metabolic and genetic disorders linked to MASLD.[1,2,3]

In the United States, the prevalence of MASLD and MASH in adults ranges from 30% to 40% and 3% to

12%, respectively. There is also ethnic variance in prevalence, with Hispanics having the highest prevalence, followed by Caucasians, and then African-Americans. MASH, which is characterized by ≥5% hepatic fat (steatosis) along with inflammation and hepatocyte damage (ballooning), affects 32% of people with MASLD. In certain patients, MASH may worsen and lead to hepatocellular cancer (HCC), portal hypertension, severe fibrosis, cirrhosis requiring liver transplantation, and a high risk of mortality [4, 5, 6]. It is anticipated that the number of MASLD cases in the US will rise from 83.1 million in 2015 to 100.9 million in 2030, with MASH accounting for a significant amount of these instances. As a result of the disease progression, there will be a sharp rise in HCC and patients with cirrhosis and end-stage liver disease, requiring liver transplantation .[7,8]

Currently, a liver biopsy is required to provide a clear diagnosis of MASH; however, this invasive technique carries some risk. To identify individuals with MASH and track treatment response (in the context of an approved therapy), non-invasive testing (biomarkers and/or imaging modalities) that can take the place of serial liver biopsies is desperately needed.[9]

There is currently no FDA-approved treatment for this illness, and identifying suitable therapeutic targets is essential. Since there is currently no approved medication or surgical procedure to treat MASH, lifestyle changes (diet, exercise, and physical activity) continue to be the mainstay of its management. The primary goals of these strategies are to control body weight and metabolic diseases.[10] Well-conducted clinical trials targeting. pertinent therapeutic targets as a viable treatment for NASH are still in their early stages of development.

## 2. Thyroid Hormone Signaling and Liver Metabolism: correlation with NAFLD

Thyroid hormones are molecules derived from the amino acids compounded with either three or four atoms of iodine. They are released periodically from the thyroid gland and affect anabolism, catabolism, and the regulation of biochemical cycles in most cells of the body.[11] Thyroid hormones and their analogues manage and regulate cholesterol homeostasis via multiple pathways. This is controlled largely via gene repression and expression, as permitted by thyroid hormone, coregulators, and the thyroid receptor isoform. The main processes are cholesterol biosynthesis, low-density lipoprotein [LDL] endocytosis, and reverse cholesterol transport.[12] HMG-CoA reductase is the rate-limiting step of low-density lipoproteins in the liver and has been the target of therapies for dyslipidemia. T3 hormone promotes HMG-CoA reductase in the liver, which in turn increases cholesterol production but also catalyzes conversions to high-density lipoproteins, leading to a drop in total cholesterol levels.[13]

LDL endocytosis draws circulating LDLs from the blood to the liver for its metabolism. Beta isoforms of thyroid receptors are the main regulators of LDL endocytosis, lowering the blood levels of LDL.[12] Thyroid hormone also facilitates reverse cholesterol transport, primarily transporting excess cholesterol from peripheral tissues via peripheral HDL back to the liver for excretion, resulting in lower plasma cholesterol and LDL concentrations. This step is crucial, as excess cholesterol is toxic to the cells. Apolipoprotein A1 and cholesteryl ester transfer protein assist the HDL in reverse cholesterol transportation. This cholesterol is then converted to bile acids in the liver and excreted via the intestine and kidneys.[12,14] Thyroid hormone is also an activator for de novo lipogenesis and a regulator for beta-oxidation of fatty acids. Hypothyroidism and low levels of the T4 hormone in euthyroid states have been associated with increased risk of MASLD.[15] TSH levels are often used as off-label predictors of MASLD as well. Evidence shows that hepatocyte injury due to increased lipotoxicity, inflammation, and fibrosis; altered insulin secretion; and contributions to hepatic tissue insulin resistance are co-products of hypothyroidism, which, in turn, lead to MASLD.[16,17,18] Focusing on the liver-dominant thyroid hormone isoform (THB) for the management of MASLD reduces these harmful biochemical processes while having virtually no effect on other organs, such as the heart and bones. Resmetirom is one such FDA-approved drug for metabolic dysfunction-associated steatohepatitis.

