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REVIEW

A Review on Resmetirom: An Oral Thyroid Hormone Receptor-β Agonist for the Treatment of Metabolically Dysfunction-Associated Steatohepatitis (MASH)

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Abstract: Metabolically dysfunction-associated steatohepatitis (MASH) is a progressive liver condition associated with type 2 diabetes (T2D), obesity, and dyslipidaemia, all of which are components of metabolic syndrome. In 2024, resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, became the first treatment for non-cirrhotic MASH with mild to advanced fibrosis to receive FDA approval, and in 2025, it was conditionally approved by the European Medicines Agency (EMA) for fibrotic MASH. Resmetirom enhances β-oxidation and lipid metabolism, leading to a reduction in hepatic fat, inflammation, and fibrosis, while minimizing systemic effects on the thyroid or heart. It is intended to be used alongside lifestyle modifications, such as dietary changes and exercise, to optimize patient outcomes. Nevertheless, discrepancies between clinical trial populations and real-world payer criteria reveal access challenges that necessitate policy reform. Effective screening programs rely on educating healthcare providers from various disciplines and establishing consistent standards. Future research should investigate the potential of resmetirom in combination with agents such as GLP-1 receptor agonists, SGLT2 inhibitors, and statins, particularly in light of recent long-term safety data regarding these drug classes and their effects on the thyroid axis. Achieving equitable access will require fair payer endpoints, cost-effectiveness evaluations, and consideration of patient-reported outcomes. Resmetirom signifies a significant advancement in the management of MASH, providing metabolic advantages in conjunction with clinical and lifestyle interventions. Metabolically-dysfunctional-associated steatotic liver disease (MASLD) impacts nearly one-third of adults globally, with 10–30% of cases progressing to MASH or fibrosis, especially in individuals with obesity or type 2 diabetes. Current guidelines endorse resmetirom for non-cirrhotic fibrotic MASH (typically LSM-VCTE 10–20 kPa or MRE 3.1–4.4 kPa), while excluding patients with cirrhosis, active liver disease, substantial alcohol consumption, or untreated thyroid disorders. Monitoring protocols include assessing hepatic safety, thyroid function when necessary, and evaluating response through non-invasive tests and ALT measurements after 6–12 months. Data from the real world indicate a swift adoption of non-invasive eligibility tools, initial enhancements in liver stiffness, and a common concurrent use of GLP-1 receptor agonists, with the response being independent of weight-loss therapies. With the recent approval of semaglutide for fibrotic MASH, determining the optimal integration of resmetirom within treatment algorithms, exploring combination strategies with GLP-1 receptor agonists, and assessing the long-term impacts on liver and cardiometabolic outcomes are essential priorities. This review consolidates the evidence supporting the conditional approval of resmetirom, delineates current clinical guidelines, shares early real-world experiences, and emphasizes the ongoing challenges and future directions in the management of fibrotic MASH.

Keywords: Resmetirom, MASLD, MASH, NASH, liver fibrosis

1 Introduction

Metabolic dysfunction-associated steatohepatitis (MASH), formerly referred to as non-alcoholic steatohepatitis (NASH), represents the progressive inflammatory form of metabolic dysfunction-associated steatotic liver disease (MASLD) and has emerged as one of the most challenging chronic liver disorders worldwide [1]. Characterized by excessive hepatic fat accumulation accompanied by hepatocellular injury, inflammation, and varying degrees of fibrosis, MASH constitutes a major contributor to liver-related morbidity and mortality [2]. The disease is closely

linked to metabolic abnormalities, including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and metabolic syndrome, while endocrine disorders such as hypothyroidism, polycystic ovary syndrome, hypogonadism, and hypopituitarism have also been recognized as important risk modifiers. The increasing prevalence of these metabolic conditions has paralleled the rapid rise of MASLD, making it the most common chronic liver disease globally [3,4].

Current epidemiological evidence indicates that MASLD affects nearly one-third of the adult population worldwide, with prevalence continuing to increase across both developed and developing regions. Among affected individuals, approximately 30% progress to MASH, while 10–30% develop clinically significant fibrosis [5]. The risk of disease progression is substantially greater in patients with obesity or T2DM, populations in which advanced fibrosis and liver-related complications occur more frequently. Although progression to cirrhosis is relatively slow, occurring in a minority of patients over several decades, the consequences are profound, including portal hypertension, liver failure, hepatocellular carcinoma, and increased all-cause mortality. Because fibrosis stage is the strongest predictor of long-term clinical outcomes, preventing fibrotic progression has become a central therapeutic objective in MASH management [6,7].

Lifestyle modification remains the cornerstone of treatment and includes caloric restriction, dietary optimization, and regular physical activity. Sustained weight reduction can improve hepatic steatosis and, in some cases, reverse fibrosis; however, achieving and maintaining clinically meaningful weight loss remains difficult in routine practice [8]. Additional interventions such as vitamin E supplementation and bariatric surgery have demonstrated benefits in selected patient populations, yet important limitations remain regarding patient eligibility, long-term adherence, and fibrosis-specific efficacy. Consequently, despite increasing disease burden, effective pharmacological treatment options for MASH remained unavailable for many years [9].

The development of drug therapy for MASH has been particularly challenging due to the multifactorial pathogenesis of the disease and the stringent regulatory requirements for approval. Several promising agents, including selonsertib, elafibranor, obeticholic acid, and cenicriviroc, advanced to late-stage clinical development but ultimately failed to secure regulatory approval because of insufficient efficacy, safety concerns, or inability to meet predefined histological endpoints [10]. Regulatory agencies currently require demonstration of either fibrosis improvement without worsening of MASH or MASH resolution without worsening of fibrosis, emphasizing the need for therapies capable of modifying disease progression rather than merely improving biochemical markers.

