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REVIEW

The first MASH drug therapy on the horizon: Current perspectives of resmetirom

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Abstract

The rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) poses a significant global health challenge, affecting over 30% of adults worldwide. MASLD is linked to increased mortality rates and substantial healthcare costs, primarily driven by its progression to metabolic dysfunction-associated steatohepatitis (MASH), which can lead to severe liver complications including cirrhosis and hepatocellular carcinoma. Despite its growing burden, effective pharmacotherapy for MASLD/MASH has been lacking until the recent conditional approval of resmetirom by the FDA. Resmetirom, a liver-targeted thyroid hormone receptor-β selective drug, has shown promise in clinical trials for treating non-cirrhotic MASH with moderate to advanced fibrosis. It has demonstrated efficacy in reducing hepatic fat content, improving liver histology (both MASH resolution and fibrosis improvement), and ameliorating biomarkers of liver damage without significant effects on body weight or

Abbreviations: ACACA, acetyl coenzyme A (CoA)-carboxylase; BMD, bone mineral density; BMI, body mass index; CAP, controlled attenuation parameter; CPT1a, carnitine palmitoyltransferase I; DIO, deiodinase; DNL, de novo lipogenesis; EMA, European Medicines Agency; FDA, food and drug administration; HCC, hepatocellular carcinoma; LDL, low-density lipoprotein; LSM, liver stiffness measurement; Lp(a), lipoprotein (a); MASLD, metabolic dysfunction associated steatotic liver disease; MASH, metabolic dysfunction associated steatohepatitis; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, NAFLD activity score; NITs, non-invasive tests; PRO-C3, N-terminal type III collagen propeptide; SREBPF1, sterol regulatory element binding transcription factor; THR, thyroid hormone receptor; TSH, thyrotropin; T3, triiodothyronine; T4, levothyroxine; VCTE, vibration controlled transient elastography.

glucose metabolism. Notably, resmetirom also exhibits favourable effects on circulating lipids, potentially reducing cardiovascular risk in MASLD/MASH patients. The safety profile of resmetirom appears acceptable, with gastrointestinal adverse events being the most common, though generally mild or moderate. However, long-term surveillance is warranted to monitor for potential risks related to thyroid, gonadal, or bone diseases. Clinical implementation of resmetirom faces challenges in patient selection and monitoring treatment response, and will heavily rely on non-invasive tests for liver fibrosis assessment. Nonetheless, resmetirom represents a landmark breakthrough in MASLD/MASH treatment, paving the way for future therapeutic strategies aiming to mitigate the multifaceted risks associated with this complex metabolic liver disease.

1 | A LANDMARK ACHIEVEMENT

Metabolic dysfunction-associated steatotic liver disease (MASLD), whose hallmark is excess fat in the liver, is increasingly prevalent worldwide. Indeed, MASLD affects more than 30% of the world's adults, and regional prevalence can reach ~40%–45% in South America and the Middle East Region.[1,2] MASLD is associated with increased cardiovascular and liver-related mortality rates while also determining substantial healthcare costs for national health systems.[1,3] Liver-related mortality is the major consequence of the development of metabolic dysfunction-associated steatohepatitis (MASH), the histologic phenotype of MASLD characterized by liver injury (ballooning) and inflammation in addition to steatosis and potential progression to cirrhosis and hepatocellular carcinoma (HCC). In recent years, MASLD/MASH has also become the primary aetiology for liver transplantation due to HCC in many Western countries.[4,5]

The development of effective treatment strategies to avoid the progression to cirrhosis and its sequelae, therefore reducing liver-related morbidity and mortality in patients with MASLD/MASH, has been one of the main topics, and probably one of the main struggles of clinical and experimental research in liver diseases in the last decade.[6] The challenges have been many and include: (1) the need to develop surrogate endpoints given the slow rate of clinical progression of the liver disease; (2) the lack of validated serological/biochemical biomarkers associated with liver disease progression, which have required repeated histological assessment to determine response to treatment; (3) the intrinsic limits and variability of liver pathology assessment, which have been magnified by heterogeneous results observed in the placebo arm of published randomized clinical trials; (4) the low awareness of the general population, which has negatively impacted on enrolment in clinical trials based on repeated histological liver evaluation; and (5) the limited knowledge of disease pathogenesis that initially led to consider pharmacological approaches not tackling the main disease driver, namely hepatic steatosis.[7,8]

For such reasons, until 14 March 2024, no pharmacotherapy had been approved for MASLD/MASH and clinical recommendations focused mainly on weight loss, lifestyle changes, and control of associated metabolic disorders.[9,10]

The recent FDA conditional approval of resmetirom (formerly known as MGL-3196, which will be marketed under the name 'Rezdiffra'), which is an orally administered, liver-targeted thyroid hormone receptor (THR)-β selective drug for the treatment of adults with non-cirrhotic MASH with moderate to advanced fibrosis, should therefore be viewed as a breakthrough for the field and people affected by MASH. The FDA conditional approval of resmetirom was primarily based on results from the phase 3 MAESTRO clinical programme, designed to evaluate a range of

