

Review

Open Access



Pharmacologic approach to metabolic dysfunction and related diseases: focus on liver aspects

Annarita Valeria Piazzolla, Antonio Napolitano, Alessandra Mangia

Liver Unit, Fondazione IRCCS “Casa Sollievo della Sofferenza” Hospital, San Giovanni Rotondo 71013, Italy.

Correspondence to: Prof. Alessandra Mangia, Liver Unit, Fondazione IRCCS “Casa Sollievo della Sofferenza” Hospital, San Giovanni Rotondo 71013, Italy. E-mail: a.mangia@tin.it

How to cite this article: Piazzolla AV, Napolitano A, Mangia A. Pharmacologic approach to metabolic dysfunction and related diseases: focus on liver aspects. *Metab Target Organ Damage*. 2025;5:67. <https://dx.doi.org/10.20517/mtod.2025.152>

Received: 10 Sep 2025 **First Decision:** 28 Oct 2025 **Revised:** 30 Nov 2025 **Accepted:** 17 Dec 2025 **Published:** 30 Dec 2025

Academic Editor: Amedeo Lonardo **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects nearly 1.5 billion adults worldwide. It is closely associated with type 2 diabetes mellitus and obesity. Longer duration of MASLD increases risk of progression to metabolic dysfunction-associated steatohepatitis (MASH, the progressive form of MASLD that requires pharmacological therapy), cirrhosis and hepatocellular carcinoma, as well as development of cardiovascular complications. Despite the need for MASH pharmacologic intervention, several studies on new investigational compounds have failed, with only Resmetirom and Semaglutide recently conditionally approved by the Food and Drug Administration (FDA). The role of incretins may be more critical in the early phase of MASH development, but integration with drugs that directly target the liver may represent the winning strategy. The armamentarium of drugs for MASH is rapidly expanding, and several promising drugs are under investigation in phase 2 of development. Integrating fibrosis stage-specific combination therapies targeting different steps of the complex pathogenic mechanism of MASLD/MASH may lead to successful treatment rates larger than the currently obtained 25%-30%. The effects of both FDA-approved compounds (Resmetirom and Semaglutide) on clinical outcomes remain to be shown and will not be available before the conclusion of the respective outcome studies in 2027 and 2028.

Keywords: Resmetirom semaglutide, incretins, MASLD, MASH



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), recently re-named metabolic dysfunction-associated steatotic liver disease (MASLD), is a complex, systemic disease that affects multiple body systems where insulin resistance (IR) and related metabolic dysfunction play a driving role^[1].

MASLD is diagnosed based on the detection of at least 5% fat buildup in the liver, as shown by imaging or histology, in addition to at least one of five cardiometabolic risk factors, including abdominal obesity, elevated triglycerides (TGs), low high-density lipoprotein cholesterol levels, hyperglycaemia, and hypertension^[1]. Diagnosis requires the absence of other secondary reasons of fat accumulation in the liver, including excessive alcohol consumption or specific drugs such as tamoxifen, corticosteroids, antiretroviral or antipsychotic, antidepressant and anticonvulsant.

The prevalence of MASLD ranges from 25.5% to 38% in accordance with population heterogeneity; given the escalating epidemic that is tied to the surge in metabolic syndrome, obesity and type 2 diabetes mellitus (T2DM), the proportion of subjects affected worldwide is expected to grow exponentially in the years to come^[2,3].

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), is the progressive form of MASLD^[4]. Histologically, MASH is characterized by hepatocellular ballooning, lobular inflammation and potentially fibrosis, in addition to steatosis. With progression, MASH can eventually lead to various degrees of fibrosis, resulting in cirrhosis and liver failure^[4-6]. An overall mortality rate of 12.6 per 1,000 person-years has been reported, with 4.2 per 1,000 person-years cardiac-specific mortality. Liver diseases represent a cause of death in about 20% of cases^[7].

The prevalence of MASH in the general population ranges from 5% to 7%, while MASH-related cirrhosis has a prevalence of 1.8%^[7]. A bidirectional association between MASH and T2DM exists. Indeed, in subjects with MASH, an increased risk of incident T2DM, peaking at up to 33%, as well as cardiovascular (CV) disease, has been described^[8]. Conversely, in people with T2DM, the prevalence of MASH reaches 35%, and that of the cirrhotic form 7%^[7-10]. IR and T2DM are the strongest predictors of progression to advanced fibrosis and cirrhosis^[9].

MASLD/MASH arises from a combination of factors acting on genetically predisposed individuals. These factors include IR, adipose tissue-derived hormones, dietary influences and genetic and epigenetic modifications^[8-11]. Gut dysbiosis, bacterial overgrowth, and increased intestinal permeability have been reported in MASLD/MASH^[12]. A high dietary sugar and saturated fat-rich diet may induce dysbiosis, leading to an imbalance in gut microbiota and disruption of the gut vascular barrier. Consequences of this disruption include the systemic translocation of bacteria and bacterial products, endotoxemia, and inflammation. Diet management and, possibly, the cure of disruptions of intestinal epithelial and gut vascular barriers are of utmost importance in MASH development^[13].