A major breakthrough occurred in March 2024 with the approval of resmetirom (Rezdiffra®), the first pharmacological therapy approved by the United States Food and Drug Administration for adults with non-cirrhotic MASH and moderate liver fibrosis. Resmetirom is an orally administered, liver-targeted, selective thyroid hormone receptor-β (THR-β) agonist designed to enhance hepatic lipid metabolism, reduce lipotoxicity, and mitigate fibrogenic pathways [11]. In the landmark Phase III MAESTRO-NASH trial, resmetirom achieved both key regulatory endpoints by demonstrating significant rates of MASH resolution and fibrosis improvement, thereby becoming the first therapeutic agent to successfully translate mechanistic promise into regulatory approval. Its approval represents a pivotal milestone in the evolution of MASH management and signals the beginning of a new era of disease-modifying pharmacotherapy.

At the same time, the therapeutic landscape of MASH continues to evolve rapidly. Several investigational agents, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), fibroblast growth factor 21 (FGF21) analogues, and pan-peroxisome proliferator-activated receptor (PPAR) agonists, are currently undergoing advanced clinical evaluation and may further reshape treatment paradigms in the coming years [12,13]. Understanding the relative advantages, limitations, and potential positioning of resmetirom within this expanding therapeutic framework is therefore of considerable.

2 Metabolic Dysfunction-Associated Steatohepatitis

MASH (Metabolic dysfunction-Associated Steatohepatitis) is simply the updated medical term for what was formerly called NASH (Non-Alcoholic Steatohepatitis). The global prevalence of metabolic-associated fatty liver disease (MAFLD) is rising due to urbanization, obesity, poor diet, sedentary lifestyles, and genetic factors [14]. Steatosis, an early stage of MASH progression, is linked to metabolic syndrome factors like obesity and type 2 diabetes [15]. Mechanisms such as increased lipolysis and hepatic lipogenesis contribute to liver lipid accumulation, exacerbated by insulin resistance. Natural compounds show promise in regulating lipid metabolism and inflammation. Liver fibrosis predicts MASH and hepatocellular carcinoma development, emphasizing its

importance in treatment strategies. Risk factors for MASH-associated hepatocellular carcinoma include advanced liver fibrosis, older age, male gender, metabolic syndrome, genetics, and dietary habits, highlighting the need for effective surveillance and diagnostics [16]. Further studies are needed to understand the biochemical impact of these risk factors for targeted therapies to prevent hepatocellular carcinoma or reduce hepatocellular carcinoma risk.

3 Pathogenesis of MASH

The pathogenesis of MASH is complex and multifactorial, involving metabolic, genetic, environmental, and immunological factors that interact through a series of interconnected mechanisms. The currently accepted concept is the ”multiple-hit” hypothesis, which proposes that several parallel insults contribute simultaneously to disease initiation and progression. Insulin resistance represents a central pathogenic event in MASH development. In conditions such as obesity, type 2 diabetes mellitus, and metabolic syndrome, insulin resistance promotes increased lipolysis in adipose tissue, resulting in excessive release of free fatty acids (FFAs) into the circulation [17, 18]. The liver takes up these FFAs and, together with enhanced de novo lipogenesis and dietary lipid intake, accumulates triglycerides within hepatocytes, leading to hepatic steatosis. Although triglyceride storage initially serves as a protective mechanism, persistent lipid overload results in the accumulation of toxic lipid intermediates, including diacylglycerols, ceramides, and free cholesterol, which induce lipotoxicity [19].

Lipotoxicity triggers multiple cellular stress responses that contribute to hepatocyte dysfunction and injury. Excessive fatty acid oxidation generates reactive oxygen species (ROS), leading to oxidative stress, mitochondrial damage, lipid peroxidation, and DNA injury [20]. Simultaneously, endoplasmic reticulum (ER) stress develops due to the accumulation of misfolded proteins and altered lipid metabolism, activating the unfolded protein response. Persistent oxidative and ER stress promote hepatocyte apoptosis, necroptosis, and pyroptosis, resulting in the release of damage-associated molecular patterns (DAMPs) that further amplify hepatic inflammation [21, 22].

The innate immune system plays a crucial role in MASH progression. Hepatocyte injury activates resident hepatic macrophages (Kupffer cells), which secrete pro-inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β) [23]. These mediators recruit circulating monocytes, neutrophils, and lymphocytes into the liver, creating a chronic inflammatory microenvironment. Activation of pattern recognition receptors, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), further enhances inflammatory signaling through pathways involving nuclear factor-kappa B (NF-κB) and inflammasome activation [24].

Gut-liver axis dysfunction also contributes significantly to MASH pathogenesis. Alterations in gut microbiota composition (dysbiosis) increase intestinal permeability, allowing bacterial endotoxins, particularly lipopolysaccharides (LPS), to enter the portal circulation. These microbial products activate hepatic immune cells and stimulate inflammatory cascades, thereby exacerbating liver injury and fibrosis. In addition, microbial metabolites influence bile acid metabolism, glucose homeostasis, and lipid handling, further contributing to disease progression [25, 26].

Fibrosis, the principal determinant of liver-related outcomes, develops through activation of hepatic stellate cells (HSCs). Persistent inflammation, oxidative stress, and cytokine signaling stimulate the transformation of quiescent HSCs into activated myofibroblast-like cells [27]. Activated HSCs produce excessive extracellular matrix components, including collagen types I and III, resulting in progressive scar formation. Continued fibrogenesis eventually disrupts normal hepatic architecture, leading to advanced fibrosis, cirrhosis, portal hypertension, and liver failure. The schematic representation of MASLD progression to cirrhosis in Figure 1.