## 3. Resmetirom: Mechanism of Action

Resmetirom (MGL-3196) is a highly selective thyroid hormone receptor beta (THR-β) agonist that primarily targets hepatic tissues, where THR-β is predominantly expressed. It selectively targets THR-β, minimizing off-target effects such as cardiac stimulation, in contrast to non-selective thyroid hormone analogs. For patients suffering from MASH and cardiovascular comorbidities, this selectivity offers a good safety profile.[19,20] Table 1 depicts the characteristics of Remetirom.

**Table 1: Key Characteristics of Resmetirom**

| Property | Description |
|---|---|
| Drug Name | Resmetirom (MGL-3196) |
| Class | Selective thyroid hormone receptor-β agonist |
| Mechanism of Action | Enhances hepatic fat metabolism via THR-β activation |
| Indications Under Study | MASH, dyslipidemia |
| Administration | Oral |
| Status | Phase 3 clinical trials (MAESTRO-NASH, etc.) |

Resmetirom's hepatocyte-selective properties allow for focused control of hepatic lipid metabolism. It stimulates the gene transcription linked to mitochondrial biogenesis, fatty acid oxidation, and cholesterol homeostasis by activating the hepatic THR-β receptor.[19,20] Clinical results typically show significant decreases in triglycerides, apolipoprotein B concentrations, liver fat content, and serum LDL cholesterol.[21,22] Resmetirom is positioned as a therapeutic drug that can concurrently address the hepatic and systemic metabolic abnormalities prevalent in MASH patients due to its combination of hepatocyte-targeted activities.[23] Figure 1 summarizes the multifactorial pathogenesis of NASH, including lipid accumulation, oxidative stress, inflammation, and fibrosis. Resmetirom intervenes early at the stage of fatty liver.

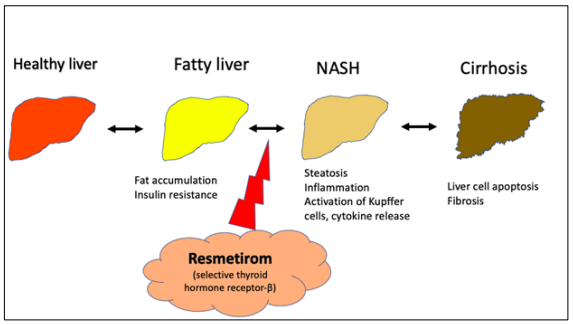


**Figure 1: NASH Pathogenesis and Points of Intervention**

Resmetirom's dose-dependent therapeutic benefits, such as decreased hepatic steatosis, inflammation, and fibrosis markers, have been shown in preclinical investigations employing rodent and primate models of MASH. The models' transcriptome analysis showed increased expression of genes linked to mitochondrial function and lipid metabolism, emphasizing the direct effect of resmetirom's THR-β agonist action.[22] Figure 2 illustrates the function of Resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, enhancing mitochondrial β-oxidation, decreasing lipogenesis, and improving lipid metabolism in treating MASH.

Furthermore, preclinical safety evaluations validated its selective hepatic profile by confirming little cardiovascular effects.[24] These fundamental preclinical research results provided significant support for the advancement to the next stages of clinical trials, which have validated the safety and effectiveness profiles of resmetirom to date.

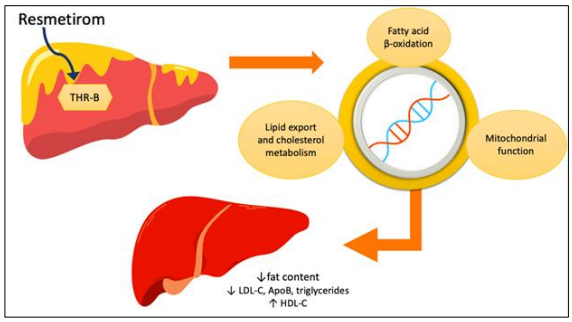


**Figure 2: Mechanism of Action of Resmetirom**

## 4. Clinical Evidence on the Efficacy of Resmetirom: Analysis of Clinical Trials

The safety and clinical efficacy of resmetirom in treating MASH have been thoroughly assessed in multiple clinical trials. Its therapeutic potential for MASH management was reinforced by these trials, which showed consistent benefits in terms of liver fat reduction, MASH resolution, fibrosis improvement, and improved lipid profiles.[19,20,24]

