

Resmetirom: A New FDA-approved Drug as a Targeted Therapeutic Strategy in Metabolic Dysfunction Associated Steatohepatitis: Translational Evidence from Current Clinical Trials

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Abstract: Metabolic dysfunction-associated steatohepatitis (MASH) represents a significant global health burden, affecting 3–5% of the population and projected to become a leading cause of liver transplantation by 2030. This review examines Resmetirom, the first FDA-approved drug for non-cirrhotic MASH with moderate to severe hepatic fibrosis. As a selective thyroid hormone receptor beta (THR- β) agonist, Resmetirom enhances hepatic lipid metabolism through increased mitochondrial β -oxidation and improved lipoprotein profiles. Multiple clinical trials have demonstrated its efficacy in reducing hepatic fat content, improving liver histology, and resolving MASH without worsening fibrosis. While generally well-tolerated, gastrointestinal side effects including diarrhea and nausea were more common with Resmetirom than placebo. This breakthrough therapy offers a promising option for MASH management, though long-term studies and broader geographic representation in trials remain necessary to fully establish its role in clinical practice.

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Introduction

On March 14, 2024, the United States Food and Drug Administration (FDA) approved Resmetirom (Rezdiffra™) for the treatment of non-cirrhotic, non-alcoholic steatohepatitis (NASH) with moderate to severe hepatic fibrosis in adults, coupled with diet and lifestyle changes (US Food and Drug Administration, 2024).

Nonalcoholic fatty liver disease (NAFLD) is defined by hepatic steatosis, with fatty tissue comprising 5–10% of liver weight. NAFLD can progress to NASH, a subset characterized by hepatic inflammation and fibrosis in addition to the fat accumulation (Xu et al., 2022). The recent change in nomenclature reclassifies NAFLD and NASH as metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), respectively (Rinella, 2023). Hepatic inflammation caused by MASH gradually progresses to hepatic fibrosis and cirrhosis, ultimately predisposing to hepatocellular carcinoma (HCC) (Younossi and Henry, 2016; Gariani and Jornayvaz, 2021; Fahim et al., 2023). Diabetes mellitus, obesity, hypertension, dyslipidemia, and metabolic syndrome are among the comorbidities frequently associated with MASH (Gariani and Jornayvaz, 2021; Niriella et al., 2023). Individuals diagnosed with MASLD/MASH are at heightened risk for developing cardiovascular diseases (CVD), chronic renal disease, and specific extrahepatic malignancies. CVD stands out as a leading cause of morbidity and mortality (Tilg et al., 2023). The liver is primarily composed of hepatocytes along with immune modulators like Kupffer cells and hepatic stellate cells. Each of these cells contributes to the progression of MASH, though the exact mechanism remains poorly understood. Therefore, managing to limit the progression of the disease has become more difficult. Our limited understanding of the mechanisms and the molecular interactions involved have complicated our attempts at managing MASLD and preventing progression to MASH (DeBosch, 2022; Xu et al., 2022).

Prevalence

Hepatic steatosis is amongst the most prevalent chronic liver diseases affecting nearly 25% of the global population, while MASH affects approximately 3–5% (Tong et al., 2022; Xu et al., 2022). It is estimated that by 2030, MASH will become one of the leading causes of liver transplantation, imposing a significant burden on the global healthcare system. Among the patients affected by MASLD about 20% develop MASH and

40% of the patients with MASH progress to fibrosis (Xu et al., 2022). Complications associated with these conditions contribute significantly to morbidity and mortality burden worldwide (Tong et al., 2022). According to Global Health Estimates (GHE) 2025, MASLD will account for 21.6% of all deaths due to cirrhosis and other chronic liver diseases, and 11.8% of all deaths due to liver cancer (Sarin et al., 2020). Currently, 6–8 million people in the US are suffering from MASH with moderate to advanced liver scarring and this number is expected to increase (Younossi and Henry, 2016). The Asia-Pacific region accounts for 54.3% of the global deaths due to cirrhosis and more than 50% of the deaths due to MASLD (Sarin et al., 2020). There is limited data available regarding the prevalence of MASH in Pakistan due to the unavailability of a national registry. However, a study conducted by Shah et al. (2018) reported a MASH prevalence of 12.3% among the study participants. In Pakistan the prevalence of MASLD has been reported to be 9–27% in rural areas and 21–42% in urban areas. MASLD is becoming an important cause of liver disease-related mortality in Pakistan (Sarin et al., 2020).