Despite the need for pharmacologic intervention, several studies on new investigational compounds have failed, with Resmetirom and Semaglutide both recently conditionally approved by the Food and Drug Administration (FDA) for the treatment of MASH^[14-16]. Resmetirom obtained European Medicines Agency (EMA) approval for the treatment of MASH in August 2025. Approval of Semaglutide for MASH by the EMA is pending^[17]. However, the drug is already widely used in patients with T2DM and obesity^[18], and real-world data on CV outcomes are available. Moreover, many patients randomized to all current experimental compounds under evaluation are already receiving glucagon-like peptide 1 receptor agonists

(GLP-1RA)^[19]. Resmetirom is an oral, liver-directed, thyroid hormone receptor- β (THR- β)-selective agonist^[20], while Semaglutide is a drug pure targeting metabolic drivers and consequent dysfunctions^[21].

This review will focus on the mechanisms of action of these two compounds according to disease pathophysiology, and on the results of registration and real-world studies currently available in patients without liver cirrhosis. Given the vast current and historical pipeline, compounds in phase 1 development will not be discussed here.

PATHOPHYSIOLOGY

Pathophysiology of MASLD/MASH is complex. Excessive caloric intake associated with IR is responsible for hepatic fat accumulation. Peripheral IR associated with MASLD/MASH requires higher insulin secretion, but insulin-impaired action favors - in the liver and adipose tissue - incomplete suppression of glucose production and adipose tissue lipolysis. The consequence is a higher fasting glucose concentration and higher levels of circulating Free Fatty Acids (FFAs). Increased fasting insulin levels, decreased post-hepatic insulin clearance, increased endogenous insulin release, and reduced glucose breakdown and lipid oxidation characterize the MASLD/MASH metabolic derangement. The impairment of insulin action at the liver and adipose tissue levels is proportional to both hepatic and visceral fat. Dysfunctional adipose tissue, unable to expand in response to an excess of lipids derived from an increased rate of lipolysis, contributes to the development of MASLD/MASH, leading to ectopic fat accumulation at the visceral level, including the liver^[8-11].

Muscle IR is also an early event in MASLD/MASH. Increases in intramyocellular lipid content, which typically occur prior to the onset of MASLD, cause muscle IR and result in inhibition of insulin signaling and decreased insulin-stimulated glucose transport and muscle glycogen synthesis. Since ingested glucose cannot be adequately stored as muscle glycogen, in the presence of excessive carbohydrate intake, it is redirected to the liver. In the liver, glucose excess in combination with compensatory portal vein hyperinsulinemia, because of muscle IR, promotes increased expression of hepatic enzymes that regulate *de novo* lipogenesis (DNL), resulting in increased very-low-density lipoprotein (VLDL) production and hypertriglyceridemia.

Interestingly, although MASLD/MASH and T2DM share pathophysiological pathways, including IR, altered insulin secretion, and adipose tissue dysfunction, not all IR conditions associated with MASLD/MASH lead to overt T2DM. As shown in recent studies, there are two main MASLD/MASH phenotypes: metabolic and genetic. In patients with “genetic” MASLD/MASH, liver fat accumulates because of genetic causes; by contrast, IR causes metabolic MASLD/MASH.

Genetic studies evaluating PNPLA3 (Patatin-like phospholipase domain-containing 3), TMSF2 (Transmembrane 6 superfamily Member 2), GCKR (Glucokinase regulatory protein), MBOAT7 (Membrane-Bound O-acyltransferase Domain-containing 7) and HSD17B13 (Hydroxysteroid 17-beta-dehydrogenase 13) polymorphisms suggest that an excess of fat in the liver causes progressive liver disease without increasing the risk of T2DM^[21-23]. This characterizes the genetic type of MASH in the absence of IR/T2DM. In particular, the PNPLA3 variant, associated with a higher risk of MASLD/MASH, cirrhosis and hepatocellular carcinoma (HCC), favors lipid accumulation in the hepatocytes by reducing the lipidation of VLDL cholesterol^[22,23]. Environmental factors, including lifestyle, excess caloric intake, social alcohol use and smoking, act synergistically to increase the risk of MASH in genetically predisposed individuals.

The liver plays a major role in the metabolism of fat, as FFAs are the major source of lipids for the liver. In the healthy liver, lipid uptake and synthesis, esterification, β -oxidation, and elimination through VLDL are well-balanced processes. Only when the liver is unable to cope with the excess of VLDL in the presence of increased TG uptake and intra-hepatic fat production, MASLD and then MASH develop^[24].

The key role of the liver in such a complex metabolic mechanism emerges when MASH patients are compared with healthy individuals. The liver acts as an adaptor to stress caused by an excess of FFAs; it increases mitochondrial β oxidation, re-esterification in TG, release of VLDL cholesterol into the systemic circulation and storage of FFAs as lipid droplets. In patients with MASH, the liver's adaptive capacity declines^[25].

Excess FFAs delivered to the liver, accumulation of lipotoxic lipid intermediates, and mitochondrial dysfunction lead to an increase in oxidative stress and release of toxic metabolites^[26]. Reactive oxygen species (ROS) are generated, and macrophages are recruited in response to cytokine release. All these events induce inflammatory cells activation, cytokine release and hepatocyte damage. Chronic necroinflammation results in the activation of stellate cells and a fibrogenic response. Indeed, in an attempt to repair the damage, extracellular matrix proteins accumulate in the liver. Severity of fibrosis has been shown to be the main driver of liver-related morbidity and mortality in patients with MASH^[27,28]. In particular, fibrosis of stage 2 or greater is considered "at risk" and represents the criterion on which to decide the start of pharmacologic treatment^[29].