According to the MRI-proton density fat fraction (MRI-PDFF), resmetirom drastically reduces the amount of fat in the liver. Improvements in liver histology are strongly correlated with significant reductions in hepatic fat according to the analysis of clinical trials results. Table 2 summarises the major clinical trials on resmetirom and their key findings.

**Table 2: Summary of Major Clinical Trials Involving Resmetirom**

| Trial Name | Phase | Sample Size | Duration | Primary Endpoints | Key Findings |
|---|---|---|---|---|---|
| MAESTRO-NAFLD-1 (NCT04197479) [25] | 3 | 1,143 | 52 Weeks | Incidence of treatment-emergent adverse events (TEAEs). | Resmetirom demonstrated a favorable safety and tolerability profile, with TEAEs reported in 86.5% of patients receiving open-label 100 mg resmetirom, 86.1% in the 100 mg group, 88.4% in the 80 mg group, and 81.8% in the placebo group. |
| MAESTRO-NASH (NCT03900429) [27] | 3 | 966 | 52 Weeks | NASH resolution and fibrosis improvement | Both the 80 mg and 100 mg doses of resmetirom outperformed placebo in achieving NASH |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | resolution and in improving liver fibrosis by at least one stage. |

The studies showed that resmetirom effectively supports the resolution of MASH without exacerbating fibrosis with improved liver enzymes when taken for at least 36 weeks. Additionally, patients with progressing liver disease benefit from its dual therapeutic advantages, since it shows a notable improvement in the fibrosis stage.[19,21,24] Resmetirom therapy significantly improves lipid profiles, particularly by lowering LDL cholesterol, triglycerides, and apolipoprotein B levels. These lipid alterations may significantly reduce cardiovascular risk, which is an important consideration when treating MASH patients, who frequently have elevated cardiovascular risk factors.[21,23]

**5. Safety and Tolerability Profile of Resmetirom**

Although the studies have shown the efficacy of resmetirom, the increased occurrence of gastrointestinal side effects, including diarrhea and nausea, has emphasized the need for careful surveillance and control of these unfavorable incidents in clinical settings. Notably, no significant difference has been found in the incidence of urinary tract infections (UTIs) or headaches between the resmetirom and placebo groups in the studies, indicating a generally favorable safety profile for resmetirom. In one of the clinical trial studies involving 80 mg of resmetirom, 100 mg of resmetirom, and a placebo group, 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 resmetirom group, and 11.5% in the placebo group.

The 100-mg resmetirom dose showed consistently greater reductions in hepatic fat (measured by MRI-PDFF) than 80 mg; however, patients who achieved a target level of sex hormone binding globulin (SHBG) on 80 or 100 mg resmetirom showed a similar reduction in hepatic fat. SHBG is a marker analyzed for liver function and metabolic activity along with THR-β. There was also found to be a dose-dependent effect on the increased rates of gastrointestinal side effects. Compared to placebo, resmetirom achieved greater reductions from baseline in hepatic fat content assessed by MRI-PDFF.[25] Figure 3 bar graph demonstrates the efficacy of Resmetirom in reducing hepatic fat content compared to placebo at Weeks 16 and 52. The data, measured via MRI-PDFF, show a significant percentage reduction in liver fat among patients treated with resmetirom.