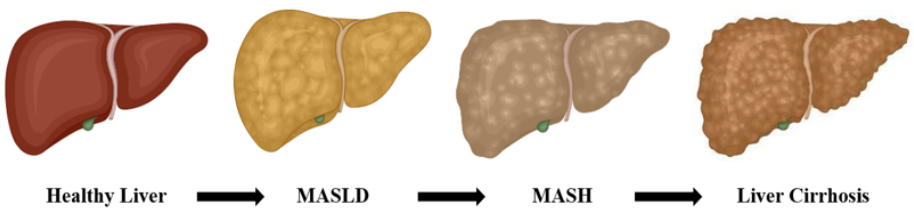

Figure 1 Schematic Representation of MASLD Progression to Cirrhosis

Genetic and epigenetic factors modulate susceptibility to MASH and influence disease severity.

Variants in genes such as PNPLA3, TM6SF2, MBOAT7, and GCKR have been associated with increased hepatic fat accumulation, inflammation, and fibrosis [28]. Furthermore, epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, regulate pathways involved in lipid metabolism, inflammation, and fibrogenesis [29].

Collectively, MASH arises from a complex interplay among metabolic dysfunction, lipotoxicity, oxidative stress, mitochondrial and ER dysfunction, immune activation, gut microbiota alterations, and fibrogenic signaling pathways [30]. These mechanisms drive the progression from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and ultimately hepatocellular carcinoma, highlighting multiple potential therapeutic targets for disease management [31].

4 Treatment

Management primarily emphasizes lifestyle changes, including dietary adjustments and increased physical activity, which are fundamental to MASH treatment. A weight reduction of 5%–10% has been demonstrated to significantly decrease hepatic steatosis and enhance fibrosis markers, rendering it an essential aspect of therapy [31]. Nevertheless, maintaining weight loss poses challenges, and for patients for whom lifestyle modifications prove inadequate, pharmacological treatments and bariatric surgery are options to consider [32, 33].

The significance of pharmacological interventions has risen, particularly following the FDA's approval of resmetirom, a thyroid hormone receptor-beta (THR-β) agonist, as the first treatment specifically targeting MASH [34]. In addition to resmetirom, other promising classes of medications are under investigation, such as GLP-1 receptor agonists (GLP-1RAs), peroxisome proliferator-activated receptor (PPAR) agonists, fibroblast growth factor (FGF) analogues, and sodium-glucose cotransporter-2 (SGLT2) inhibitors, all of which address various pathophysiological mechanisms associated with MASH [35].

4.1 Mechanism of Action of Resmetirom

Resmetirom is a novel, orally administered, small-molecule selective thyroid hormone receptor-β (THR- β) partial agonist. Resmetirom is classified as a small-molecule pharmacologic agent. The reduced affinity for THR- β, which is expressed in the heart and bone, decreases the risk of cardiovascular and skeletal side effects [36]. This targeted selectivity allows resmetirom to deliver therapeutic effects primarily within hepatic tissues, significantly reducing the systemic side effects associated with non-selective thyromimetics. The chemical structure and mechanism of action of resmetirom are illustrated in Figure 2 [37, 38].

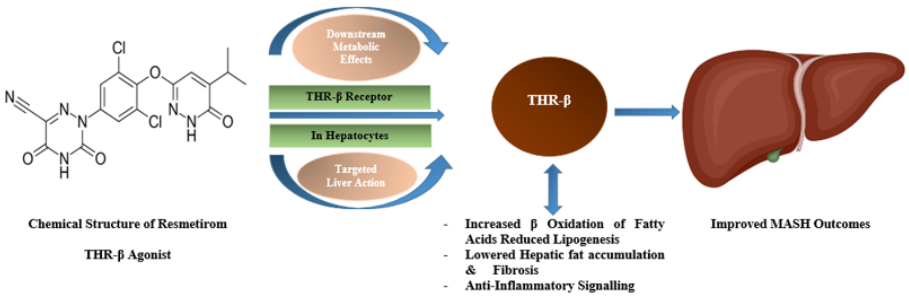

Figure 2 Chemical Structure and Mechanism of Action of Resmetirom (THR-β agonist)

4.1.1 Molecular Targets

The primary mechanism by which resmetirom operates is through its selective agonism of the THR-β. Thyroid hormone receptors are classified as nuclear receptors that oversee the transcription of numerous genes essential for metabolic functions. THR-β is mainly found in the liver, where it governs vital metabolic activities such as cholesterol homeostasis, triglyceride metabolism, and the regulation of hepatic lipogenesis [39]. By selectively binding to THR-β, resmetirom emulates the effects of natural thyroid hormones in the liver while avoiding the activation of THR-α, thus reducing off-target effects in the heart and other peripheral tissues [40]. This selectivity is vital, as the activation of THR-α can result in adverse side effects, including tachycardia, bone loss, and muscle catabolism [41]. The pronounced selectivity of resmetirom for THR-β is accomplished through structural modifications that improve its binding affinity to the receptor [42]. Research suggests that the compound induces a conformational alteration in THR-β upon binding, which aids in the recruitment of specific coactivators and boosts the

transcription of target genes that promote lipid metabolism and diminish hepatic steatosis. This activation of the receptor results in increased fatty acid oxidation, reduced de novo lipogenesis, and improved cholesterol clearance by the liver. The synergy of these effects is believed to decrease lipid accumulation in hepatocytes, thereby mitigating the primary pathological characteristics of NASH [43, 44].