The balance between the liver's capacity to cope with stress and hepatic fat toxicity, and upstream drivers of disease, explains the heterogeneity of MASH, progression, and severity of fibrosis, and emphasizes the key role of the liver. Despite the focus on a broad metabolic disorder that involves the CV system and is associated with co-morbidities, and increased risk of cancer, MASLD/MASH is a liver disease rather than the hepatic manifestation of systemic IR.

Once the disease has progressed to "at-risk" fibrosis, liver-directed drugs are required.

On the other hand, obesogenic environments and metabolic drivers require the timely use of pharmacologic compounds associated with metabolic and CV benefits.

RESMETIROM

Hepatic activity and thyroid signaling are closely intertwined. THR- β agonists have attracted attention due to their selectivity for THR- β over thyroid hormone receptor- α (THR- α). The liver has more THR- β receptors than any other organ. Triiodothyronine (T3) and thyroxine (T4) are essential for the regulation of liver function, whereas the liver, in turn, is involved in the metabolism of thyroid hormone^[30]. T3 and T4 play a role in liver lipid homeostasis and have direct effects on both cholesterol and fatty acid synthesis and metabolism, promoting the expression of low-density lipoprotein receptors (LDL), and activity of lipid-lowering liver enzymes with consequent reduction of LDL levels. The expression of apolipoprotein A1, a major component of HDL, is also increased by thyroid hormone.

T3 and T4 modulate lipolysis of fat stores from white adipose tissue (which generates circulating FFAs), promote hepatic cholesterol synthesis as VLDL from acetyl acetyl-coenzyme-A (CoA), and increase HDL metabolism by stimulating cholesteryl ester transfer lipoprotein A activity to accelerate cholesterol clearance^[30].

These observations have provided the rationale for therapeutic interventions with T3 and T4 in preclinical models of MASLD. A small clinical trial showed that low-dose levothyroxine administration resulted in a significant reduction in liver fat content from baseline.

Resmetirom targets the significant overlap of metabolic and liver mechanisms of MASH development. The primary mechanism of action of Resmetirom in MASH relies on modulation of hepatic lipid metabolism by enhancing cholesterol and TG breakdown and reducing DNL^[31], thereby reducing liver fat content - the major driver of MASH development - and decreasing inflammation and fibrosis progression. Metabolic dysregulation, which characterizes MASLD, is based on the abrogated action of deiodinase 1. This enzyme in the normal liver converts the inactive circulating pro-hormone T4 into its active form T3. In the setting of MASLD, deiodinase 1 is not active, while deiodinase 3 is upregulated and converts T4 to reverse T3, resulting in less conversion of T4 to free T3. Stimulating THR- β function restores normal deiodinase 1 activity. Moreover, Resmetirom provides benefits in atherogenic coronary artery disease by decreasing levels of LDL cholesterol and other lipoproteins.

In a randomized, double-blind, placebo-controlled phase 2 clinical trial, Resmetirom was studied in patients with MASH (fibrosis stage 1-3)^[32]. Eighty-four patients were randomized to 80 mg of Resmetirom and 41 to placebo for 36 weeks. Patients treated with Resmetirom showed a relative reduction of hepatic fat at weeks 12 and 36 compared to placebo (in both cases, least squares mean differences of -22.5% and -37.3% were statistically significant, $P < 0.0001$ for both). Biopsy - performed at 36 weeks - showed that the histological features of MASH were reduced.

The phase 3 study MAESTRO-NASH (the original name refers to the old nomenclature) (NCT03900429) led to FDA approval of this compound for patients with MASH with at least three metabolic risk factors, histological features of MASH, and fibrosis stage 3. Overall, 966 patients were randomized 2:1 to Resmetirom 80 mg, 100 mg, or placebo^[19]. Patients with cirrhosis (F4) were excluded. The inclusion of only a limited number of Black and Asian patients may require confirmatory studies in other ethnic groups.

MAESTRO-NASH demonstrated 30% vs. 10% MASH resolution and 26% vs. 14% fibrosis improvement by ≥ 1 stage, in patients receiving 100 mg of Resmetirom vs. placebo^[19]. LDL cholesterol levels significantly declined by 16.3% vs. 0.1% in the placebo group at week 24. Apolipoprotein B declined by 19.8% vs. 0.4% in the placebo group. Lipoprotein A declined by 35.9% vs. 0.8% in the placebo group^[19]. Although the outcome results will be available in 2027, a reduction in apolipoprotein B and LDL cholesterol levels of this magnitude may be predictive of improvements in CV outcomes^[33].

Resmetirom has not been associated with significant safety issues. Diarrhea is the most frequent side effect observed in 33% of patients treated with 100 mg as compared to 16% in the placebo group. Nausea was reported in 16% of patients receiving 100 mg as compared to 13% in the placebo group. Reduced T4 levels have not been associated with clinical consequences^[19]. Increased levels of sex hormone-binding globulin (SHBG) were also not associated with any changes in sex hormones.

Interestingly, although real-world data highlight the limitations of current non-invasive diagnosis of fibrosis, the FDA approval of Resmetirom does not require liver histology for diagnosis^[15]. Liver biopsy represents the gold standard for the identification of MASH. However, due to the invasive nature, the high rate of patient reluctance makes its use impractical for both diagnosis and response monitoring. Non-invasive assessments of liver disease are essential for assisting in diagnosis; they include Fibrosis-4 index for liver fibrosis (FIB-4), liver stiffness measurement (LSM) by Transient Elastography, and magnetic resonance

elastography^[34]. In MASH with fibrosis, a 30% reduction from baseline in magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) is considered the most accurate tool to assess treatment response; however, it is not available everywhere^[33]. In addition, treatment response monitoring will be based on a combination of alanine aminotransferase (ALT), LSM by FibroScan, and MRI-PDFF^[35]. Response assessment should not be performed before 12 months of treatment^[36,37].

