Invited Leading Article

Thyroid hormone receptor-beta agonists: new MASLD therapies on the horizon

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading chronic liver disease worldwide in the past decade [1]. The spectrum of liver diseases in MASLD ranges from metabolic dysfunction-associated simple steatosis to steatohepatitis (MASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma. The pathophysiology of MASLD involves many diverse pathways, including lipotoxicity, insulin resistance, gut dysbiosis, dietary factors and innate and adaptive immunity, all reflecting critical aspects of the disease process [2, 3]. Liver inflammation and progressive fibrosis, as observed in many patients with MASH, are considered crucial driving forces of disease progression and, therefore, patients with MASH are the key target population for the development of new therapeutic drugs [2, 4]. Identification of patients with MASH has historically been dependent on liver biopsy and analysis of liver histology, although promising biomarker panels have recently been developed [5] that might replace the need for liver biopsy in the diagnosis and monitoring of treatment responses in the near future. MASLD reflects a prototypic multisystem disorder whereby extrahepatic complications, such as cardiovascular events and malignancies, dominate mortality [6]. Although many clinical trials have been performed in people with MASLD/MASH in the past two decades, there is currently no licensed therapy for this highly prevalent metabolic liver disease.

Role of thyroid hormone receptor-beta (THR-β) in MASLD: preclinical concepts

Thyroid hormone activity is well established as a key regulator of metabolism, and hepatic thyroid hormone activity has emerged as a promising target for novel therapies for MASLD. There are two active thyroid hormones, i.e., thyroxine, abbreviated to T4 and tri-iodothyronine, abbreviated to T3. The equilibrium between these key molecules and the formation of two minor inactive thyroid hormone metabolites (i.e., reverse T3 and di-iodothyronine) determines overall thyroid hormone activity. T4 is de-iodinated to T3 in the

liver by a hepatic-specific deiodinase, and it is predominantly T3 activity that is the key thyroid hormone regulator of metabolism. Thus, deiodinases are important for the regulation of intracellular thyroid hormone concentrations [7]. In the liver, type 1 deiodinase is the most abundant deiodinase and is highly regulated by T3 itself via two thyroid hormone response elements in the human gene encoding deiodinase-1. Specifically, deiodinase-1 mRNA expression is highest in hepatocytes followed by hepatic stellate cells [7]. Deiodinase 1 catalyzes the outer and inner ring deiodination of T4, T3, and reverse T3, and, thus, may both activate and inactivate thyroid hormones. Therefore, deiodinase-1 expression and activity are the best indicators of intrahepatic T3 status. Conversely, deiodinase-3 expression is much lower than deiodinase-1 in the liver and most abundantly found in hepatic stellate cells (and only little in hepatocytes). Type 3 deiodinase catalyzes the inner ring deiodination of both T4 and T3 producing reverse T3 and di-iodothyronine, respectively. Deiodinase-3 expression is exclusively found in liver macrophages [7]. The free T3 (FT3) concentration is ~0.33% of total circulating T_3 and most thyroid hormone is strongly bound to plasma proteins (principally thyroxine-binding globulin, thyroxine-binding prealbumin and albumin) with only a tiny amount of the free hormone available to enter and regulate cell activity. There are two known genes for thyroid hormone receptors (i.e., THR-α and THR-β) [8]. Multiple receptor isoforms and related proteins are expressed through alternative splicing of mRNAs. Of these, THR-α_1, THR-β_1, THR-β_2, and THR-β_3 are 'bona fide' THRs in that they bind T_3 and confer transcriptional regulation of target genes[8]. THRα1 is the predominant isoform in the heart, bone and brain, whereas THR-β_1 is the major isoform in the liver (mainly expressed on hepatocytes), kidney and thyroid, and THR-β_2 is found in the retina, cochlea and pituitary gland [9].

It is known that primary hypothyroidism is associated with hypercholesterolemia, decreased hepatic β-oxidation, increased hepatic lipotoxicity and insulin resistance.