Key points

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent global health concern affecting over 30% of adults worldwide, with significant regional variations.
- The recent FDA conditional approval of resmetirom marks a breakthrough in MASLD treatment, offering promise for non-cirrhotic metabolic dysfunction-associated steatohepatitis patients with moderate to advanced fibrosis.
- Resmetirom, a liver-targeted thyroid hormone receptor-β selective drug, demonstrates efficacy in reducing hepatic fat content, improving liver histology, and ameliorating biomarkers of liver damage and dyslipidaemia.
- Despite its favourable effects, resmetirom's clinical implementation faces challenges in patient selection and monitoring treatment response, and will rely on non-invasive tests for liver fibrosis assessment.
- Resmetirom's safety profile appears acceptable, with gastrointestinal adverse events being the most common, though long-term surveillance is warranted to monitor potential risks related to thyroid, gonadal, or bone diseases.

safety and efficacy endpoints.[11,12] In the MAESTRO-NASH trial, the dual primary endpoints at Week 52 (codefined with FDA and EMA) consisted of MASH resolution – defined as ballooning score 0, lobular inflammation score 0 or 1 and ≥2-point NASH activity score (NAS) reduction – with no worsening of fibrosis, or fibrosis improvement by ≥1 stage with no worsening of MASH. These two histological surrogate endpoints are considered likely to predict clinical benefit as previous analyses have shown that MASH severity (quantified by NAS and fibrosis stage) is strongly correlated with the risk of liver-related mortality and transplant-free survival.[13]

2 | RATIONALE AND PRECLINICAL DATA

Primary hypothyroidism is a well-established risk factor for MASLD/MASH,[14] including in patients with new-onset type 2 diabetes.[15] The existence of a possible causal association between hypothyroidism and MASLD/MASH is in line with results of Mendelian randomization studies.[16] In addition, even in euthyroid individuals advanced liver disease has been associated with increased conversion of free levothyroxine (T4) to the inactive reverse-triiodothyronine (rT3) in the liver, at the expense of deiodinase (DIO)-mediated conversion to free triiodothyronine (T3),[17] and THR-β signalling was reported to be impaired in patients with MASH, resulting in reduced hepatic thyroid hormone signalling.[18]

There has been a long-appreciated link between overt primary hypothyroidism and increased hepatic lipids, with a graded association between elevated serum thyrotropin (TSH) levels (i.e. a measure of the pituitary response to decreased serum thyroid hormones) and markers of hepatocellular injury.[19] In a recent study that utilized liver biopsies in patients with suspected MASH as a histological readout, even individuals with low-normal thyroid function, defined as a TSH level in the upper half of the 'normal' range, showed increased propensity to a MASLD diagnosis and higher liver fibrosis stage.[20] These and other epidemiologic data prompted investigators to perform a phase 2b study of ultra-low dose levothyroxine, at a median near-homeopathic dose of less than 20-μg daily. Remarkably, without changes in circulating free T3 and free T4 levels, levothyroxine treatment was able to reduce liver lipid content in patients with type 2 diabetes and MASLD.[21] On the other hand, in euthyroid individuals with metabolic dysfunction and early-stage MASLD, the upregulation of T3 counteracting hepatic fat accumulation seems to be limited by the consequent feedback mechanism that curtails TSH secretion by the pituitary gland.[22,23]

These data suggest that thyroid hormones have a beneficial impact on hepatic fat accumulation, but all the above studies were partly confounded by known inverse effects of thyroid hormone levels and body weight. Thus, subjects with subclinical or overt primary hypothyroidism had slightly but significantly higher body mass index (BMI) and adiposity than comparators, and even patients treated with ultra-low levothyroxine doses showed modest weight loss. Thus, whether the relationship between thyroid status and hepatic fat accumulation was mediated by body weight and/or adiposity remained unclear, and if not, what would the liver-intrinsic mechanism of action be? The latter prospect was raised by work showing the importance of the deiodinase DIO1, which converts the pro-hormone-free T4 to the active metabolite-free T3, which then binds its cognate nuclear hormone receptors, THR-α or THR-β. Using mice fed a lipid-laden diet, the investigators observed that knockdown of hepatocyte DIO1 was sufficient to increase hepatic fat content.[24] These experimental data nicely paralleled similar data from THR-β loss-of-function knock-in mice, which also showed increased hepatic fat content.[25] Of note, THR-α knock-out mice analysed at the same time showed unchanged hepatic fat content, consistent with greater THR-β > THR-α expression in hepatocytes.[26] Consistent with these mouse observations, linkage studies showed that humans bearing THR-β loss-of-function variants had greater hepatic fat content on ultrasound than relatives with wild-type alleles,[27] interrupting the expected positive relationship between BMI and hepatic fat accumulation.