In another study, the risk of adverse events, including diarrhea and nausea, was found to be significantly increased for the resmetirom group as compared to the placebo group.[26]

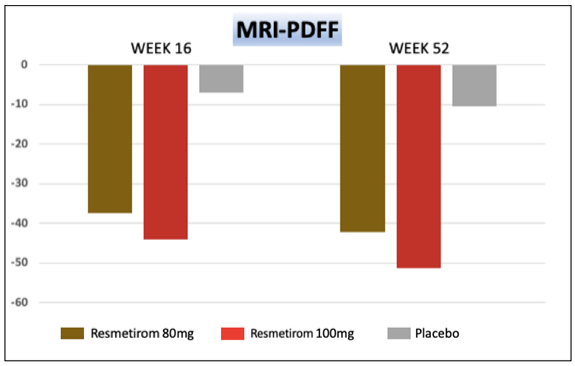


**Figure 3: Percent Change from Baseline in Hepatic Fat as Measured by Magnetic Resonance Imaging-Proton Density Fat Fraction at Week 16 and 52**

**6. Comparative Efficacy with Other Investigational Agents**

The study compared the efficacy of various drugs in resolving MASH and regressing hepatic fibrosis. The study results showed that Pegozafermin, cilofexor + firsocostat, denifanstat, survodutide, obeticholic acid, tirzepatide, resmetirom, and semaglutide were found to be significantly better than placebo in reversing fibrosis. Although resmetirom was found to be an effective option, FGF21 analogues (pegzomib), dual agonists (tirzepatide), and GLP-1R agonists (semaglutide) were found to be much better options for fibrosis regression and NASH resolution.[28] Figure 4 presents longitudinal data showing the reduction in serum alanine aminotransferase (ALT) levels in patients treated with Resmetirom versus placebo.

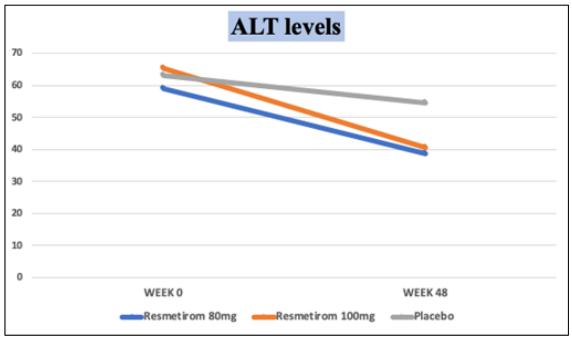


**Figure 4: Effect of Resmetirom on Serum ALT Levels Over 48 Weeks Compared to Placebo**

**Table 3: Comparative Overview of Emerging Therapies for MASH**

| Agent | Mechanism | Key Benefit | Limitations |
|---|---|---|---|
| Resmetirom | THR-β agonist | Fat reduction, lipid profile | Fibrosis data pending |
| Obeticholic acid | FXR agonist | Fibrosis regression | Pruritus, LDL ↑ |

| | | | |
|---|---|---|---|
| Lanifibranor | Pan-PPAR agonist | Steatosis & fibrosis ↓ | Weight gain |
| Semaglutide | GLP-1 agonist | Weight loss, NASH resolution | Fibrosis impact unclear |

The interim analysis of MAESTRO-NASH, the clinical trial, involved the use of resmetirom, with MASH resolution and fibrosis reduction after 52 weeks of treatment. Resmetirom is the only drug showing both MASH resolution and fibrosis improvement in the clinical trials done till now, while other drugs, such as semaglutide, showed a significant dose-dependent MASH resolution without worsening fibrosis in one of the clinical trial studies.[29] Thus, resmetirom serves as a unique link between safety and efficacy compared to the other drugs in use. Table 3 provides a comparative overview of resmetirom with other drugs for MASH treatment.