4.1.2 Biochemical Pathways

At the biochemical level, the activation of THR-β by resmetirom results in the modulation of several essential metabolic pathways. Upon binding to THR-β, the receptor-ligand complex moves to the nucleus, where it attaches to thyroid hormone response elements (TREs) located in the promoter regions of target genes [45, 46]. This interaction triggers the transcription of genes that facilitate lipolysis, enhance mitochondrial β-oxidation, and encourage energy expenditure. Specifically, the activation of THR-β by resmetirom increases the expression of genes associated with fatty acid oxidation, including carnitine palmitoyltransferase 1 (CPT1) and acyl-coenzyme A oxidase. Simultaneously, there is a downregulation of lipogenic genes such as sterol regulatory element-binding protein 1c (SREBP-1c), which is crucial for the synthesis of fatty acids and triglycerides [47]. The overall effect is a transition in hepatic metabolism from a storage phenotype to one that prioritizes the use of fats as an energy source, leading to a reduction in liver fat content, enhancement of liver enzyme profiles, and the potential reversal of fibrosis progression [48].

At the molecular level, the interaction of resmetirom with the THR-β receptor also affects secondary signalling pathways. For instance, there is evidence indicating that the activation of thyroid hormone receptors can intersect with pathways that regulate carbohydrate metabolism and inflammatory responses, ultimately leading to improvements in insulin sensitivity and a decrease in hepatic inflammation [49]. Notably, the effects of resmetirom extend beyond lipid metabolism; it also has an anti-inflammatory impact by lowering the expression of cytokines and inflammatory mediators that contribute to liver damage and fibrosis. This dual effect on metabolic and inflammatory pathways is crucial for its effectiveness in treating metabolic liver diseases such as NASH [50].

4.2 Pharmacodynamics of Resmetirom

Resmetirom is a selective, orally active THR-β agonist that primarily targets hepatic THR-β while reducing the activation of THR-α receptors found in the heart, bone, and thyroid gland. In contrast to previous thyromimetics like Eprotirome and MB07811, resmetirom shows no measurable THR-α activity, which enhances its safety profile [51]. Clinical trials have shown no notable effects on heart rate, blood pressure, electrocardiographic parameters, or other vital signs, even at doses reaching 200 mg [52].

The main pharmacological effect of resmetirom is the activation of THR-β-mediated gene transcription in hepatocytes, leading to improved lipid metabolism. Activation of THR-β facilitates cholesterol breakdown, boosts fatty acid oxidation, and inhibits de novo lipogenesis, thus decreasing hepatic lipid accumulation. Additionally, resmetirom enhances hepatic iodothyronine deiodinase-1 (DIO1) activity, promoting the conversion of thyroxine (T4) into the biologically active triiodothyronine (T3) and reverse T3 [39, 53].

Treatment with resmetirom is linked to a decrease in circulating free T4 levels, especially at higher doses (100–200 mg), which aligns with THR-β activation. However, levels of free T3 and thyroid-stimulating hormone (TSH) remain relatively stable, indicating minimal impact on the hypothalamic–pituitary–thyroid axis [54]. Similar results were observed in the phase III MAESTRO-NASH trial, where reductions in free T4 were noted without any clinically significant thyroid dysfunction.

Moreover, resmetirom enhances the expression of sex hormone-binding globulin (SHBG), a hepatic protein regulated by THR-β. After 52 weeks, SHBG levels significantly increased compared to placebo and were correlated with histological improvements in MASH, indicating its potential as a biomarker for therapeutic response [55]. Minimal alterations were noted in circulating testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), with no clinically significant adverse effects observed.

4.3 Pharmacokinetics of Resmetirom

4.3.1 Absorption

Resmetirom is administered orally and is rapidly absorbed following dosing. Its solubility is pH-dependent, exhibiting poor solubility under acidic conditions and improved solubility at

neutral to basic pH levels. Solubility studies conducted at 37°C in aqueous buffers across a pH range of approximately 1–8, as well as in unbuffered distilled water, demonstrated enhanced solubility with increasing pH [56, 57]. Following multiple oral doses of 80 or 100 mg once daily, the median time to reach maximum plasma concentration (T_{max}) is approximately 4 hours. Food does not have a clinically significant effect on overall absorption; however, it decreases C_{max} by about 33%, reduces AUC by 11%, and delays T_{max} by approximately 2 hours compared with administration in the fasted state. Steady-state concentrations are achieved within 3–6 days of once-daily dosing. At steady state, systemic exposure increases proportionally with doses ranging from 40 to 100 mg and more than proportionally with doses between 100 and 200 mg [58].

4.3.2 Distribution

The apparent volume of distribution at steady state (Vdss) is around 68 L. Resmetirom shows extensive binding to plasma proteins, with over 99% bound. Exposure levels are generally similar in patients with MASH and those with stage F2 or F3 fibrosis [59]. An increase in body weight correlates with a higher apparent volume of distribution and clearance, leading to reduced systemic exposure at equivalent doses.

4.3.3 Metabolism

Resmetirom is mainly metabolized by cytochrome P450 2C8 (CYP2C8). The main metabolite, MGL-3623, has approximately 28 times lower THR-β potency compared to the parent compound. At steady state, MGL-3623 represents about 33 to 51% of the parent drug's AUC following the oral administration of 100 mg once daily [60].

4.3.4 Excretion/ Elimination

The median terminal elimination half-life (t½) is roughly 4.5 hours. The steady-state apparent clearance is 17.5 L/h. Resmetirom is primarily eliminated as metabolites through both fecal and urinary pathways. After the administration of a radiolabelled dose: 67% of the administered dose is recovered in feces. 24% is recovered in urine [59, 61].

4.4 Safety Considerations

The most frequently reported adverse events linked to resmetirom were mild to moderate gastrointestinal issues, including diarrhoea and nausea, which generally arise after the initiation of the drug and subside by week 12. Notably, there was no indication of drug-induced liver damage or cartilage toxicity, unlike other THR-β-agonists (such as eprotirome), for which further development was halted due to safety concerns [62]. Pruritus was observed slightly more often in both treatment groups compared to the placebo [63].