Mechanistically, hepatocyte-specific DIO1 or THR-β loss-of-function showed reduced mitochondrial lipid oxidation,[24,25] associated with decreased expression of carnitine palmitoyltransferase I (CPT1a), a rate-controlling enzyme regulating mitochondrial fatty acid import.[25] In addition, these authors also noted a parallel increase in expression of acetyl coenzyme A (CoA)-carboxylase (Acaca) and fatty acid synthetase (Fasn),[25] which is consistent with increased hepatic de novo lipogenesis (DNL), the hallmark abnormality in patients with MASLD.[28] These data are also consistent with earlier work showing that free T3, via THR-β, directly increased expression of sterol regulatory element binding transcription factor (Srebf1), the master transcriptional regulator of DNL.[29] In sum, these data indicate that lipid excess in primary hypothyroidism, modelled here by hepatocyte-specific loss of T3 function, is likely pleiotropic, and that THR-β agonists would have potential to reverse these hepatic lipid abnormalities.

Resmetirom was developed to specifically target THR-β, being 28-fold selective for over THR-α, with the aim of treating lipid metabolism disorders. It was safe in rodents and active in preclinical models at doses that showed no impact on the central thyroid axis.[30] In healthy volunteers, resmetirom had an excellent safety profile and decreased circulating lipids at once daily oral doses of 50 mg or higher given for 2 weeks.[31] Resmetirom induced DIO1 and CPT1 in hepatocytes,[32] and in an experimental model of dietary MASH, resmetirom improved disease activity and hepatic fibrogenesis independently of body weight.[33]

A model showing the mechanism of action of resmetirom is presented in Figure 1.

3 | THE CLINICAL IMPACT

The randomized clinical trials already published in extenso and reporting the effect of resmetirom in patients with MASLD/MASH are summarized in Table 1.

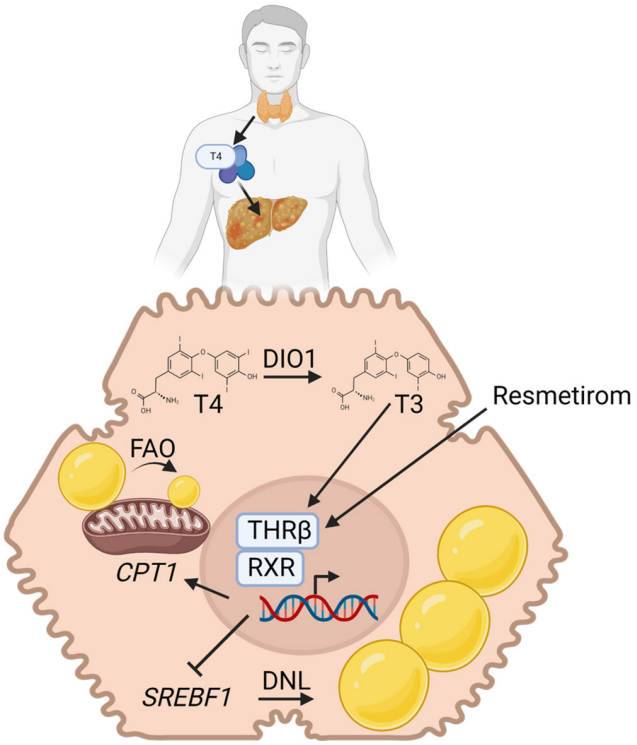

FIGURE 1 Mechanisms of action of thyroid hormones and resmetirom in regulation of hepatocyte lipid metabolism. Thyroxine (T4) released from the thyroid gland is de-iodinated by iodothyronine deiodinase 1 (DIO1) to the metabolically active free triiodothyronine (T3) in the liver. Free T3 binds its nuclear thyroid receptor β (THR-β), which heterodimerizes with Retinoid X receptor (RXR) to alter transcription of *carnitine palmitoyltransferase I (CPT1)* that regulates mitochondrial fatty acid oxidation (FAO) and *Sterol regulatory element binding transcription factor 1* (*SREBF1*), the master regulator of hepatic de novo lipogenesis (DNL). In patients with MASH and advanced fibrosis, intrahepatic thyroid hormone signalling is impaired; consequently, this impairment would decrease conversion of free T4 by DIO1 to free T3 and increase conversion of free T4 by DIO3 to inactive reverse T3 (rT3), leading to further accumulation of lipotoxic species. These data indicate that intrahepatic hypothyroidism may be a driver of MASH pathogenesis. Resmetirom is an oral, liver-directed THR-β-selective agonist (being its uptake into hepatocytes mediated by liver-specific organic anion transporting polypeptides 1B1) that reduces hepatic lipid content and improved liver inflammation and fibrosis by mimicking the action of free T3 mainly through the direct activation of THRβ. Resmetirom also upregulates the expression of DIO1, increasing the hepatic conversion of free T4 to free T3 and reducing rT3 levels.