Other compounds in the same category are in development. VK2809, a liver-specific THR- β agonist^[38], was tested in a multicenter, randomized, double-blind, placebo-controlled phase 2 trial for safety, tolerability, and efficacy in patients with MASLD; no liver histology-based MASH diagnosis was required. Overall, 337 patients with MASLD and liver fat content measured by MRI-PDFF $\geq 8\%$ were assigned to three different doses (2.5, 5, or 10 mg) of VK2809 or placebo for 12 weeks. At the end of treatment, a statistically significant reduction in liver fat was observed in patients treated with VK2809 compared with placebo-treated patients. These effects were maintained at the week-16 assessment. Safety was also assessed at week 16 (4 weeks following completion of the treatment with active compound). VK2809 was well tolerated, and no serious adverse events were reported in any cohort^[38]. These data reinforce the utility of THR- β agonists in MASLD/MASH.

SEMAGLUTIDE

Glucagon-like peptide 1 (GLP-1) is a hormone produced by enteroendocrine L cells, endocrine pancreas and nucleus tractus solitarius neurons in the brain^[39]. It promotes satiety and weight loss through direct effect on the central nervous system^[40]. In addition to reversing IR and targeting lipotoxicity, Semaglutide offers additional extrahepatic benefits at the CV and kidney level. GLP-1 acts via the GLP-1 receptors (GLP-1Rs). As GLP-1Rs are not present in the liver, semaglutide is a pure metabolic dysfunction regulator, as proven in phase 3 trials for T2DM (NCT03989232), obesity (NCT 03548935), CV disease (NCT 03574597), chronic kidney disease (NCT03819153)^[38], obstructive sleep apnea (OSA) (NCT07281196), and polycystic ovary syndrome (PCOS) (NCT03919929). While earlier suggestions supported a direct effect on hepatic glucose/lipid metabolism, more recent studies favor the amelioration of IR through changes in body weight^[41]. Thus, the primary value of Semaglutide in MASH lies in its capacity to reduce caloric intake, thereby significantly reducing body weight and improving glycemic control. A first phase 2 study (NCT01237119), namely the Liraglutide efficacy and action in NASH (LEAN) study, including 14 patients randomized to Liraglutide, the ancestor of GLP-1RA, demonstrated the possible mechanisms by which the metabolic effects of this drug class in patients with MASH can be explained^[42]. On this background, studies on Semaglutide were started. Preliminary evidence from a phase 2 study (NCT02970942) in non-cirrhotic patients suggested that Semaglutide, at doses ranging from 0.25 to 2.6 mg weekly, reduces body weight, improves glycemic control, and significantly improves MASH. However, significant improvement in MASH in phase 2b was not accompanied by a significant reduction in fibrosis^[43].

The recent phase 3 study (NCT04822181), ESSENCE, evaluating weekly 2.4 mg subcutaneously, demonstrated in patients with fibrosis stages 2 and 3 that, after 72 weeks, Semaglutide was associated with a significant improvement in MASH (62.9% vs. 34.3% in the placebo group)^[44]. In this study, improvement of fibrosis was also observed in 38.8% of patients receiving Semaglutide as compared to 22.4% for the placebo group. Both comparisons were statistically significant ($P < 0.001$). As recent trials [cardiovascular disease (NCT03574597); chronic kidney disease (NCT03819153)] further underscore the CV and renal benefit of Semaglutide^[45], based on the interconnection between obesity, T2DM and MASH, the benefit of Semaglutide on liver-related outcomes is expected. It will be assessed at the outcome completion final analysis of the ESSENCE study in 2028. Semaglutide results were supported by data illustrating the holistic benefits of the compound^[46].

However, although comparison between studies may be limited by baseline differences in patient populations, readout timing, histology scoring, adjudication, and definition variances, it should be noted that the rate of patients with F3 (Fibrosis stage 3) in the ESSENCE study is lower than in MAESTRO-NASH^[19,45]. The placebo-adjusted histologic benefits of Semaglutide for fibrosis improvement are modest, 14.4% vs. 13.4% for Resmetirom. In the subgroup of patients with T2DM, Semaglutide shows a placebo-adjusted subtracted effect of 8.9% as compared to the corresponding rate of 11% for Resmetirom. American Association for the Study of Liver Diseases (AASLD)^[47], European Association for the Study of the Liver (EASL) and European Association for the Study of Obesity (EASO)^[36] suggest starting Semaglutide in the presence of T2DM and Obesity.

Semaglutide side effects are primarily gastrointestinal (GI) in nature and dose-related. They include nausea and vomiting and resolve over time. In the ESSENCE study, nausea, vomiting, diarrhea, and constipation were reported in 30%-50% of patients, compared with 12%-13% in controls^[45]. Rapid weight reduction and loss of lean muscle mass might represent emerging concerns. The strong effects leading to sarcopenia might represent a limitation in patients with lean MASH and cirrhosis. However, conclusions on this aspect may be limited by the short follow-up study published on Semaglutide treatment of cirrhotic patients^[48]. Moreover, a rapid glucose drop may induce hypoglycemia when semaglutide is associated with insulin or insulin secretagogues^[49]. All in all, the ESSENCE study provides compelling evidence for Semaglutide as a potential cornerstone of MASH patients' therapy, although some questions remain to be answered.