## 7. Challenges and Limitations in Current Evidence

The analysis of recent clinical trials on the efficacy and safety profile of resmetirom in MASH has provided valuable information on the biopharmacokinetics of the drug. However, as extensive as the trials were, there are certain limitations that need to be addressed and overcome in future trials. Most of the patients in these trials had to undergo extensive and multiple invasive tests for liver biopsies to gauge response to therapy. Even though these can be replaced with non-invasive biomarkers for a potentially less stressful test in the future, the accuracy of the biomarkers still needs to be determined to replace the gold standard biopsies. Liver biopsy is an invasive, logistically heavy, costly test, needing alternatives. Clinical biomarkers, if proven to be effective in future studies, are a cheaper and logistically easier alternative, which may even lead to much higher patient compliance. Most of the population in the analyzed clinical trials was also 50 years or older and of Caucasian race. This does not help us gauge a response or treatment activity when managing patients of other races or age groups. Since Resmetirom is not globally available for the treatment of MASH and has limited evidence, it might be more difficult to get access to it for larger and much more geographically and demographically diverse clinical trials. More population heterogeneity should be encouraged in future trials. All the current major clinical trials have focused on the primary outcomes and endpoints for about 36 to 52 weeks of duration after starting therapy.[39] Potential adverse effects of thyroid receptor beta modulators could be uncontrolled regulation of lipid levels, injury to hepatocytes, or poor outcomes in other organ pathophysiologies. Longer-term follow-ups and post hoc data analyses need to be carried out to better understand the long-term effects of anti-MASH therapy.[40] Even though the use of resmetirom for MASH is a progressive step, there is still a lot to consider when thinking of the wide-ranging generalized applicability and availability of the therapy.

## 8. Future Directions

The MAESTRO–NASH trial is an important, ongoing, double-blind, randomized, placebo-controlled phase 3 study evaluating the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and fibrosis stages F1B to F3.[27] The phase 3 MAESTRO-NASH trial demonstrated that resmetirom, which was compared to placebo at 52 weeks, significantly improves both histologic endpoints, including MASH resolution without worsening of fibrosis and fibrosis improvement by at least one stage. These findings support the ongoing development of resmetirom as a potential disease-modifying agent and provide a foundation for future research directions, including combination regimens and biomarker-driven approaches in MASH management.

Combination therapy is becoming a potential strategy to improve treatment outcomes. Agents such as GLP-1 receptor agonists (e.g., semaglutide, tirzepatide) have been reported to show efficacy in reducing steatohepatitis,[30,31,32] while other medications like pioglitazone and vitamin E have also shown histologic benefits in selected populations.[33,34] Although these therapies were excluded from the MAESTRO-NASH trial, many patients in clinical practice are already using them, raising important questions about how precisely to integrate resmetirom into existing treatment plans. At present, decisions around combination therapy must be guided by individual patient characteristics, comorbidities, and potential drug interactions, particularly with statins and CYP2C8 inhibitors.[35] Further research is needed to define the safety and effectiveness of such combinations and to inform treatment sequencing in routine care.

Biomarker-driven approaches in MASH management require further evaluation. Four randomized controlled trials were performed and revealed a substantial reduction in liver fat as measured by MRI-PDFF, in the treatment of Resmetirom.[36,37] The AASLD practice guidance reported that a ≥30% reduction in MRI-PDFF after one year of therapy is associated with improved histologic outcomes, but the positive predictive value remains below 50%.[38,39,40] Therefore, while MRI-PDFF may offer supportive evidence, careful assessment should be considered to improve treatment outcomes.

# CONCLUSION

MASH is a concerning public health disorder with a rise in metabolic disorders, with a few available treatments, including conservative treatments and managing comorbidities. The study offers strong support for resmetirom as a possible treatment for MASH. Resmetirom is effective in treating important

aspects of MASH, such as lowering the amount of fat in the liver, enhancing liver fibrosis, and maybe enhancing metabolic health with a safer profile. Even though these findings are promising, more research is required to examine the long-term safety and efficacy profile, the best dosages for various patient populations, and the possible advantages of combination therapy. Despite certain limitations, including a dearth of long-term efficacy and safety evidence, resmetirom is currently utilized in clinical practice. Based on weight and clinical response, the dosage should be adjusted.

Furthermore, a better comprehension of the mechanism by which Resmetirom works helps direct the creation of even more specialized treatments. It is positioned as a viable new weapon in the fight against MASH because of its capacity to target the disease's underlying pathophysiology, potentially alter its trajectory, and enhance patient outcomes. Resmetirom provides hope for patients looking for long-term, efficient treatment of this difficult and complex illness with further study and development.

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