Patients with hypothyroidism have a higher rate of MASLD and lower levels of FT4 and FT3, which are associated with increased hepatic triglyceride accumulation [10]. The THR-β pathway seems crucial in regulating liver lipid metabolism as this pathway influences hepatic *de novo* lipogenesis, cholesterol synthesis, fatty acid β-oxidation, as well as circulating low-density lipoprotein (LDL), apolipoprotein B (apoB) and lipoprotein (a) [Lp(a)] levels [11]. Indeed, THR-β-deficient mice show elevated serum levels of free fatty acids (FFA) and triglycerides [12]. In support of the notion that THR-β signalling is essential for influencing liver lipid metabolism, individuals with resistance to thyroid hormone beta (RTHβ), who have mutations in the *THRB* gene, experience loss-of-function of THR-β and have substantial hepatic steatosis, compared with their wild-type first-degree relatives [13].

Preclinical studies and results in humans have, therefore, supported the importance of THR-β in hepatic steatosis and stimulated interest in developing THR-β agonists as potential treatments for MASLD. In euthyroid patients with biopsy-proven MASLD, Bohinc et al. reported strong associations of advanced liver fibrosis with greater hepatic induction of deiodinase 3, higher hepatic and serum reverse T3 accumulation, greater suppression of intra-hepatic FT3 concentrations, and inhibition of T3-responsive hepatic gene expression [14]. These data clearly suggest that advanced MASLD is in a state of intrahepatic hypothyroidism [14]. Stimulation of THR-β using novel THR-β agonists results in significant reductions in serum reverse T3 concentrations, most likely due to the THR-β-mediated stimulation of type 1 deiodinase [15].

VK2809 (formerly known as MB07811) is one such oral THR-β agonist that has been shown to substantially reduce hepatic steatosis, plasma FFA and triglyceride levels, and VK2809 also increases hepatic fatty acid oxidation in rodent MASLD-models [16]. THR-β agonists administered to high-fat-fed male Sprague-Dawley rats dramatically reduced

hepatic triglycerides but caused hyperglycaemia and hyperinsulinaemia, raising some concerns about the unwanted effects of these drugs [17]. Importantly, when using another liver-targeted THR-β agonist (MGL-3196), or resmetirom, in mice with diet-induced obesity, this drug resulted in a significant reduction in liver weight, steatosis, hepatic and plasma cholesterol levels and plasma glucose levels, although resmetirom did not affect body weight [18]. Furthermore, in another preclinical model of MASH, administration of thyroid hormones improved lipotoxicity, hepatic inflammation, oxidative stress and, importantly, also liver fibrosis [19]. Suppression of liver fibrosis would suggest that THR-β agonists can also potentially suppress hepatic inflammation. Indeed, it has been shown that resmetirom efficiently suppressed signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B (NF-kB) signalling pathways in a mouse model of MASH [20].

THR-β can also affect diverse metabolic pathways in patients with MASH who have lower THR-β expression in their livers [21]. A recent study in mice demonstrated that THR-β expression is decreased in those mice fed a choline-deficient diet, and mice lacking THR-β had less liver fibrosis [22]. Importantly, when generating hepatic bulk RNA sequencing data in a large set of patients with histologically defined MASLD, the authors observed that THR-β regulon activity was identified as a critical suppressor of liver disease progression, thus supporting the notion that the THR-β receptor pathway is important in human MASLD [23]. Thus, the effects of THR-β agonists in pre-clinical models and the emerging data in man suggest that THR-β agonists might benefit patients with MASLD [24, 25]. In **Figure 1**, we have illustrated the potential mechanisms by which THR-β agonism via specific drugs, such as resmetirom, might benefit liver disease in MASLD or MASH.

Effects of THR-β agonists in MASLD/MASH: data from randomized placebo-controlled trials

The encouraging preclinical data in animals and the studies in man have subsequently prompted testing the effects of THR-β agonists, principally resmetirom, on liver and cardiometabolic risk factors in randomised placebo-controlled trials in patients with MASLD or MASH. A phase 2b randomized placebo-controlled trial testing the efficacy of VK2809 (administered for 52 weeks) in patients with biopsy-proven MASH is also ongoing (NCT04173065).