DRUGS IN DEVELOPMENT: PHASE 2

Dual and triple GLP-1 receptor agonists

Dual agonists combining GLP-1RAs with glucose-dependent insulintropic polypeptide (GIP) (tirzepatide) or GLP-1RA with glucagon (Survodutide, Efinopegdutide or Pemvidutide) have been shown to be promising for their potential role in T2DM, obesity and MASH.

The dual GLP-1RA/GIP agonist tirzepatide combines the action of GLP-1R inhibition with that of GIP. The role of GIP in MASH seems to decrease liver fat content, but the exact mechanism of action in MASH is not clear^[50].

Dual GLP-1RA/Glucagon agonists are Survodutide, Efinopegdutide and Pemvidutide. The rationale for their use in MASH relies on the combined metabolic effects with direct hepatic action via glucagon receptor agonism. Glucagon increases energy expenditure, mobilizing hepatic fat and inducing lipolysis and fatty acid oxidation^[51].

Dual GLP-1RA-GIP agonist tirzepatide

Tirzepatide has been evaluated in patients with T2DM and MASH after 52 weeks of treatment, in a sub-study of the main SURPASS-3 trial (NCT04255433)^[52-54]. As compared to insulin degludec, in patients who underwent magnetic resonance imaging (MRI), a significant difference in liver fat content of -4.7% in favor of Tirzepatide was observed ($P < 0.0001$)^[54]. In the SYNERGY NASH study (NCT04166773), a phase 2 multicenter, double blind, randomized, placebo-controlled study on 190 patients with histologically diagnosed MASH of fibrosis stage 2 or 3, Tirzepatide dosages of 5, 10, and 15 mg were administered subcutaneously once weekly. The percentage of those who had resolution of MASH without worsening of fibrosis at week 52 of treatment was 44%, 56%, and 62% with 5, 10, and 15 mg once weekly, as compared to 10% with placebo. Fibrosis improvement of at least one stage without worsening of MASH was observed in 55%, 51% and 51%, in comparison to 30% in the placebo group^[52].

In the SURPASS phase 3 study, focusing on T2DM^[53], Tirzepatide-treated subjects reported the most common mild to moderate GI adverse events that decreased over time. Nausea was reported by 12%-24%, diarrhea by 15%-17%, decreased appetite by 6%-12%, and vomiting by 6%-10%. These rates were higher than those observed in patients treated with insulin degludec (2%, 4%, 1%, and 1%, respectively). Hypoglycemia (< 54 mg/dL or severe) was reported by 1%, 1%, and 2% of subjects on Tirzepatide 5, 10, and 15 mg, respectively, *vs.* 7% by those receiving insulin degludec^[53]. Adverse events leading to treatment discontinuation were more common in the tirzepatide groups than in the insulin degludec group. Five subjects died during the study; in none of them was death considered to be related to the study treatment.

Mild to moderate side effects were a driver of premature treatment discontinuations and might have some impact in real-life experience.

Dual GLP-1RA/glucagon agonists

Survodutide is an investigational dual agonist, a promising candidate for the management of MASH. As a probable consequence of increased glucagon-related energy expenditure, it has demonstrated superior weight loss and glycemic control compared with GLP-1RA^[55].

In a phase 2, multicenter, double-blind, randomized, placebo-controlled study (NCT04771273) for 24 weeks of treatment, efficacy, safety, and tolerability of multiple subcutaneous doses of Suvdudutide were evaluated for the treatment of patients with MASH and Fibrosis of stage 2 and 3^[56]. The primary endpoint, defined as improvement in MASH (≥ 2 -point decrease in the MASLD activity score with at least 1 point decrease in either lobular inflammation or hepato-cellular ballooning) without worsening of fibrosis, was achieved in a significant proportion of participants across different dosage groups ($P < 0.001$). Specifically, 47% of the patients in the 2.4 mg group, 62% in the 4.8 mg group, and 43% in the 6 mg group met the endpoint, in comparison to only 14% in the placebo group. Furthermore, improvement in fibrosis was noted in 50%, 45%, and 50% of the participants in the 2.4, 4.8, and 6.0 mg groups, respectively, in contrast to 21% in the placebo group^[56].

The most commonly reported adverse effects were nausea, vomiting, and diarrhea^[56]. Diarrhea was reported in 50% and nausea in 66% of patients on 6.0 mg as compared to 23% for patients in the placebo group.

As shown in a very recent meta-analysis including different studies on incretins and also analyzing Tirzepatide, the risk of cholelithiasis was higher than with anti-diabetic drugs not associated with weight loss, although the difference did not reach statistical significance^[57]. Pancreatitis and intestinal obstruction have also been reported at an increased rate, but the results are not consistent across the studies. Gastroesophageal reflux disease (GERD) has also been reported at a higher rate in patients with MASH and obesity, treated with GLP-1RA, which induces weight loss, potentially as a result of delaying gastric emptying and slowing GI mobility^[57].