In a 36-week randomized, double-blind, placebo-controlled phase 2 trial of 125 overweight or obese adults with biopsy-confirmed MASH (fibrosis stages 1–3) and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) >10%, once-daily resmetirom 80-mg was more effective than placebo in achieving the primary outcome of reducing MRI-PDFF assessed hepatic fat content by 22.5%, respectively, at Week 12 and by 28.8% at Week 36 (end of treatment).[34] This was accompanied by significant reductions in serum liver enzymes and blood-based fibrosis biomarkers, including enhanced liver fibrosis (ELF) and N-terminal type III collagen propeptide (PRO-C3). There was also a trend for improvement in histological disease activity, which was more marked in patients at higher drug exposure, as captured by higher resmetirom doses or increase in circulating levels of sex hormone-binding globulin (SHBG), a reliable marker of drug-related THR-β target engagement. These data confirmed a strong positive effect of resmetirom on hepatic fat content, leading to amelioration of biomarkers of liver damage. In the same trial, patients with improvement in steatosis and liver histology also ameliorated health-related quality of life (HRQL).[36] In an open-label extension (OLE) of this trial in 31 patients who had persistently elevated serum liver enzymes (14 previously exposed to placebo), resmetirom treatment resulted in an absolute and relative mean reduction of MRI-PDFF assessed hepatic fat content of −11.1% and −52% at 36 week, which consistently translated into a significant improvement in serum liver enzymes, PRO-C3 and liver stiffness (LSM) assessed by transient elastography.[35] Since the safety profile of resmetirom was acceptable, subsequent phase 3 clinical trials have tested once-daily resmetirom at a dose of both 80 and 100-mg.

The phase 3 MAESTRO-NAFLD-1 trial confirmed the safety profile of resmetirom 80/100-mg doses for 52 weeks in 1143 obese patients with MASLD/presumed MASH who did not meet the histological criteria for enrolment in the MAESTRO-NASH (see below), but confirmed the efficacy of resmetirom on the relative reduction of MRI-PDFF assessed hepatic fat content (−34.9/38.6% at Week 16, and slightly lower −28.8/33.9% at Week 52), which translated also into a significant reduction in LSM assessed by Fibroscan.[37]

In the phase 3 MAESTRO-NASH trial enrolling 966 obese adults with biopsy-confirmed MASH (fibrosis stages 1–3), both the 80-mg and the 100-mg doses were superior to placebo with respect to MASH resolution and improvement in liver fibrosis by at least one stage at Week 52. In the resmetirom 80-mg, 100-mg versus placebo groups, NASH/MASH resolution with no worsening of fibrosis was observed in 25.9%, 29.9% versus 9.7% (difference between resmetirom 80-mg or 100 mg-mg vs. placebo: 16.4% and 20.7%), whereas liver fibrosis improvement by at least one stage with no worsening of MASH was observed in 24.2%, 25.9% versus 14.2% of patients (difference 10.2% and 11.8%), thereby meeting the requirements of governmental agencies for efficacy.[11] Both co-primary histological endpoints were also achieved in significantly more patients who received resmetirom than in those receiving placebo (14.2% in the 80-mg group and 16.0% in the 100-mg group vs. 4.9% in the placebo group). It is worth noting that many other histological outcomes were consistently and robustly met by both doses of resmetirom compared to placebo, as well as a significant decrease in MRI-PDFF assessed hepatic fat content (up to −46.6% with the 100-mg dose at Week 52), a reduction in serum liver enzyme levels, Fibroscan-measured LSM values, ELF and other non-invasive blood-based fibrosis biomarkers, including tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) and aminoterminal propeptide of procollagen type III (P3NP) levels.[11] Results were consistent across

TABLE 1 Published randomized clinical trials evaluating resmetirom for the treatment of non-cirrhotic MASLD/MASH.

Reference, NCT	Patients	Duration	Design and phase	Outcomes
Harrison et al.[34] NCT02912260 MGL-3196-05	125 patients with biopsy-confirmed NASH, metabolic syndrome and MRI-PDFF ≥10% hepatic fat, randomized 2:1 to resmetirom 80-mg ($n=78$) or placebo ($n=38$)	36 weeks	Phase 2, randomized, double-blind, placebo-controlled trial	Primary: relative reduction in MRI-PDFF assessed hepatic fat content at Week 12: −22.5% for resmetirom vs. placebo, −28.8% at Week 36; Secondary: histological improvement in those with higher drug exposure; −22.6% plasma LDL-C, −37.9% Lp(a), reduction in serum liver enzymes and noninvasive fibrosis biomarkers
Harrison et al.[35] NCT02912260	31 patients with biopsy-confirmed NASH who completed NCT02912260 with persistently elevated serum liver enzymes, received resmetirom 80/100 mg	36 weeks	OLE	MRI-PDFF assessed hepatic fat content: −11.1% absolute reduction; −52% relative reduction of hepatic fat content Markers of fibrosis were reduced, including LSM assessed by VCTE −2.1 kPa N-terminal type III collagen pro-peptide (PRO-C3) −9.8 ng/mL Reduction in plasma LDL-C level −26.1%
Younossi et al.[36] NCT02912260	125 patients with biopsy-confirmed NASH, metabolic syndrome and MRI-PDFF ≥10% hepatic fat, randomized 2:1 to resmetirom 80-mg ($n=78$) or placebo ($n=38$)	36 weeks	Phase 2, multicentre, double-blind, randomized, placebo-controlled trial	Primary: HRQL Patients with improvement in MASH and fibrosis on liver biopsy also showed improvement in components of HRQL. Patients with MASH treated who improved their MRI-PDFF values and/or NAS on serial liver biopsy experienced improvement of HRQL
Harrison et al.[37] NCT04197479 MAESTRO-NAFLD-1	Patients with MASLD and metabolic syndrome and MRI-PDFF ≥8% hepatic fat: resmetirom 80-mg ($n=327$), resmetirom 100-mg ($n=325$) or placebo ($n=320$), or open-label resmetirom 100-mg ($n=171$)	52 weeks	Phase 3, randomized, double-blind, placebo-controlled trial, *plus* open-label arm	Primary: TEAEs Resmetirom was safe and usually well tolerated; diarrhoea and nausea were more frequent with resmetirom than placebo, especially at the beginning of treatment. Key secondary endpoints included least square means difference from placebo at 80-mg, 100-mg resmetirom doses: LDL-C (−11.1%, −12.6%), apolipoprotein B (−15.6%, −18.0%), triglycerides (−15.4%, −20.4%), 16-week MRI-PDFF assessed hepatic fat (−34.9%, −38.6%), ($p<.0001$) and VCTE assessed liver stiffness (−1.02, −1.70) and MRI-PDFF hepatic fat at 52-week (−28.8%, −33.9%)
Harrison et al.[11] NCT03900429 MAESTRO-NASH	966 patients with biopsy-proven NASH and metabolic syndrome, NAS ≥4, fibrosis stage F1-F3 were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo: 322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group	52 weeks	Phase 3, randomized, double-blind, placebo-controlled trial Registration study with histological liver outcomes	Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to MASH resolution and improvement in liver fibrosis by at least one stage. In the resmetirom 80 mg, 100 mg vs. placebo groups: MASH resolution with no worsening of fibrosis 25.9%, 29.9% vs. 9.7%. Fibrosis improvement by at least one stage with no worsening of MASH were 24.2%, 25.9% vs. 14.2%. Secondary: change in plasma LDL-C level at Week 24: −13.6%, −16.3% vs. +.1%