In **Table 1,** we have summarized the published and ongoing phase 2 and phase 3 multicenter, randomized, placebo-controlled trials testing the efficacy and safety of resmetirom for the treatment of MASH and liver fibrosis.

In a multicentre, randomized, placebo-controlled, phase 2 trial of overweight or obese adults with biopsy-confirmed MASH (fibrosis stages 1-3) and MRI-proton density fat fraction (MRI-PDFF) ≥10%, Harrison *et al*. [15] reported that treatment with resmetirom (80 mg daily for 36 weeks) resulted in a significantly greater relative reduction of hepatic fat content on MRI-PDFF than placebo both at week 12 (-32.9% resmetirom vs. -10.4% placebo) and week 36 (-37.3% resmetirom vs. -8.5% placebo). Resmetirom also significantly improved serum liver enzymes, non-invasive fibrosis biomarkers (including plasma N-terminal type III collagen propeptide and the enhanced liver fibrosis test), plasma LDL-cholesterol levels and other atherogenic lipoproteins. Resmetirom did not significantly change adiposity measures, insulin resistance, serum thyroid hormone concentrations (FT3, FT4 and TSH), heart rate on electrocardiogram and bone mineral density. Adverse events were mostly mild or moderate, except for a higher incidence of transient mild diarrhea and nausea with resmetirom than placebo [15].

Subsequently, in 2021, the same investigators conducted a 36-week active treatment open-label extension (OLE) trial in a small subset of 31 patients with biopsy-proven MASH, showing that resmetirom treatment resulted in a significant relative reduction of approximately 50% in hepatic fat content on MRI-PDFF at OLE week 36 [26].

The phase 3 MAESTRO clinical program was sponsored/funded by Madrigal Pharmaceuticals and was designed in conjunction with regulatory authorities to support the approval of resmetirom for treating MASH [27]. In particular, the design of the MAESTRO development program includes four ongoing phase 3 randomized clinical trials testing resmetirom for the treatment of MASH and liver fibrosis (MAESTRO-NAFLD-1 [NCT04197479], MAESTRO-NAFLD-OLE [NCT04951219], MAESTRO-NASH [NCT03900429], MAESTRO-NASH-OUTCOMES [NCT05500222])[27]. All participants included in the phase 3 MAESTRO clinical program had at least three metabolic risk factors and were ≥18 years of age.

The MAESTRO-NAFLD-1 is a 52-week randomized, double-blind, placebo-controlled phase 3 trial that examined the safety of resmetirom in ~1200 overweight or obese adults with MASLD/presumed MASH (based on non-invasive testing) [28]. Patients were randomly assigned to either 100 mg resmetirom, 80 mg resmetirom or placebo, or open-label 100 mg resmetirom. As expected, resmetirom treatment significantly reduced reverse T3 levels from baseline by week 52 in both thyroxine-treated and euthyroid patients compared to placebo and improved the FT3/reverse T3 ratio, both indicative of normalization of thyroid hormone function in the liver. No signs or symptoms related to systemic hyperthyroidism or hypothyroidism were noted. Circulating levels of sex hormone binding globulin (SHBG) gradually increased (with a plateau at week 12) reflecting the

degree of THR-β activation in the liver and correlated with resmetirom exposure. Resmetirom was safe and well tolerated and key secondary endpoints demonstrated significant reductions in atherogenic lipid levels (plasma LDL-cholesterol, triglycerides, apolipoprotein B, apolipoprotein C-III and Lp(a)), serum liver enzymes (especially in participants with serum ALT levels ≥30 UI/L at baseline), MRI-PDFF hepatic fat content (at 16 weeks and 52 weeks) and liver stiffness assessed by Fibroscan® or magnetic resonance elastography (over 52 weeks) in the 80-mg and 100-mg resmetirom groups compared to placebo [28]. The resmetirom-induced effects on these key secondary endpoints were essentially comparable between thyroxine-treated and euthyroid participants. A major limitation of this phase 3 trial was the early liver fibrosis stage of participants, which restricted evaluation of the effect of resmetirom treatment on non-invasive fibrosis measures. Another limitation was the impact of COVID-19-related dose interruptions on the evaluation of safety and efficacy in the double-blind arms.