Triple GLP-1RA/GIP/glucagon agonist

Retatrutide is a triple GLP-1/GIP/Glucagon receptor agonist evaluated in a 48-week phase 2a international trial involving 98 individuals with MASLD, not MASH. The primary objective of this study was to assess the main relative change from baseline in liver fat, not to study MASH resolution and or fibrosis improvement as in all the previously reported studies. Patients were treated with weekly subcutaneous 1, 4, 8 and 12 mg of Retatrutide^[58]. The study demonstrated significantly greater mean liver fat change as compared to placebo (-42.9%, -57.0%, -81.4% and -82.4%, respectively, *vs.* +0.3). A phase 3 study (NCT05931367) is currently ongoing.

PPAR agonists: lanifibranor

Lanifibranor is a triple peroxisome proliferator-activated receptor (PPAR) agonist, targeting the α , γ , and δ isoforms. PPAR γ agonists can increase lipolysis and modulate lipogenesis and lipoprotein secretion, reducing IR in the adipose tissue, as previously demonstrated by Pioglitazone. PPAR α stimulates β oxidation in various organs, and PPAR δ promotes fatty acid oxidation and increases energy metabolism and energy expenditure, leading to increased insulin sensitivity. All the PPARs reduce inflammation, and PPAR γ is associated with stellate cells inactivation^[59,60].

Lanifibranor improves IR at the liver, muscle and adipose tissue level, reduces intrahepatic TGs in the liver and inflammation, and increases adiponectin. Positive results were attained in a phase 2b NATIVE trial (NCT03008070) that in a 24 weeks course of treatment showed a significant reduction of MASH evaluated by 2 points Steatosis-Activity-Fibrosis score (SAF-score) reduction without worsening of fibrosis (55% and 48% after 1,200 or 800 mg vs. 33% in placebo group) and a significant improvement in fibrosis in the group receiving 1,200 mg (48% vs. 29%). After 24 weeks of treatment, tolerability was good^[61].

At variance with GLP-1RA, Lanifibranor acts as an insulin sensitizer. Indeed, a study conducted by Barb *et al.* included 38 patients with T2DM with good glycemic control, and MASLD treated with Lanifibranor 800 mg daily or placebo for 24 weeks. The primary endpoint was the change in intrahepatic fat quantified by magnetic resonance spectroscopy. Although only 28 individuals completed the study, a remarkable reduction of IR at the liver and muscle levels was demonstrated^[62].

Phase 3 NATIV3 study (NCT04849728) includes 900 patients with F2/F3 fibrosis treated for 72 weeks. Final results are expected in 2026.

In the phase 2 study (NCT03008070), the safety profile of Lanifibranor was favorable^[61]. Diarrhea was reported in 12% and fatigue in 13% of patients treated with 1,200 mg as compared to 1% and 10%, respectively, in the placebo group. A discussed side effect is the modest weight gain (2.5%-3%) in the majority of patients treated^[61].

The increase in body weight is due to the increase in subcutaneous fat mass and may raise the question whether, as for Pioglitazone (PPAR α agonist), the risk of heart failure exists. Interestingly, the interim analysis of the Legend phase 2 study that combines 800 mg Lanifibranor with Empaglifozin showed that no weight gain was observed with this combination, suggesting positive results with this approach. Reduction of visceral adipose fat was also registered in the Empaglifozin/Lanifibranor arm^[62].

FGF21 analogues: efruxifermin

Fibroblast growth factor 21 (FGF21) is an endocrine regulator of glucose and lipid metabolism and of whole-body energy homeostasis, able to increase insulin sensitivity^[63].

FGF21, acting in an autocrine fashion, also reduces cellular stress. It increases mitochondrial capacity, induces antioxidant pathways, and restores proteostasis. In adipose tissue, FGF21 stimulates glucose uptake, suppresses lipolysis in the fed state, and enhances adiponectin secretion^[64].

FGF21 analogs can reduce hepatic steatosis, inflammation, and fibrosis in patients with metabolic-associated diseases, resulting in a possible treatment option for MASH. Efruxifermin is a long-acting Fibroblast Growth Factor 21 (FcFGF21) fusion protein analog^[64-66].

In phase 2a randomized controlled study (NCT 03976401), treatment with Efruxifermin for 12 weeks was associated with a reduction of MRI-derived absolute hepatic fat fraction (HFF) changes from baseline. Fat reduction ranged from 12% to 14% across all doses^[67]. Within MASH patients, all the patients treated with Efruxifermin achieved $\geq 30\%$, and 88% achieved $\geq 50\%$, relative reduction in liver fat. HFF was normalized in 67% of subjects at the highest dose (70 mg). Across all Efruxifermin-treated patients, when an end-of-treatment biopsy was available, a ≥ 2 -point reduction in NAFLD Activity score (NAS) was observed in 85% and a ≥ 2 -point reduction in NAS without worsening of fibrosis, in 78% of cases^[67].

In 16- to 24-week phase 2 trials (NCT 03976401) of patients with Fibrosis stage 1 to 3 (F1 to F3) or cirrhosis, Efruxifermin improved liver fibrosis and resolved MASH^[67]. In particular, in the phase 2b HARMONY study (NCT04767529)^[68], Efruxifermin was evaluated at the doses of 50 or 28 mg subcutaneously in patients with Fibrosis stage 2-3 (F2-F3) fibrosis stage with baseline histological diagnosis and on treatment liver biopsy at weeks 24 and 96. The primary endpoint of the study was at least one stage improvement in fibrosis and no worsening in MASH at week 24; at week 96, the secondary endpoint was not only the improvement of 1 or 2 fibrosis stages, but also resolution of MASH without worsening of fibrosis. Combined MASH resolution and fibrosis improvement represented an additional secondary endpoint. The phase 3 trial SYNCHRONY (NCT06528314) is ongoing.