Challenges in drug development

Given the limited number of approved therapies for MASH, the imperative need for more treatment options led to the recent development of Resmetirom. One of the main challenges in the development of drugs for MASH was the invasive nature of liver biopsies needed to assess the primary end point of disease resolution. In the past decade, several non-invasive approaches have been developed that correlate with liver histology, assessing disease severity and progression over time (Harrison et al., 2023a). A phase 3 trial of Resmetirom by Harrison et al. (2023b) used magnetic resonance imaging proton density fat fraction (MRI-PDFF) to assess hepatic fat. This non-invasive quantitative biomarker serves as a counterpart to liver biopsy for assessment of MASH (Caussy et al., 2018). During this trial, fibro scan and magnetic resonance electrography (MRE) were also utilized to assess the residual hepatic fat at baseline, week 16, and week 52 (Harrison et al., 2023b).

The drug (Resmetirom)

Thyroid hormone mediates its effects through two receptors, thyroid hormone receptor alpha (THR- α) and thyroid hormone receptor beta (THR- β). THR- α is mainly expressed in the heart and bones, while

THR- β is the dominant receptor in hepatocytes (Kokkorakis et al., 2024). Thyroxine is involved in metabolism within adipocytes, including those in the liver. Its nonselective binding to THR- α and THR- β accounts for its systemic adverse effects and thus makes it an unsuitable treatment option for MASH (Singha et al., 2024). Resmetirom serves as an attractive pharmacological option in patients diagnosed with MASH. It exhibits a preference for binding to THR- β over THR- α , showing approximately 28-fold greater affinity as compared to free Triiodothyronine (T3). It acts as an agonist of THR- β , promoting receptor activation in the liver to mitigate the hepatic steatosis (Kokkorakis et al., 2024; US Food and Drug Administration, 2024). Binding to THR- β promotes β -oxidation in the mitochondria of hepatocytes, leading to increased uptake of free fatty acids (FFA) from external sources and enhanced de novo synthesis of FFAs within hepatocytes. It also enhances the expression of low-density lipoprotein (LDL) receptors in the liver lowering LDL levels in blood. In addition, it decreases the synthesis and release of very-low-density lipoprotein (VLDL). These processes ultimately improve hepatic steatosis, dyslipidemia and obesity (Kokkorakis et al., 2024). Thus, THR- β agonists, whose mechanisms of action include stimulation of β -oxidation in liver mitochondria, reduced production and secretion of very low-density lipoprotein, free fatty acid (FFA) uptake and synthesis, as well as enhancing expression of the LDL receptor in the liver, have been a principal approach for drug development for the treatment of dyslipidemia, obesity, and hepatic

steatosis (Figure 1). Importantly, THR- β agonists show minimal effects on other tissues that are observed with THR- α agonists.

Evidence from the current trials

A thorough literature search was conducted in PubMed up to May 2024, using the MeSH terms “(Resmetirom) OR (Rezdiffra) OR (MGL-3196)” AND “(MASH) OR (Nonalcoholic steatohepatitis)” with additional filters for randomized controlled trials (RCTs) or clinical trials and articles in English language. This search yielded six studies. After an initial screening, one study was excluded because its aim was to present the design of the phase 3 MAESTRO clinical program. The remaining studies were examined thoroughly, and the key findings are summarized in Table 1. The majority of the studies were conducted in the United States.

The therapeutic potential of Resmetirom in MASH has been evaluated through multiple clinical trials from 2019 to 2024. Initial phase 2 studies demonstrated significant efficacy in reducing hepatic fat content and improving liver histology, particularly in patients with higher drug exposure. The 36-week open-label extension study confirmed these findings, showing consistent benefits at both 80 mg and 100 mg daily doses (Harrison et al., 2021). The studies then progressed to larger phase 3 trials, notably NCT04197479 and NCT03900429, which enrolled 1,143 and 966 patients, respectively (Harrison et al.,