Abbreviations: HRQL, health-related quality of life; LSM, liver stiffness measurement; MASH; metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, NASH activity score; OLE, open label extension; TEAEs, treatment emergent adverse events; VCTE, vibration-controlled transient elastography.

different patient subgroups, including between those with/without pre-existing type 2 diabetes, exposed or not to GLP-1 receptor agonists, and those treated or not with low-dose levothyroxine replacement therapy.[11] However, more overweight patients tended to have a suboptimal response to 80-mg dose, leading the FDA to recommend resmetirom 100 mg/day in those heavier >100 kg.

In all published clinical trials resmetirom had neutral effects on body weight, blood glucose and insulin resistance. An important observation, as cardiovascular disease is the leading cause of morbidity and mortality in people with MASLD or MASH,[38] is the significant beneficial effect of resmetirom on circulating lipids, including plasma LDL cholesterol, triglycerides, apolipoprotein B and lipoprotein(a) [Lp(a)], throughout the whole MAESTRO clinical development programme. The lipid-lowering effect of resmetirom on circulating lipids in the MAESTRO-NASH, consistent with the overall data, is reported in Table 2. Resmetirom 100-mg achieved >15% decrease in plasma LDL cholesterol, >20% in triglycerides and >35% in lipoprotein (a) concentrations in MASH patients already treated with statins. The latest finding is of special interest as statins are not able to reduce plasma lipoprotein (a) levels, which may contribute to residual cardiovascular risk in statin-treated patients.[39] Based on Mendelian randomization studies,[40] it could be estimated, as shown in Table 2, that the observed resmetirom-induced improvement in circulating lipids would reduce major adverse cardiovascular events by 16–21%, respectively. Whether this will also translate into a clinically meaningful benefit in MASH patients treated with resmetirom and will not be counterbalanced by side effects related to the weak THR-α agonism on the cardiovascular system, which was not so far observed in short-term clinical trials, will have to be addressed with longer follow-up duration.

4 | SAFETY PROFILE

Resmetirom was generally well tolerated in both the MAESTRO-NAFLD-1 trial (whose primary outcome was safety) and the MAESTRO-NASH trial.[11,37] The safety data from these two phase 3 clinical trials (that had a duration of 52 weeks) are reported in supplementary Tables S1 and S2, respectively. When analysing the adverse-event profile, a possible limitation of the MAESTRO-NAFLD-1 includes the impact of COVID-19-related dose interruptions on the evaluation of safety and efficacy in the double-blind arms of the trial.

Overall, almost 90% of adult patients who received resmetirom and 90% of those who received placebo reported an adverse event in both clinical trials.[11,37] Most adverse events were usually mild or moderate in severity. The most common adverse events affecting at least 5% of participants that occurred more frequently in the resmetirom group than in the placebo group were gastrointestinal (principally diarrhoea and nausea followed by abdominal pain, vomiting, or constipation), with the highest rates generally reported by those receiving resmetirom 100 mg/day. Diarrhoea and nausea typically began early in therapy initiation (within 12 weeks) and were transient (median duration of self-limited diarrhoea was approximately 2 weeks) and mild or moderate in severity. No episodes of severe diarrhoea were reported. However, the more frequent occurrence of diarrhoea questions the relative specificity of the effect of resmetirom on the liver. Future studies are needed to test whether resmetirom does not have off-target effects on other extrahepatic tissues expressing the THR-β.