At the week-24 analysis of this phase 2 study [Table 1], the results failed to demonstrate achievement of the primary endpoint. However, fibrosis improvement of 2 points without worsening of MASH was attained after 96 weeks of treatment. Both dosages were associated with results higher than placebo, 31% and 36% vs. 3%, respectively. In this case, the results were also confirmed by the intention-to-treat analysis. In particular, an extremely relevant result was that participants on 50 mg showed fibrosis improvement in 30% of cases and participants on 28 mg in 8%, in comparison to 0% in the placebo. Fibrosis improved to Fibrosis stage 0-1 (F0 or F1) in combination with MASH resolution and liver fat content normalization^[68].

Recently, results from the phase 2b SIMMETRY study (NCT05039450) in patients with compensated cirrhosis due to MASH, treated for 96 weeks, were presented. MASH resolution was achieved in 55% of patients on 50 mg and in 50% of those on 28 mg vs. 15% on placebo. Cirrhosis reversal was observed in 27% after higher dosages and in 21% after lower dosages vs. 11% on placebo^[69]. This is the first trial showing cirrhosis reversal after treatment. An increase in the number of patients with cirrhosis reversal from week 36 to week 96 was demonstrated. In addition, improvement in Homeostatic Model Assessment (HOMA) IR was demonstrated, suggesting that Efruxifermin has a positive effect on metabolic outcomes.

Treatment-associated adverse events (TEAE) of Efruxifermin were observed in 9% of subjects on placebo as compared to 10% and 16% on the 28 and 50 mg groups. No TEAE leading to death were reported. TEAE leading to discontinuation were 0 in placebo vs. 10% and 12% for subjects receiving 28 and 50 mg, respectively. The most frequently reported drug-related TEAEs were GI with diarrhea in 16% of patients on placebo vs. 40% and 37% in those receiving 28 and 50 mg, respectively. Corresponding rates of nausea were 12% vs. 30% and 33%, and of increased appetite 7% vs. 18% and 33%. While no significant changes in bone mineral density (BMD) were observed at week-24, at week-96 the BMD reduction was statistically significant; its clinical relevance remains to be determined^[68].

Pegozafermin

Pegozafermin is a long-acting glyco-pegylated recombinant FGF21 analog, evaluated in a phase 2b study (ENLIVEN) (NCT 02371369)^[70]. MASH resolution with no worsening of fibrosis was observed in 2% of patients on placebo as compared to 37%, 23%, and 26% of patients on 15, 30 and 44 mg of Pegozafermin,

Table 1. Characteristics of drugs in phase 2/3 of development for MASH/MASLD

Study	Year	Population	Weeks of treatment	Study phase	Intervention	MASH resolution	Fibrosis improvement
NCT 03008070	2021	MASH F2/F3	24	2b	Lanifibranor	49% ^a	48% ^b
SYNERGY-NASH	2024	MASH F2/F3	52	2 (dose finding)	Tirzepatide	62% ^c	51% ^d
NCT 04771273	2024	MASH F2/F3	52	2b	Survodutide	43% ^e	34% ^f
HARMONY	2023	MASH F2/F3	24	2b	Efruxifermin	57%	46%
NCT 04906421	2024	MASH F2/F3	52	2b	Denifanstat	26%	30%
NCT 04881760	2024	MASLD	48	2a	Retatrutide	N/A	N/A
NCT 04880031	2025	MASH	24	2	Efimosfermin	67.7% ^g	45.2% ^h
NCT 04929483	2023	MASH	24	2b	Pegozafermin	26% ⁱ	27% ^j

^{a,b}Using Lanifibranor 1,200 mg; ^{c,d}using Tirzepatide 15 mg; ^{e,f}using Survodutide 6 mg; ^{g,h}using Efimosfermin 300 mg; ^{i,j}using Pegozafermin 44 mg. Percentages of MASH resolution and fibrosis improvements are provided based on the dosages expressly reported. MASH: Metabolic-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; NCT: National Clinical Trial.

respectively. Fibrosis improvement of at least 1 stage was observed in 22%, 26% and 27% of patients receiving 15, 30 and 44 mg, respectively, as compared to 7% in the placebo group. The phase 3 ENLIGHTEN study (NCT06318169) is ongoing. Nausea and diarrhea were the most common adverse events associated with Pegozafermin therapy.

Efimosfermin

Efimosfermin α is a long-acting FGF-21 analog that can be administered once a month. This compound has been evaluated in a phase 2a study (NCT 07221227) on 31 patients receiving active treatment and 34 patients on placebo over 24 weeks^[71]. Efimosfermin α at a dosage of 300 mg has demonstrated improved fibrosis in 45.2% of treated patients, compared with 20.6% of those on placebo ($P = 0.038$). MASH resolution without worsening of fibrosis was observed in 67.7% vs. 29.4% of the placebo group ($P = 0.002$). The most frequent TEAE were GI (nausea, vomiting and diarrhea) in nature, mild to moderate in severity, and resolved spontaneously. GI TEAEs were reported in 46% of participants receiving 300 mg as compared to 49% of patients on placebo.