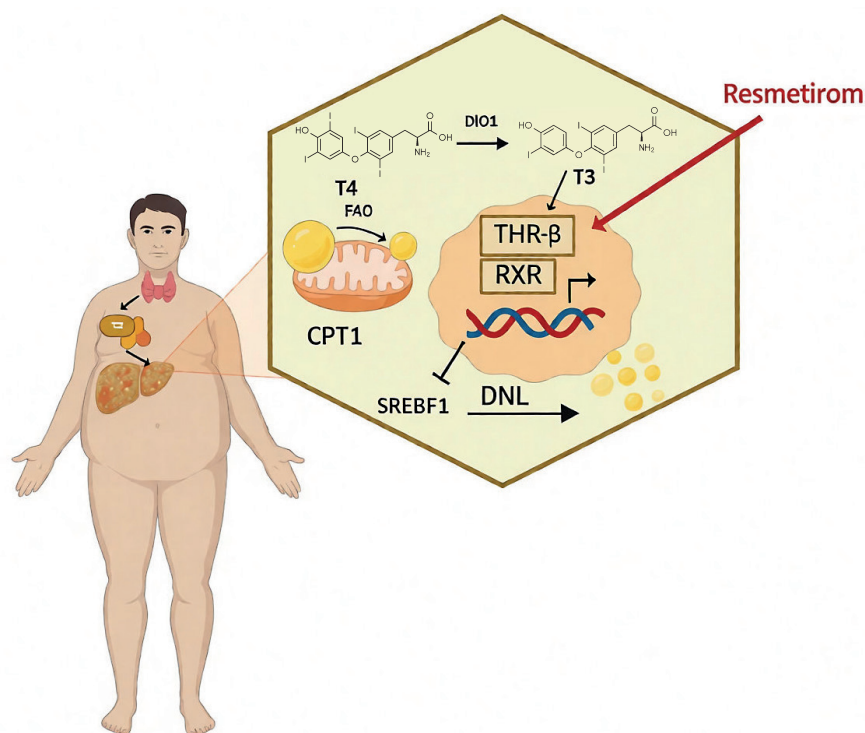


Figure 1: Illustrates the mechanism of action of Resmetirom in hepatocyte lipid metabolism. Iodothyronine deiodinase 1 (DIO-1) transforms thyroxine (T4) into its active form, triiodothyronine (T3). The transcription of genes involved in lipid metabolism is regulated when free T3 binds to the thyroid hormone receptor β (THR- β). The regulating genes for lipid metabolism are sterol regulatory element binding transcription factor 1 (SREBF1), which is the main regulator of hepatic de novo lipogenesis (DNL), and carnitine palmitoyl transferase 1 (CPT1), which regulates mitochondrial fatty acid oxidation. Resmetirom is a liver-selective THR- β agonist which mimics the actions of free T3. By upregulating DIO1 expression it enhances the conversion of free T4 to free T3 and concurrently decreasing levels of inactive reverse T3 (rT3). This results in reduced hepatic lipid accumulation, which aids in improving liver inflammation and fibrosis.

Table 1: Summary of key findings from the included studies

Author, year, NCRT	Study design	Duration	Randomization sequence and intervention	Patients	Conclusion
Harrison et al. (2019), NCT 02912260	Multicenter, phase 2, randomized, double-blind, placebo-controlled trial	36 weeks	2:1 to Resmetirom 80-mg or placebo	Adults with biopsy-confirmed MASH (fibrosis stages 1–3) and hepatic fat fraction $\geq 10\%$ at baseline, as assessed by MRI-PDFF, were included. Of 348 screened patients, 125 were randomly assigned to Resmetirom and 41 to placebo	Resmetirom treatment demonstrated significant efficacy in MASH patients, evidenced by substantial reductions in hepatic fat content, improvements in histology among those with higher drug exposure, decreases in LDL-C and Lp(a), and reductions in serum liver enzymes and noninvasive fibrosis biomarkers
Harrison et al. (2021), NCT 02912260	Open-label extension	36 weeks	2:1 ratio to either Resmetirom or a matching placebo, administered orally once daily	A subsequent study was conducted involving 31 patients, including 14 individuals previously assigned to the placebo group, who exhibited persistently mild to markedly elevated liver enzymes at the conclusion of the main study (NCT02912260)	This 36-week open-label extension study demonstrated the efficacy and safety of Resmetirom at daily doses of 80 mg and 100 mg, evidenced by significant reductions in hepatic fat content, fibrosis markers, and LDL-C levels
Younossi et al. (2022), NCT 02912260	Phase 2, multicenter, double-blind, randomized, placebo-controlled trial	36 weeks	2:1 to Resmetirom 80-mg or placebo	The study included 125 patients with biopsy-confirmed MASH, metabolic syndrome, and MRI-PDFF $\geq 10\%$ hepatic fat. 78 patients were assigned to the intervention group and 38 to the placebo group	Resmetirom treatment resulted in improvements in health-related quality of life (HRQL), particularly in those who demonstrated reductions in hepatic fat as measured by MRI-PDFF and histological improvements in MASH activity score and fibrosis. These HRQL improvements were most notable in the domains of physical functioning, vitality, and mental health
Harrison et al. (2023b), NCT 04197479	A phase 3, randomized, double-blind, placebo-controlled trial with an additional open-label arm	52 weeks	Participants were randomized to receive 100 mg Resmetirom (n=325), 80 mg Resmetirom (n=327), or placebo (n=320) in the double-blind portion of the trial, an additional 171 patients were randomized to an open-label arm receiving 100 mg Resmetirom	Of 1,988 screened patients, 1,143 with MASLD, metabolic syndrome, and $\geq 8\%$ hepatic fat (MRI-PDFF) was randomized. The double-blind portion included 972 patients, while 171 patients entered an open-label arm	Resmetirom demonstrated a favourable safety profile, with adverse events comparable to placebo over 52 weeks, except for initial mild gastrointestinal symptoms. Both 80-mg and 100-mg doses showed significant reductions in LDL-C, apolipoprotein B, triglycerides, hepatic fat, and liver stiffness
Harrison et al. (2024), NCT 03900429	Phase 3, randomized, double-blind, placebo-controlled trial	52 weeks	1:1:1 ratio to receive once daily Resmetirom at a dose of 80 mg or 100 mg or placebo	Included 966 subjects with biopsy-confirmed MASH and fibrosis stages F1B, F2, or F3. 322 received Resmetirom 80 mg, 323 received Resmetirom 100 mg, and 321 received placebo	Both the 80-mg and 100-mg doses demonstrated superiority over placebo in achieving MASH resolution without worsening fibrosis (25.9% and 29.9% vs. 9.7%, respectively) and in improving liver fibrosis by at least one stage without worsening MASH. Additionally, Resmetirom showed significant reductions in LDL-C levels week 24 compared to placebo