Overall, the incidence of serious adverse events was similar in the resmetirom and placebo arms in both clinical trials. In the MAESTRO-NASH,[11] the incidence of serious adverse events was similar among patients who received resmetirom and those who received placebo: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg group, and 11.5% in the placebo group, respectively (Table S2). Serious adverse events included gastrointestinal disorders, acute gallstone-related disorders (acute cholecystitis, gallstone-related pancreatitis, or cholelithiasis), cardiac disorders, respiratory/thoracic disorders, COVID-19 infections, musculoskeletal and connective tissue disorders, or nervous system disorders. There was no incidence of drug-induced acute liver injury. Cancer

TABLE 2 Predicted cardiovascular risk reduction based on the reported 52-week resmetirom-induced beneficial effects on circulating lipid levels.

Resmetirom dose	Basal	Final	% variation	Delta	CVD risk reduction, %[a]
80 mg					
LDL-C, mg/dL	179.6	154.4	−13.6	−25.2	−12.6
Triglycerides, mg/dL	189.2	146.3	−22.7	−42.9	−2.3
Lp(a), nmol/L	44.7	31.1	−30.4	−13.6	−1.1/1.6
Overall	−16.0/16.5				
100 mg					
LDL-C, mg/dL	176.9	148.1	−16.3	−28.8	−14.4
Triglycerides, mg/dL	188.7	147.8	−21.7	−40.9	−2.2
Lp(a), nmol/L	43.8	28.1	−35.9	−15.7	−2.9/4.4
Overall	−19.5/21.0				

[a]20% CVD risk reduction observed for reduction 40 mg/dL LDL-cholesterol, 200 mg/dL triglycerides, and 165–250 nmol/L Lipoprotein (a).

was reported in 1.0% of the patients in the 80-mg group, 3.4% in the 100-mg group, and 3.7% in the placebo group.[11] In both clinical trials,[11,37] no major adverse cardiovascular events, increases in bone fractures, or substantial changes in bone mineral density (BMD) T-scores were noted with resmetirom. In the MAESTRO-NASH trial,[11] at Week 52, trial discontinuations due to adverse events were more common in the 100-mg resmetirom group than in the other two trial groups (7% in the 100-mg resmetirom group, 2% in the 80-mg resmetirom group, and 2% in the placebo groups). Thereafter, trial discontinuations were comparable across the trial groups.

In both trials, no increase in endocrine adverse events was reported. Safety observations related to possible thyroid axis or thyroid hormone effects showed no increases in signs or symptoms of hypothyroidism or hyperthyroidism relative to placebo. In particular, treatment with resmetirom for 52 weeks reduced serum-free T4 levels by approximately 16% to 19%, with no significant effects on circulating TSH or free T3 levels, irrespective of thyroxine-replacement status at baseline. No significant effects on heart rate, electrocardiograms, or diabetes biomarkers were also noted.[11,37]

It is important to note that among patients receiving resmetirom, the drug markedly increased levels of plasma SHBG but not thyroxine-binding globulin (TBG), as well as increased levels of plasma total oestradiol and total testosterone (although free testosterone levels were unchanged).[11,37] Although elevations in plasma SHBG levels closely reflect the pharmacological action of resmetirom due to its THR-β engagement, it is unclear whether long-term elevations in plasma SHBG levels may promote clinically significant gonadal axis changes or influence various traits and diseases. For example, a Mendelian randomization phenome-wide association study using the UK Biobank database showed that genetically elevated circulating SHBG levels were causally associated with lower BMD T-scores, higher risk of hip replacement and gallbladder removal and lower plasma total and LDL cholesterol levels.[41]

Resmetirom should not be used in patients with decompensated cirrhosis. Using resmetirom at the same time as certain drugs, such as lipid-lowering medications (statins and fibrates), clopidogrel or cyclosporine, may result in potentially significant drug interactions that clinicians should consider reducing the recommended daily dosages of resmetirom (60 mg daily). Finally, whether resmetirom is safe and effective in adolescents (<18 years) is currently unknown.

Collectively, therefore, resmetirom has an acceptable safety profile in the MAESTRO-NAFLD-1 and MAESTRO-NASH trials, although careful surveillance to detect early thyroid, gonadal, or bone diseases seems to be warranted to avoid any potential risks from long-term treatment.[42] Definitive answers will come from the 54-month long-term safety and efficacy results of the ongoing MAESTRO-NASH trial, as well as the routine post-marketing surveillance of adverse events once the drug is on the market.

In addition, the action of resmetirom is based on an increased intracellular energy substrate utilization by stepping on the gas of the thyroid axis. Specifically, resmetirom induces the breakdown of fatty acids in the mitochondria by beta-oxidation that in turn produces reactive oxygen species (ROS). Since most of the intracellular ROS derive indeed from these organelles,[43] it remains to be determined what are the possible drug-induced effects of long-term exposure to higher intracellular ROS levels in hepatocytes.