The MAESTRO-NASH is a pivotal serial biopsy phase 3 trial in adults with biopsy-confirmed at-risk MASH. Patients are randomly assigned 1:1:1 to receive either once-daily 80 mg resmetirom, 100 mg resmetirom, or placebo. Liver biopsies are performed at screening, week 52 and month 54. In June 2023, the 52-week results of the MAESTRO-NASH have been presented in abstract form at the EASL Congress in Vienna [29]. This trial continues blinded to 54 months to evaluate the number of composite clinical outcomes (all-cause mortality, liver transplant, liver-related events, histological progression to cirrhosis, and confirmed increase in the model for end-stage liver disease [MELD] score from <12 to ≥15) as well as long-term safety.

At the 2023 EASL Congress, the investigators of the phase 3 MAESTRO-NASH trial reported that resmetirom met both 52-week primary histological endpoints among the 966

adult patients with biopsy-confirmed at-risk MASH enrolled in the trial [29]. At week 52, the histologic resolution of MASH without worsening of fibrosis occurred in 10% of 318 patients in the placebo group compared to 26% of 316 patients in the 80 mg group and 30% of 312 patients in the 100 mg group ($p<0.0001$ for both comparisons vs. placebo). At least one stage fibrosis improvement with no worsening of MASH occurred in 14% of the placebo group, compared with 24% of the 80 mg group and 26% of the 100 mg group ($p<0.0001$ vs. placebo). 14.2%, 16.0% and 4.9% of patients in the 80mg group, 100mg group and placebo group respectively, had both MASH resolution plus ≥1 stage improvement in fibrosis. At week 52, MRI-PDFF hepatic fat content (-42.1% in the 80-mg resmetirom and -51.4% in the 100-mg resmetirom), Fibroscan-liver stiffness, and markers of liver injury were also significantly improved with resmetirom compared to placebo. At week 52, plasma LDL cholesterol concentrations did not change in the placebo group, and was decreased by 14% in the 80-mg resmetirom group and 20% in the 100-mg resmetirom group ($p<0.0001$ vs. placebo). Besides lowering plasma LDL cholesterol significantly more than placebo, either dose of resmetirom also produced significant benefits versus placebo in improving plasma levels of triglycerides, Lp(a), apolipoprotein B, apolipoprotein C-III, and non-high-density lipoprotein cholesterol. The most common adverse events were transient mild-to-moderate diarrhoea and nausea, mostly at treatment initiation [29]. As reported in **Table 1**, two other randomized, double-blind, placebo-controlled trials included in the phase 3 MAESTRO clinical program (i.e., the MAESTRO-NASH [NCT03900429] and MAESTRO-NASH-OUTCOMES [NCT05500222] trials) are still ongoing.