MASH – metabolic dysfunction-associated steatohepatitis; MRI-PDFF – magnetic resonance imaging proton density fat fraction; LDL – low-density lipoprotein; MASLD – metabolic dysfunction-associated steatotic liver disease

2023b, 2024). These trials provided evidence on the safety and efficacy of Resmetirom over 52 weeks. Key findings included significant improvements in MASH resolution without worsening fibrosis and consistent reductions in multiple metabolic parameters, including LDL-C, apolipoprotein B, and triglycerides. Beyond clinical endpoints, quality of life assessments revealed meaningful improvements. This comprehensive clinical development program, spanning multiple years and involving both phase 2 and phase 3 trials, establishes Resmetirom as a promising therapeutic option for MASH patients.

Adverse effects

In all studies, Resmetirom was administered orally and was generally well tolerated. A recent systematic review reported that there was no significant difference of mild, moderate, and severe treatment emergent adverse events (TEAEs) between placebo and Resmetirom (Suvarna et al., 2024). Common side effects included gastrointestinal problems such as diarrhea, nausea, abdominal pain, vomiting, and constipation. These adverse effects were most frequently reported by participants receiving Resmetirom at a dosage of 100 mg/day (Harrison et al., 2021, 2024). A recent systematic review and meta-analysis by Hashim et al. (2024) found that the Resmetirom group had a significantly increased risk of diarrhea (risk ratio [RR] 1.81; 95% confidence interval [CI] 1.40–2.35; $p < 0.001$) and nausea (RR 1.72; 95% CI 1.31–2.27; $p < 0.001$), compared to placebo. However, no significant differences were observed for fatigue or urinary tract infections (Hashim et al., 2024). Another meta-analysis carried out by Ayesh et al. (2025) reported that Resmetirom shows dose-dependent improvement in liver histology and function as compared to placebo but was linked to higher rates of nausea, diarrhea, leading to treatment discontinuation.

Conclusion

MASH is a complex condition influenced by genetic factors, environmental triggers, and other health conditions, all contributing to liver fibrosis in affected individuals. Fibrosis is a key predictor of clinical outcomes. Clinical trials have shown that Resmetirom improves liver fibrosis when compared to placebo. It also exhibits a favourable safety profile, with no statistically significant differences in overall treatment-related adverse events compared to placebo. Long-term follow-up and large-scale trials are necessary

to confirm these findings. To enhance the validity of the results and the generalizability of the findings, future trials should aim to include diverse geographical populations. In addition, the availability of Resmetirom in the Asia-Pacific region can potentially revolutionize clinical outcomes and reduce complications.

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