Among over 1300 patients who were administered resmetirom at doses of 80 or 100 mg/day for a duration of up to one year, two instances of liver injury were deemed possibly related to the medication. The toxicity observed was primarily hepatocellular, with ALT levels recorded at 236 and 578 U/L, alongside low levels of alkaline phosphatase and bilirubin [64]. Liver injury manifested within three months of starting treatment and completely resolved within two months following discontinuation. An additional case of severe hepatotoxicity was documented, which, upon subsequent liver biopsy, was identified as interface hepatitis consistent with autoimmune hepatitis [65]. In one patient, the reintroduction of resmetirom resulted in a recurrence of liver injury, leading to the permanent discontinuation of the drug. In line with these observations, the AASLD recommends routine monitoring of liver enzymes during treatment to identify rare instances of hepatotoxicity and advises stopping the treatment if significant liver injury is detected [66].

Resmetirom is mainly metabolized by the cytochrome P450 enzyme CYP2C8, which may lead to interactions with drugs that inhibit CYP2C8, such as clopidogrel and gemfibrozil, or with substrates like pioglitazone [67]. These interactions carry significant clinical implications. When co-administered with clopidogrel, a moderate CYP2C8 inhibitor, it is necessary to adjust the dose of resmetirom [68]. Conversely, the concurrent use of gemfibrozil, a strong CYP2C8 inhibitor, is not advisable [69]. Pioglitazone, being a CYP2C8 substrate, may exhibit elevated plasma concentrations when taken alongside resmetirom; however, no dose adjustment is required, although clinical monitoring is recommended [34, 39]. Additionally, resmetirom is a substrate for the OATP1B1, OATP1B3, and BCRP transporters, which may interact with inhibitors such as cyclosporine. Similar considerations are relevant for statin use, as resmetirom can elevate plasma levels of various statins [70]. Consequently, lipid profiles should be monitored to ensure effective cardiovascular risk reduction. According to the manufacturer's recommendations, the maximum daily dosages are set at 20 mg for rosuvastatin and simvastatin, and 40 mg for atorvastatin and

pravastatin [71].

In terms of treatment discontinuation, clinical trial data reveal low dropout rates. In the MAESTRO-NAFLD trial, the discontinuation rates were 1.5% and 1.2% for the 100 mg and 80 mg doses, respectively, compared to 0.9% for the placebo group after one year of treatment. The MAESTRO-NASH trial showed slightly higher discontinuation rates of 6.8% and 2.2% for the 100 mg and 80 mg groups, respectively, against 2.2% in the placebo group. Preliminary data from the MAESTRO-NASH OUTCOMES trial presented at the EASL indicated a dropout rate of approximately 8% during the interim analysis [34, 72].

4.5 Regulatory Approval

Resmetirom, marketed under the brand name Rezdiffra, has received regulatory approval in multiple major regions to treat adults with metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH) [73, 74]. Figure 3 summarizes the path towards conditional approval of resmetirom.

United States: Approved by the U.S. Food and Drug Administration (FDA) in March 2024 via the accelerated approval pathway. It is the first and only FDA-approved medication specifically for MASH [75].

Europe: Granted conditional marketing authorization by the European Medicines Agency (EMA) and the European Commission (EC) in August 2025 [76].

United Kingdom: Authorized by the Medicines and Healthcare products Regulatory Agency (MHRA) in June 2026 [77].

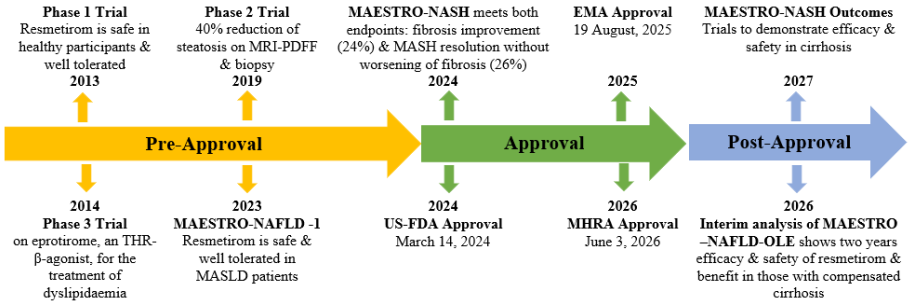

Figure 3 Yearwise timeline towards approval of resmetirom and anticipated trials. The anticipated future trials of which the preliminary results of the MEASTRO-NAFLD-OLE trial as presented during the EASL and AASLD 2025 already have been incorporated [34, 75–77].

4.6 Clinical Trials

Clinical research regarding resmetirom has progressed to phase 3. In trials involving healthy volunteers, resmetirom exhibited an excellent safety profile and led to a reduction in circulating lipids (LDL-C and triglycerides) following 2 weeks of daily oral administration at doses of 50 mg or more (NCT01519531). A meta-analysis encompassing various resmetirom studies indicated that it significantly lowered levels of LDL, triglycerides, non-HDL, ApoB, apolipoprotein CIII (ApoCIII), and lipoprotein(a) [62, 78]. Additionally, it was found to elevate adiponectin levels, although it did not affect HDL levels. The rise in adiponectin implies that resmetirom may confer further therapeutic advantages by mitigating hepatic steatosis and enhancing insulin sensitivity, potentially offering protection against liver fibrosis and cardiovascular diseases [79].

4.6.1 Phase-2 Clinical Trials

A 36-week, randomized, double-blind, placebo-controlled Phase 2 trial (MGL-3196-05; NCT02912260) evaluated the efficacy and safety of resmetirom in 125 overweight or obese adults (BMI $\geq$ 25 kg/m^2) with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH), fibrosis stages F1–F3, a NAFLD Activity Score (NAS) $\geq$ 4, and MRI-proton density fat fraction (MRI-PDFF) $>$ 10% at baseline. Participants were randomized in a 2:1 ratio to receive resmetirom 80 mg once daily or placebo [66, 80].