Clinical benefits of THR-β agonists beyond the liver

Based on the randomized controlled trial evidence mentioned above, it is reasonable to hypothesize that the results of the ongoing phase-3 MAESTRO outcomes trials will be key to the drug's accelerated conditional approval for the treatment of MASH and liver fibrosis. That said, however, other classes of drugs such as the incretin receptor agonists have been shown to benefit MASH [4, 30] and these drugs that are licensed for the treatment of type 2 diabetes mellitus (T2DM) and obesity have also been shown to have clinically important benefits beyond the liver [4, 30], decreasing the risk of relevant cardiovascular outcomes [31]. Since there is now convincing evidence that NAFLD/MASLD is a multisystem disease [6], it would be very valuable if resmetirom also produced benefits beyond the liver. For example, if resmetirom also reduces the risk of cardiovascular disease [CVD], T2DM and chronic kidney disease [CKD] [32] [33] that would be a major additional bonus that would markedly improve the uptake of the drug in clinical practice. With that in mind, what can we learn from current evidence as to whether resmetirom will produce benefits beyond the liver in treating MASLD as a multisystem disease? A decade ago, it was shown for the first time that the resolution/improvement of liver steatosis (detected by ultrasound) was independently associated with a reduced risk of developing incident T2DM [34], suggesting that a marked reduction in liver fat can significantly benefit glucose tolerance. Although the effect of resmetirom on the primary outcome of MASH resolution in the MAESTRO-NASH trial was highly significant, it is important to bear in mind that not all treated patients benefitted from resmetirom treatment [29]. MASH resolution with no worsening of fibrosis was achieved in 28% of patients treated with the higher dose of resmetirom (100 mg daily). To date, the effect of resmetirom on incident T2DM is uncertain, but the observed hepatoprotective effects of resmetirom on MASH resolution may not be sufficient to have much of a beneficial effect on the ~2.2-fold increased risk of developing incident T2DM seen in people with NAFLD/MASLD [35]. In

contrast, the positive effects of resmetirom on CVD risk factors (and thereby on risk of CVD events and potentially CKD) seem more promising. After a 52-week treatment with resmetirom (100 mg daily), plasma LDL-C concentration was decreased by 20%, apolipoprotein B100 by 22%, lipoprotein (a) by 38%, triglycerides by 28% and apolipoprotein C-III (an inhibitor of lipoprotein lipase activity that is important for facilitating clearance of atherogenic triglyceride-rich lipoproteins) by 17%. Thus, the positive effects of resmetirom on plasma LDL-cholesterol levels and other atherogenic lipoproteins are very promising and in all ongoing MAESTRO trials, patients are being closely monitored for signs/symptoms consistent with clinically significant CVD events and/or cardiac toxicity.

In conclusion, the first three years of this decade have shown real progress in the treatment of steatotic liver disease in MASLD. THR-β agonism with resmetirom seems safe (see **Table 1**) and is a promising therapeutic strategy for treating MASH and liver fibrosis. Given the evidence that CVD is the leading cause of mortality in MASLD, the beneficial effects of resmetirom on CVD risk factors are also encouraging. We believe that the future for MASLD treatment might be a combination therapy with resmetirom targeting the liver, and other agents added to resmetirom, to attenuate the high cardiovascular risk associated with MASLD. This holistic approach to treating MASLD as a multisystem disease might therefore additionally include the use of statins (to decrease plasma LDL-C concentration), incretin receptor agonists (to lower plasma glucose, facilitate weight loss, improve insulin sensitivity and reduce the risk of CVD outcomes), sodium-glucose cotransporter-2 inhibitors (to lower plasma glucose and protect renal function), and renin-angiotensin-system inhibitors (to lower high blood pressure, reduce CVD outcomes and preserve renal function). Additionally, when not contraindicated, there may be a place in certain patients for treatment with pioglitazone [36] and also possibly fibroblast growth factor (FGF) 21 agonists [37] which have been shown to be effective in the treatment of

NASH. However, for the latter, we consider that uncertainty remains about the robustness and clinical benefit of FGF-21 analogues and future large phase-3 RCTs with long-term follow-up are needed.