5 | CLINICAL IMPLEMENTATION

When looking at the resmetirom target population, the MAESTRO-NASH trial,[11] as for FDA recommendations,[44] enrolled adult patients with histological diagnosis of at-risk MASH, defined as MASH with fibrosis stage F2/F3. This issue – as for all MASH trials – led to a high rate of screening failure more frequently related to the lack of MASH criteria – mostly ballooning – at centralized reading, while raising concerns about the use of liver biopsy to select patients for treatment. In this contrasting landscape, the FDA licensed resmetirom for patients with at-risk MASH without any recommendation on the need for liver biopsy.[45] The label of resmetirom as licensed by the FDA opens new scenarios in the complex setting of patient selection. In the last few years, research consortia such as LITMUS and NIMBLE in Europe/USA invested millions focusing on the identification of non-invasive tests (NITs) based on unconventional variables and/or imaging tools aimed at the identification of patients with at-risk MASH to be included in clinical trials.[46,47] Overall, these NITs have acceptable-good accuracy, but the real question is whether they can be nowadays used in routine clinical practice to select patients for treatment. The response is probably not because NITs are primarily based on patented blood-based biomarkers and/or devices that are not broadly available, expensive, and not reimbursable. Using NITs as tools for identifying patients to be treated with resmetirom raises another key question: should we search for patients with at-risk MASH or look only at liver fibrosis? A recent analysis on a cohort of about 2000 patients with biopsy-proven MASLD and with a long clinical follow-up has clearly shown that the risk of developing liver-related events is similar in patients with at-risk MASH compared to those with the same stages of liver fibrosis but without evidence of MASH at the time of liver biopsy.[48] Indeed, MASH is a dynamic process with intermittent flares that is also influenced by non-uniform distribution within the liver, so liver fibrosis is more closely linked to the disease prognosis and less susceptible to the interpretation of liver histopathologists.[49,50] Moreover, the accuracy of Fibroscan-measured LSM in predicting liver-related events was similar or superior to that of histological at-risk MASH or histological fibrosis.[48] For all these reasons, it would be more practical to use resmetirom in patients with at-risk MASH due to more severe fibrosis.[51] For this purpose, an LSM of <8 kPa might be used to rule out patients at low risk of advanced fibrosis, while an LSM ≥10 kPa might be used to identify the so-called compensated advanced chronic liver disease at risk of liver-related events. Using the LSM cut-offs to identify the target population could change across different countries according to costs and reimbursement rules. A 10-kPa LSM threshold can

probably identify patients at most urgent clinical need, together with those with overt cirrhosis and portal hypertension, a setting where resmetirom is, however, still under investigation and cannot presently be prescribed. The use of the Agile-3+ score that is more closely and dynamically associated with an increased risk of liver-related events might represent an alternative.[52]

The availability of resmetirom in real life opens another key question: how and when to define the response to the treatment? Data from clinical trials showed that both a 3-month ≥30% improvement in MRI-PDFF assessed hepatic fat content and ≥17 IU reduction of serum ALT levels from baseline can identify histological responders.[53] However, there is an urgent need to consider alternative non-invasive approaches that can be applied in clinical settings where MRI-PDFF is not widely available. Strategies to be tested include the assessment of both serum ALT level and LSM reduction by 20% at 3–6 months.[54] Conversely, a progressive increase in response rate with time, or no further benefits in treatment prolongation as observed for rosiglitazone cannot be excluded.[55] That said, monitoring any new treatment for MASLD/MASH in clinical practice is going to require simple easily available tests for fibrosis – not least to know when to stop a treatment because it is not working. This is especially true with expensive drugs, such as resmetirom, where only 16% of patients on the highest 100-mg dose met both co-primary histological outcomes.[11] Long-term MAESTRO trial results and real-life data will be necessary to better understand how to assess and manage the treatment response of resmetirom, especially when other drugs will be available and strategies of 'add-on' or 'switch-to' could be considered.

A potential algorithm to manage resmetirom treatment in clinical practice is presented in Figure 2.

6 | SIGNIFICANCE AND IMPACT

The positive clinical trial results of resmetirom on the histological resolution of MASH and improvement of liver fibrosis confirm the prediction based on human genetics, Mendelian randomization studies and pathophysiological data that targeting hepatic fat accumulation would result in stopping and reversing the natural history of MASLD from isolated steatosis to advanced fibrosis, cirrhosis,[7,8] and even HCC,[56] as observed for cholesterol accumulation in the arterial wall for atherosclerosis.[57] This evidence is in line with MASLD/MASH, which is a predominantly metabolic liver disease in which lipotoxicity is the key pathogenic driver, as now reflected in the new steatotic liver disease nomenclature.[58] However, as THR-α is involved in regulating fibrogenesis in hepatic stellate cells, a direct effect of modulation of the thyroid axis on hepatic fibrogenesis cannot presently ruled out.[59,60]

All these data highlight that we are now at the beginning of a new era where a first drug, resmetirom, is available for the treatment of adults with non-cirrhotic MASH with moderate to advanced fibrosis, opening up the ground for new and combined therapeutic approaches, but more research is needed to provide robust ground to build the rules of this game looking at what is feasible and clinically relevant.