Key exclusion criteria included significant alcohol consumption, use of MASLD-associated medications, hypothyroidism, HbA1c $>$ 9.5%, treatment with GLP-1 receptor agonists, other chronic liver diseases, cirrhosis, liver decompensation, or serum transaminase levels exceeding

five times the upper limit of normal [81].

MRI-PDFF assessments were conducted at baseline, weeks 12 and 36, while repeat liver biopsies were performed at week 36. The primary endpoint was the change in liver fat fraction (LFF) at week 12 [82]. Secondary endpoints included absolute and relative reductions in LFF, the proportion of patients achieving >30% LFF reduction, histological improvement in NAS, MASH resolution without fibrosis progression, and changes in fibrosis stage.

To optimize drug exposure, pharmacokinetic-guided dose adjustments were implemented. Based on week 2 exposure estimates, doses were modified at week 4. By week 12, 56% of treated participants achieved high drug exposure (AUC $\geq$ 2700 ng·h/mL) [83, 84].

Resmetirom significantly reduced hepatic fat content compared with placebo. In patients with evaluable MRI-PDFF data, mean LFF decreased by 32.9% versus 10.4% at week 12 and by 37.3% versus 8.9% at week 36 (both p<0.0001) [85]. Greater reductions in liver fat were observed among participants with higher drug exposure. Histological analyses demonstrated improvements in NAS and MASH resolution, particularly among patients achieving $\geq$ 30% reduction in MRI-PDFF [86].

4.6.2 Phase-3 Clinical Trials

A phase 3 clinical trial (MAESTRO-NAFLD-1) assessed the safety of resmetirom in patients with MASLD who were suspected of exhibiting MASH features [87]. The results indicated that resmetirom exhibited a favorable safety and tolerability profile within this demographic. The trial successfully achieved its primary endpoint. Throughout the 52-week treatment duration, the occurrence of treatment-emergent adverse events (TEAEs) was comparable between the resmetirom and placebo groups (86.1%–88.4% versus 81.8%), with the majority of TEAEs classified as mild to moderate in severity [88]. The most frequently reported adverse events included mild to moderate diarrhea (23.5%–31.2% versus 13.8%) and nausea (11.9%–18.2% versus 7.9%). These adverse events were predominantly observed during the initial 12 weeks of treatment and were generally transient in nature. Overall, these results suggest that resmetirom maintained a favorable safety and tolerability profile throughout the 52-week treatment period [89]. Additionally, the study verified that resmetirom effectively reduces circulating atherogenic lipid levels in these patients. After 52 weeks of treatment, LDL-C levels were reduced by 11.1% and 12.6% in the 80 mg and 100 mg resmetirom dose groups, respectively, while triglycerides decreased by 15.4% and 20.4%, respectively. Resmetirom also elevated the ratio of free triiodothyronine (FT3), the active form of thyroid hormone, to rT3, its inactive counterpart. This alteration signifies a successful reversal of local hepatic thyroid hormone dysfunction, indicating a restoration of normal thyroid hormone action within the liver [90, 91].

After 52 weeks of treatment with resmetirom, various liver injury biomarkers, including TIMP-1, CK-18, adiponectin, and elements of the enhanced liver fibrosis (ELF) score, demonstrated significant improvement when compared to the placebo group (NCT04197479). A subsequent phase 3 controlled clinical trial revealed that both the 80 mg and 100 mg doses of resmetirom led to enhancements in liver fibrosis among patients with MASH and stages F1B-F3 [92]. Additionally, these doses resulted in a notable decrease in liver fat content (LFC), as well as reductions in serum liver enzyme levels and non-invasive fibrosis markers. The study also noted a decline in circulating LDL-C levels (NCT03900429).

Overall, resmetirom was generally well tolerated, with frequent adverse reactions including mild gastrointestinal issues such as diarrhoea and nausea. The occurrence of serious adverse events was similar across the groups. Resmetirom did not significantly affect thyroid axis hormones, cardiac parameters (such as heart rate), or bone density, thereby confirming its favorable liver selectivity [93]. Additionally, treatment with resmetirom enhanced the quality of life for patients with MASH (NCT02912260, NCT03900429) [94]. An assessment of three clinical trials regarding the efficacy and safety of resmetirom was performed. This assessment revealed that, in addition to reducing hepatic lipids, demonstrating antifibrotic effects, and improving liver enzyme levels, the main side effects linked to resmetirom were diarrhoea and nausea, with most being mild to moderate in severity. Future clinical trials or practical applications should take into account the heightened risk of diarrhoea and nausea associated with resmetirom in patients. The long-term safety and efficacy profile is yet to be fully clarified in upcoming studies.

Furthermore, the phase 3 clinical trials, MAESTRO-NAFLD-OLE and MAESTRO-NASH-OUTCOMES, are currently in progress. MAESTRO-NAFLD-OLE is a supplementary 52-week extension trial that follows the completion of the 52-week MAESTRO-NAFLD-1 study (NCT04197479). This trial includes non-cirrhotic patients and those with well-compensated cirrhosis suffering from NASH, drawn from the open-label cohort of MAESTRO-NAFLD-1 [95].

The objective of this trial is to gather up to 2 years of safety data to support the regulatory submission of resmetirom. MAESTRO-NASH-OUTCOMES aims to assess composite clinical outcomes by evaluating resmetirom's ability to postpone hepatic decompensation events (such as ascites, hepatic encephalopathy, and variceal hemorrhage); an increase in the model for end-stage liver disease (MELD) score from <12 to $\geq$ 15; other signs of liver failure, including liver transplantation; and overall mortality [96]. These two ongoing trials will yield substantial evidence for the comprehensive approval and clinical utilization of resmetirom by addressing the two essential aspects of long-term safety and significant clinical endpoints. The findings will bolster its potential for safe long-term application and for effectively delaying disease progression while enhancing patient survival.