Figure Legend

Figure 1. Potential mechanisms by which thyroid hormone receptor-β agonism via specific drugs, such as resmetirom, might benefit liver disease in MASLD/MASH. Epidemiological studies have demonstrated a link between MASLD and primary hypothyroidism. The thyroid can produce both T4 and T3 but most T3 is produced by enzymatic outer ring deiodination of T4 in peripheral tissues. Normally about a third of T4 is converted to T3. In the liver, intrahepatic deiodinases (mainly type 1 deiodinase) convert FT4 to the biologically active FT3 that is also released into the circulation. Type 3 deiodinase 3 converts FT4 to the inactive reverse T3. FT3 is the key thyroid hormone regulator of metabolism. Thyroid hormone receptor-β (THR-β) signaling in liver is impaired in patients with MASLD/MASH. In fact, the lipotoxicity that usually occurs in MASLD/MASH induces intrahepatic hypothyroidism, resulting in reduced conversion of FT4 to biologically active FT3 in favor of increased conversion of FT4 to the inactive metabolite reverse T3. THR-β receptor agonism via specific drugs, such as resmetirom, helps regulate intrahepatic thyroid hormone levels in patients with MASLD/MASH, potentially addressing the underlying pathophysiology related to altered hepatic THR-β signaling in these patients (most likely through the THRβ-mediated stimulation of deiodinase 1). Resmetirom also decreases DNL, hepatic lipotoxicity, inflammation, oxidative stress and fibrosis. This is paralleled by decreased plasma levels of cardiovascular disease risk factors such as total cholesterol, LDL cholesterol, apo B, lipoprotein (a), and triglycerides in both preclinical and clinical trials. Resmetirom also improves hepatic inflammatory pathways, such as NF-*k*B or STAT3.

Abbreviations: apoB, apolipoprotein B; D, deiodinase; DNL, de novo lipogenesis; FT4, free thyroxine; FT3, free tri-iodothyronine; LDL, low-density lipoprotein; Lp(a), lipoprotein a; NF-*k*B, nuclear factor kappa B; reverse T3, reverse tri-iodothyronine; STAT3, signal transducer and activator of transcription 3; THR-β, thyroid hormone receptor β.

Table 1. Phase 2 and phase 3 multicenter randomized clinical trials testing the efficacy and safety of thyroid hormone receptor-β agonist resmetirom for treating MASH and liver fibrosis.

Authors, Year. Ref.	Trial design and ClinicalTrials.gov ID (NCT number)	Patient population and sample size	Treatment arms	Trial duration	Liver-related outcomes	Effects on plasma lipid profile	Effects on body weight, blood pressure, glycated hemoglobin (or other diabetes markers)	Adverse events
Harrison SA et al. 2019 [15]	Phase 2 multicenter, randomized, double-blind, placebo-controlled trial (NCT02912260)	Adults with biopsy-confirmed MASH (fibrosis stages 1-3) and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) ≥10% (mean BMI 35 kg/m^2; type 2 diabetes 39%; hypertension 50%); n=125	Resmertirom 80 mg/day (n=84) or placebo (n=41)	36 weeks	Resmetirom showed a significant mean relative reduction of MRI-PDFF hepatic fat content compared to placebo at week 12 (-32.9% resmetirom vs. -10.4% placebo; p<0.0001) and week 36 (-37.3% resmetirom vs. -8.5% placebo; p<0.0001). Resmetrirom improved serum liver enzymes and non-invasive fibrosis markers (including plasma N-terminal type III collagen propeptide and the enhanced liver fibrosis test)	Resmetirom showed a reduction of plasma LDL cholesterol (-11.2% vs. +6.2%), triglycerides (-15.4% vs. +20.5%), apolipoprotein C-III (-12% vs. +24.5%) and lipoprotein (a) (-22.7% vs. +15.3%) compared to placebo	Resmetirom had no effects vs. placebo	Adverse events were mostly mild or moderate and were balanced between groups, except for a higher incidence of transient mild diarrhea and nausea with resmetirom than placebo. No significant effects on thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) concentrations, bone mineral density, heart rate on ECG or cardiovascular markers were noted. Resmetirom significantly reduced plasma reverse triiodothyronine and increased plasma sex hormone-binding globulin concentrations (as