The observed hepatoprotective effects of resmetirom on MASLD/MASH also pose a question for future studies: will resmetirom be used as a treatment benchmark for future trials with other compounds being investigated for MASLD/MASH treatment? Will resmetirom use be allowed in both placebo and active drug arms in ongoing clinical trials? Good clinical practice would recommend so. However, this may not be straightforward due to the following

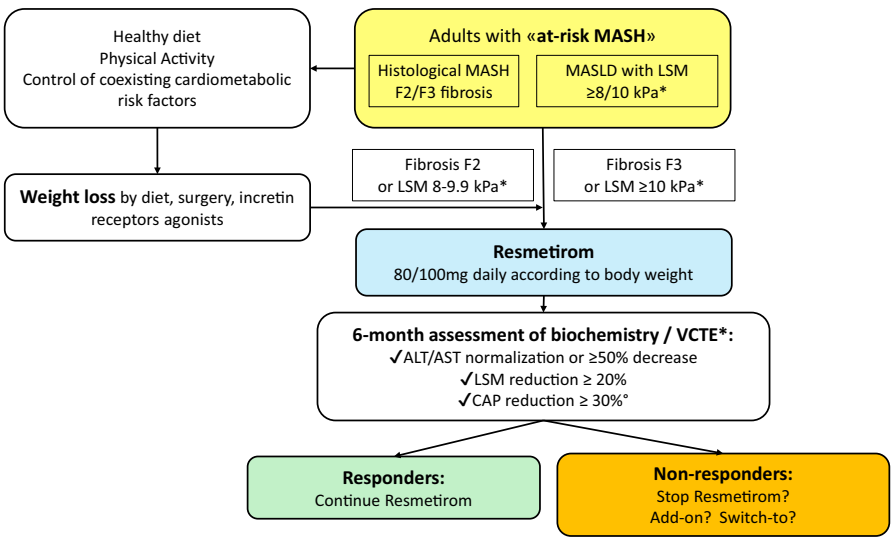

FIGURE 2 Potential algorithm to manage resmetirom treatment in clinical practice. ALT: alanine aminotransferases, AST: aspartate aminotransferases, CAP: controlled attenuation parameter, LSM: liver stiffness measurement, MASLD: metabolic dysfunction associated steatotic liver disease, MASH: metabolic dysfunction associated steatohepatitis, VCTE: vibration controlled transient elastography measured by Fibroscan. *Or at-risk MASH defined by alternative non-invasive approaches, such as Agile-3+;° Requiring further validation. Treatment of patients with stage F2 fibrosis may require previous attempts to achieve weight loss and correct metabolic alterations depending on local regulations and reimbursement approvals.

reasons: (a) the FDA approval does not result automatically in the approval of other medical agencies, for example, EMA that will independently scrutinize data from clinical trials; and (b) the current conditional approval is based on efficacy demonstrated on liver biopsy and not liver-related clinical hard endpoints.

Results of the whole MAESTRO clinical programme,[12] real-life and investigator-driven studies will be needed to confirm if resmetirom treatment will also result in significant reductions in the risk of developing clinical liver-related complications, such as cirrhosis, liver transplant, hepatocellular carcinoma and, ultimately, mortality. Moreover, despite encouraging signals deriving from the resmetirom-induced reduction in plasma LDL-cholesterol and other atherogenic lipoproteins, the effects of the drug on the long-term risk of major adverse cardiovascular outcomes remain to be investigated. However, to our knowledge, neither MAESTRO-NAFLD-OLE (NCT04951219) nor MAESTRO-NASH-OUTCOMES (NCT05500222) is investigating cardiovascular outcomes by considering a competing risk approach.

The positioning of resmetirom, or other oral selective THR-β agonists under study (i.e. VK2809 is now testing in a phase 2b randomized placebo-controlled trial: NCT04173065), in the future treatment of adult patients with non-cirrhotic MASH, for example, at early or only relatively stage of the disease, the impact on clinical events in compensated cirrhosis, the use together or after the failure of body weight reducing approaches, and the stopping rules are all key open questions that remain to be addressed. In addition, as the number needed to treat to induce resolution of MASH at 52 weeks was about five in the MAESTRO-NASH trial, it would be clinically important to identify and refine baseline and dynamic predictors of treatment response to distinguish between patients who will benefit from those for whom therapeutic alternatives should be sought. In the future, it will be also relevant to test whether the common inherited genetic variants affecting the risk of MASH may influence the response to resmetirom.

7 | CONCLUSIONS

As we celebrate the milestone of the FDA's conditional approval of resmetirom for the treatment of adults with non-cirrhotic MASH with moderate to advanced fibrosis, there are still significant challenges that require to be addressed for the widespread use of resmetirom in routine clinical practice. Based on the convincing evidence of MASLD as a multisystem disease, we believe that the future for MASLD/MASH treatment may prove to be combination therapy with resmetirom targeting the liver, and other agents with potentially hepatoprotective effects added to resmetirom (i.e. incretin receptor agonists and possibly other drug classes) to reduce the high cardiometabolic risk related to MASLD/MASH.[61]

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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