4.7 Contraindications

The prescribing information for resmetirom indicates that there are no contraindications associated with its use [97]. However, while not explicitly mentioned in the product labelling, hypersensitivity to resmetirom or any of its inactive components may serve as a potential contraindication (i.e., colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose; tablet film coating: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, red iron oxide [100 mg tablets], yellow iron oxide [80 mg and 100 mg tablets]) [59].

4.8 Adverse Reactions

The most frequently reported adverse reactions associated with resmetirom in clinical trials included diarrhoea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness; the incidence rates compared to placebo are detailed in Table 1. Adverse reactions that were more prevalent with resmetirom than with placebo, yet affected fewer than 5% of patients, encompassed decreased appetite, flatulence, abnormal feces, dysgeusia, vertigo, arrhythmia, palpitations, depression, erythema, hypoglycemia, tendinopathy, and abnormal uterine bleeding [98, 99]. Both diarrhoea and nausea generally manifested early after the initiation of treatment and were classified as mild to moderate in severity. In the MAESTRO-NASH study, diarrhoea was reported in 27% of patients receiving resmetirom 80 mg, 33.4% of those receiving resmetirom 100 mg, and 15.6% of the placebo group [100]. Diarrhoea and nausea were identified as the primary reasons for treatment discontinuation.

Table 1 Exposure-Adjusted Rates of Frequently Reported Adverse Reactions in Adults with Noncirrhotic Metabolic Dysfunction–Associated Steatohepatitis: Findings from the MAESTRO-NASH Trial [101]

Adverse Reaction	Resmetirom 80 mg Once Daily (n = 298)* (%)	Resmetirom 100 mg Once Daily (n = 296)* (%)	Placebo (n = 294)* (%)
Diarrhoea	23	33	14
Nausea	18	15	9
Pruritus	6	10	4
Vomiting	7	8	4
Constipation	5	8	4
Abdominal pain	5	7	4
Dizziness	4	4	1

Note: * Population includes adult patients with noncirrhotic MASH with liver fibrosis (stages F2 and F3 at eligibility). Median exposure duration was 74 weeks for resmetirom 80 mg once daily, 66 weeks for resmetirom 100 mg once daily, and 68 weeks for placebo. Exposure-adjusted incidence rates are per 100 person-years where total person-years were 435, 407, and 435 for resmetirom 80 mg once daily, resmetirom 100 mg once daily, and placebo arms, respectively. Exposure-adjusted incidence rate per 100 person-years can be interpreted as an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for 1 year.

5 Future Perspectives of Resmetirom in MASH Management

The endorsement of resmetirom has ushered in a new phase in the management of metabolic dysfunction-associated steatohepatitis (MASH), marking the first liver-targeted therapy to exhibit substantial improvements in hepatic steatosis and fibrosis [102]. Given that MASH is intricately associated with obesity, type 2 diabetes mellitus, dyslipidaemia, and cardiovascular diseases, forthcoming management approaches should address both hepatic and extrahepatic aspects of the condition [103]. In spite of its clinical effectiveness and inclusion in current treatment protocols, various challenges persist concerning the optimal integration of resmetirom into standard clinical practice [104]. Future research should investigate its long-term efficacy, safety, and patient adherence in real-world populations that more accurately represent the diversity and complexity

of patients seen in clinical environments. Special consideration should be given to individuals with obesity, diabetes, thyroid disorders, and varying genetic backgrounds, including variants in PNPLA3 and TM6SF2, which may affect disease progression and response to treatment [105].

Combination therapy is anticipated to become a central element in future MASH treatment strategies. Since resmetirom specifically targets hepatic thyroid hormone receptor-β signalling without causing significant weight loss, its application in conjunction with metabolic therapies such as GLP-1 receptor agonists, SGLT2 inhibitors, and statins may yield synergistic advantages [106]. Initial evidence indicates that resmetirom retains its effectiveness regardless of the baseline use of GLP-1 receptor agonists, which supports the need for further exploration of these combinations [107]. Upcoming clinical trials should also evaluate synergistic methods that involve fibroblast growth factor-21 (FGF21) analogues, pan-peroxisome proliferator-activated receptor (pan-PPAR) agonists, and dual incretin therapies that target both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors [107]. These multimodal approaches may enable personalized treatment by concurrently addressing hepatic damage and systemic metabolic disorders.

Additional research is essential to elucidate the role of resmetirom within the developing treatment frameworks. Comparative studies against semaglutide and other new therapies are necessary to establish optimal patient selection, sequencing, and combination strategies [108]. For patients undergoing treatment with GLP-1 receptor agonists for obesity or diabetes, liver-specific responses should be re-evaluated prior to the introduction of further liver-targeted therapies [109].

Long-term safety monitoring is crucial. Future studies should assess the impact of chronic resmetirom therapy on thyroid hormone balance, the hypothalamic–pituitary–thyroid axis, and individuals with existing thyroid conditions. Moreover, it is necessary to gather evidence to establish the ideal duration of therapy, including whether treatment can be safely halted after achieving improvements in fibrosis or resolution of MASH, as well as the potential risk of disease recurrence post-withdrawal [110, 111]. In addition to clinical factors, the successful incorporation of resmetirom into healthcare systems will necessitate standardized screening and fibrosis assessment protocols, multidisciplinary care approaches, and focused educational initiatives for clinicians [112]. It will be vital to address the discrepancies between clinical trial eligibility and real-world reimbursement standards to ensure fair patient access. Future health-economic research that includes quality-adjusted life years (QALYs), cost effectiveness evaluations, and comprehensive patient-reported outcomes will be critical in informing regulatory, reimbursement, and policy decisions [113].