								a marker of drug exposure)
Harrison SA et al. 2021 [26]	Phase 2 active treatment open-label extension (OLE) study at the completation of the NCT02912260 trial	Adults with biopsy-confirmed MASH (fibrosis stages 1-3) and MRI-PDFF ≥10% with persistently mild to markedly elevated serum liver enzyme levels; n=31	Resmetirom 80 mg or 100 mg/day (n=31 consenting patients, including 14 former placebo patients)	36 weeks	Resmetirom showed a mean relative reduction of MRI-PDFF hepatic fat content of -52.3% at OLE week 36. Serum liver enzymes and non-invasive fibrosis markers were also reduced, including liver stiffness assessed by transient elastography	Plasma LDL cholesterol (-26.1%), apolipoprotein B (-23.8%,), triglycerides (-19.6%) and apolipoprotein C-III were significantly reduced from baseline	Resmetirom had no effects vs. placebo	Resmetirom was well-tolerated with no severe adverse events. No central thyroid axis changes or adverse effects on vital signs were observed
Harrison SA et al. 2023 [28]	Phase 3 multicenter, randomized, double-blind placebo-controlled trial (NCT04197479), MAESTRO-NAFLD-1*	Adults with MASLD/presumed MASH diagnosed with MRI-PDFF ≥8% and VCTE-liver stiffness (mean BMI 35.5 kg/m^2; type 2 diabetes 57%; hypertension 75%; dyslipidemia 88%); n=1143	Resmetirom 100 mg/day (n=325), resmetirom 80 mg/day (n=327) or placebo (n=320) or open-label (OL) resmetirom 100 mg (n=171)	52 weeks	At week 16 resmetirom showed a significant relative reduction of MRI-PDFF-assessed hepatic fat content compared to placebo for open-label (OL) 100 mg, -47.8%; double-blind (DB) 100 mg -45.1%; 80 mg -41.4% and placebo -6.5%; P < 0.0001 vs. placebo for all three comparisons. The significant relative reduction in hepatic fat achieved by week 16 was sustained over 52 weeks with continued resmetirom treatment. At week 52, the least squares mean relative reduction	At 100 mg, significant reductions from baseline relative to placebo were observed in plasma LDL cholesterol (-13.9%), apolipoprotein B (-16.5%) and triglycerides (-23.4%). At 80 mg, significant reductions from baseline relative to placebo were observed in plasma LDL cholesterol (-12.4%), apolipoprotein B (-14.3%) and triglycerides (-18.4%). In the OL 100 mg resmetirom arm, the reductions from baseline in LDL cholesterol (-19.4%),	Resmetirom had no effects vs. placebo	Adverse events in excess of placebo included mild or moderate diarrhea and nausea especially at the initiation of treatment. No significant effects on thyroid stimulating hormone, free triiodothyronine and free thyroxine concentrations (resmetirom significantly reduced plasma reverse triiodothyronine levels), heart rate on ECG or cardiovascular events were noted

					from baseline in hepatic fat was -51.8% in the OL 100 mg resmetirom arm. Serum liver enzymes and non-invasive inflammation/fibrosis biomarkers (including liver stiffness measured by Fibroscan or magnetic resonance elastography) were also improved with resmetirom	apolipoprotein B (-21.3%) and triglycerides (-27.5%) at week 24 were numerically greater than those achieved in the DB resmetirom arms. Effects achieved at week 24 were maintained over 48 weeks with continued treatment. Additional lipid endpoints in DB 100 mg, reductions from baseline relative to placebo at week 24 were observed in lipoprotein (a) (−19.7%), apolipoprotein C-III (−17.6%) and apolipoprotein B (−16.5%)		
Harrison SA et al. 2023 [29]	Phase 3 multicenter, randomized, double-blind placebo-controlled trial (NCT03900429), MAESTRO-NASH*	Adults with biopsy-confirmed MASH (fibrosis stages 1-3) (mean BMI 36 kg/m^2; type 2 diabetes 67%; hypertension 78%; dyslipidemia 71%); n=966	Resmetirom 100 mg/day (n=323), resmetirom 80 mg/day (n=322) or placebo (n=321)	52 weeks to evaluate primary liver biopsy endpoints for the US Food and Drug Administration (FDA) conditional approval. This trial continues blinded to 54 months to assess the number of composite clinical	At week 52, histologic MASH resolved (with no worsening fibrosis) in 10% of those with placebo, 26% with 80 mg of resmetirom, and 30% with 100 mg of resmetirom (P<0.0001 vs. placebo). Proportions with an improvement of 1 or more liver fibrosis stages (with no worsening in NAFLD activity score) were 14% with placebo, 24% with 80 mg of resmetirom	At 52 weeks, plasma LDL cholesterol did not change in the placebo group, while dropping 14% in the 80-mg resmetirom group and 20% in the 100-mg resmetirom group (P<0.0001). Besides lowering LDL cholesterol significantly more than placebo, either dose of resmetirom also outdid the placebo at week 52 in improving	Resmetirom had no effects vs. placebo	Resmetirom appeared generally safe and well tolerated with similar numbers of serious adverse events across groups and an increase in the incidence of diarrhea and nausea in resmetirom treatment groups only at the beginning of treatment. No significant effects on serum thyroid stimulating hormone, free