In summary, the future of resmetirom is rooted in its integration into comprehensive, personalized, and combination-based treatment approaches that combine pharmacological interventions with lifestyle modifications. Ongoing research will clarify its long-term role in mitigating liver-related complications, enhancing cardiometabolic outcomes, and revolutionizing the management of fibrotic MASH.

6 Conclusion

The approval of resmetirom has profoundly altered the treatment landscape for MASLD, representing a significant leap forward in the management of MASH. Current evidence indicates considerable enhancements in liver histology and metabolic parameters; however, ongoing clinical trials will be crucial in assessing whether these advantages lead to long-term decreases in liver-related complications, cardiovascular incidents, and mortality rates.

The evolution of non-invasive diagnostic tools is increasingly influencing treatment choices and improving patient monitoring. While effective pharmacological treatments for individuals with compensated cirrhosis are still scarce, the outlook for MASH therapy is exceptionally bright. New treatment approaches are anticipated to emphasize combination therapies that address multiple pathogenic pathways and improve therapeutic effectiveness.

Moreover, the early detection of treatment responders and non-responders will be vital for optimizing patient outcomes and facilitating personalized, cost-efficient care. Ultimately, managing MASLD will necessitate a holistic approach to metabolic health that combines lifestyle changes with targeted pharmacological treatments. In this regard, resmetirom is not only the first approved therapy for MASH; it also lays the groundwork for a new era of precision medicine. Future research into its cardiovascular advantages, its potential synergy with mechanism-based therapies like GLP-1 receptor agonists, and the advancement of next-generation thyroid hormone receptor-β agonists is expected to broaden therapeutic possibilities and influence the future trajectory of MASH treatment.

Abbreviations

MASH	Metabolically dysfunction-associated steatohepatitis
T2D	Type 2 diabetes
THR-β	Thyroid hormone receptor-β
FDA	Food and Drug Administrations
EMA	European Medicines Agency
GLP-1	Glucagon-Like Peptide-1 Receptor
SGLT-2	Sodium-Glucose Cotransporter 2 Inhibitors
MASLD	Metabolically-dysfunctional-associated steatotic liver disease
LSM	Liver Stiffness Measurement
VCTE	Vibration-controlled Transient Elastography
MRE	Magnetic Resonance Enterography
ALT	Alanine Aminotransferase
NASH	Non-Alcoholic Steatohepatitis
T2DM	Type 2 diabetes mellitus
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
FGF21	Fibroblast growth factor 21
PPAR	pan-peroxisome proliferator-activated receptor
FFAs	Free fatty acids
ROS	Reactive oxygen species
DNA	Deoxyribonucleic Acid (DNA)
ER	Endoplasmic Reticulum
DAMPs	Damage-associated molecular patterns
TNF-α	Tumor necrosis factor-alpha
IL-1β	Interleukin-1β
IL-6	interleukin-6
TGF-β	Transforming growth factor-beta
TLRs	Toll-like receptors
NLRs	NOD-like receptors
NF-κB	Nuclear factor-kappa B
LPS	Lipopolysaccharides
HSCs	Hepatic stellate cells
PNPLA3	Patatin-Like Phospholipase Domain-Containing Protein 3
TM6SF2	Transmembrane 6 Superfamily Member 2
MBOAT7	Membrane-Bound O-Acyltransferase Domain-Containing 7
GCKR	Glucokinase Regulator
RNAs	Ribonucleic Acids
FGF	Fibroblast growth factor
TREs	Thyroid hormone response elements
CPT1	Carnitine palmitoyl transferase 1
SREBP-1c	Sterol regulatory element-binding protein 1c
DIO1	Iodothyronine deiodinase-1
T4	Thyroxine
T3	Triiodothyronine
TSH	Thyroid-stimulating hormone
SHBG	Sex hormone-binding globulin
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
T_{max}	Time to Reach Maximum Plasma Concentration
C_{max}	Maximum plasma concentration
AUC	Area under curve
Vdss	Volume of distribution at steady state
CYP2C8	Cytochrome P450 2C8
AASLD	American Association for the Study of Liver Diseases
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OATP1B3	Organic Anion Transporting Polypeptide 1B3
BCRP	Breast Cancer Resistance Protein
NAFLD	Non-Alcoholic Fatty Liver Disease
EASL	European Association for the Study of the Liver
EC	European Commission
MHRA	Medicines and Healthcare products Regulatory Agency

MRI-PDFF	Magnetic Resonance Imaging–Proton Density Fat Fraction
US-FDA	United States Food and Drug Administration
MEASTRO-NAFLD-OLE	Open-Label Extension
LDL-C	Low-Density Lipoprotein Cholesterol
LDL	Low-Density Lipoprotein
non-HDL	Non-High-Density Lipoprotein Cholesterol
ApoB	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
HDL	High-Density Lipoprotein
BMI	Body Mass Index
NAS	NAFLD Activity Score
MRI-PDFF	MRI-proton density fat fraction
HbA1c	Hemoglobin A1c
LFF	Liver fat fraction
TEAEs	Treatment-emergent adverse events
FT3	Free triiodothyronine
TIMP-1	Tissue Inhibitor of Metalloproteinases-1
CK-18	Cytokeratin-18
ELF	Enhanced liver fibrosis
LFC	Liver fat content
MELD	Model for end-stage liver disease
PNPLA3	Patatin-like Phospholipase Domain-containing Protein 3
TM6SF2	Transmembrane 6 Superfamily Member 2
FGF21	Fibroblast growth factor-21
pan-PPAR	Pan-peroxisome proliferator-activated receptor
GIP	Glucose-dependent insulinotropic polypeptide
QALYs	Quality-adjusted life years

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

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