				outcomes (all-cause mortality, liver transplant, liver-related events, histological progression to cirrhosis, and confirmed increase in model for end-stage liver disease [MELD] score from <12 to ≥15) as well as long-term safety (this part of the trial is still ongoing)	(P=0.0002), and 26% with 100 mg of resmetirom (P<0.0001). Similar results for both endpoints were obtained by both central pathologists, and results were independent of diabetes status or baseline fibrosis stage. At week 52, MRI-PDFF (-42.1% in the 80-mg resmetirom and -51.4% in the 100-mg resmetirom), Fibroscan-liver stiffness, and markers of liver injury were also significantly improved with resmetirom	apolipoprotein B (-17% in the 80-mg resmetirom and -22% in the 100-mg resmetirom), triglycerides (-23% in the 80-mg resmetirom and -28% in the 100-mg resmetirom), lipoprotein (a) (-35% in the 80-mg resmetirom and -38% in the 100-mg resmetirom), apolipoprotein C-III (-10% in the 80-mg resmetirom and -17% in the 100-mg resmetirom), and non-high-density lipoprotein cholesterol (-16% in the 80-mg resmetirom and 22% in the 100-mg resmetirom)		triiodothyronine and free thyroxine concentrations (but resmetirom increased plasma sex hormone binding globulin levels as a marker of drug exposure), heart rate on ECG or adverse cardiovascular events were noted
Ongoing trial	MAESTRO-NAFLD-OLE (NCT04951219) is a phase 3 52-week active treatment extension of MAESTRO NAFLD-1 and includes a 12-week double-blind run-in period in which patients are randomized to 80 or 100 mg resmetirom*	Adults with MASLD/presumed MASH diagnosed with non-invasive markers and imaging; n= ~700	Patients randomized to resmetirom 80 mg/day or 100 mg/day. After week 12, all patients receive 100 mg resmetirom for the duration of the trial	52 weeks	This trial is focused on safety-related endpoints, specifically monitoring for treatment-emergent adverse events. Non-invasive tests (liver biomarkers and imaging) are assessed longitudinally throughout, in addition to validated patient-reported outcomes	NA	NA	NA
Ongoing trial	MAESTRO-NASH-OUTCOMES (NCT05500222) is a phase 3 randomized, double-blind, placebo-controlled	Adults with well-compensated (Child-Pugh A 5-6) MASH-related cirrhosis diagnosed with liver biopsy or imaging or	Patients randomized to resmetirom 80 mg/day or placebo	Event-driven trial; presumed to take 2-3 years	Time to experiencing a composite clinical	NA	NA	NA

	trial*	non-invasive fibrosis markers; n= ~700			outcome (all-cause mortality, liver transplant, and significant hepatic events, including hepatic decompensation events, and confirmed increase in MELD score from <12 to ≥15			

* All patients had ≥ three metabolic risk factors and were ≥18 years of age to be initially included in the phase 3 MAESTRO clinical program. NA, not applicable.

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