Denifanstat

Fatty acid synthase (FASN) is a lipogenic enzyme playing a key role in lipogenesis. FASN inhibitor denifanstat reduces liver fat and improves metabolic, inflammatory and pro-fibrotic markers. In a phase 2b trial (NCT4906421), denifanstat achieved improvement of ≥ 1 stage in 41% of patients with MASH F2 or F3 fibrosis stage compared to 18% of placebo-treated patients and led to ≥ 2 points NAS resolution and MASH improvement without worsening of fibrosis compared to placebo^[72].

REIMBURSEMENT

Given the chronic nature of the disease, reimbursement criteria are key aspects of MASH's future treatment. Despite its efficacy, Resmetirom cost will be a major driver of its accessibility and should be adjusted to both epidemiological and economic characteristics of the different countries. If priced within a moderate range, considering the long-term treatment results in reductions of the liver failure rate, Resmetirom will have

widespread adoption. The cost of GLP-1 inhibitors is affordable; however, when a liver-targeted treatment is also needed, a reduction of costs and expenses could be desirable.

IMPROVEMENT IN CARDIOMETABOLIC PARAMETERS

In addition to demonstrating CV safety, GLP-1RAs have shown a protective CV effect^[73].

Compared with placebo, Semaglutide was associated with a statistically significant 13% reduction of non-fatal myocardial infarction, non-fatal stroke and death from CV causes. This was true in patients with T2DM or in obese, overweight patients without T2DM^[74]. For subjects treated with Resmetirom, the CV outcomes need to be demonstrated by the results of the ongoing outcome study, whose results will be available in 2027. Based on evidence of ability to lower LDL-C and other atherogenic lipid and lipoprotein levels even in patients with atherosclerotic coronary vascular disease, such as those with heterozygous familial hypercholesterolemia, an improvement of CV outcomes is not unexpected, also with Resmetirom^[75].

EXPERT CONSIDERATIONS

An upstream systemic metabolic dysfunction causes hepatic lipotoxicity, inflammation and fibrosis in the liver of patients with MASH. Treatment needs to focus on the liver, but also on controlling the metabolic drivers of the disease. Incretins, with their ability to induce weight loss, will play a key role in MASH treatment. However, a few aspects, such as the injectable administration, GI adverse events, adherence issues, and weight regain after discontinuation, may limit their impact. In theory, the role of GLP-1RAs may be more important in the early phase of the disease, but possible integration with drugs targeting liver fibrosis may represent a winning strategy. Looking ahead, combination regimens may provide answers to subgroups of patients with MASH and at-risk fibrosis presenting with T2DM and/or obesity. As shown in MAESTRO-NASH, no additional side effects were reported in patients who had been on stable GLP-1RA doses for at least three months before the start of Resmetirom^[20]. Data on the safety of GLP-1RAs initiated after the start of Resmetirom will be provided by real-world experience generated in the USA, where both Resmetirom and Semaglutide have already been approved for MASH with fibrosis. Other multi-pathway approaches, such as the combination of FG21 and Semaglutide targeting fibrosis and metabolic drivers of MASH, will be explored in the near future. Combination trials are underway, and their results will help in stratifying the risks and selecting patients who would benefit the most from a multiple-targeted approach.

After facing the surprisingly challenging search for treatments of MASLD/MASH since 2014, A substantial number of patients are waiting for single or combined therapies capable of reducing fat accumulation, inflammation, and reversing fibrosis. It is an exciting time for patients with MASH and their physicians, as we are now seeing promising results from more than one agent^[76]. Notably, the side effects of the approved drugs are manageable and not a reason for concern.

DECLARATIONS

Authors' contributions

Conceived the manuscript and critically revised and supervised the final draft: Mangia A

Wrote the first draft: Piazzolla AV

Contributed to the manuscript writing and table and reference preparation: Napolitano A

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by the Italian Ministry of Health, Ricerca Finalizzata PNRR MAD 2022: “Deciphering the Dynamic Interplay between Host Genetics, Redox-Based Epigenetics, and Gut Microbiota in the Pathogenesis of Metabolic-Associated Fatty Liver Disease (DIGEM-MAFLD)” (PNRR-MAD-2022-12375633). Funding was provided in compliance with Mission 6/Component 2/Investment 2.1: “Strengthening and Enhancing Biomedical Research of the SSN,” financed by the European Union - Next Generation EU. CUP: I23C22000890001.

Conflicts of interest

Mangia A reports receiving speaking fees from Gilead Sciences and Madrigal, and consulting fees from Akero, Angelini, Madrigal, Gilead Sciences, and Vertex. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2025.

REFERENCES

1. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274-85. DOI PubMed
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204-22. DOI PubMed PMC
3. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;7:851-61. DOI PubMed
4. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5:245-66. DOI PubMed PMC
5. Lazarus JV, Brennan PN, Mark HE, et al. A call for doubling the diagnostic rate of at-risk metabolic dysfunction-associated steatohepatitis. *Lancet Reg Health Eur*. 2025;54:101320. DOI PubMed PMC
6. Rinella ME, Lazarus JV, Ratzliff V, et al; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79:1542-56. DOI PubMed
7. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;77:1335-47. DOI PubMed PMC
8. Valenti L, Bugianesi E, Pajvani U, Targher G. Non alcoholic fatty liver disease: cause or consequence of type 2 diabetes? *Liver Intern*. 2016; 36:1563-79. DOI PubMed
9. Dongiovanni P, Rametta R, Meloni M, Valenti L. The role of insulin resistance in nonalcoholic steatohepatitis and liver disease development-a potential therapeutic target? *Expert Rev Gastroenterol Hepatol*. 2016;10:229-42. DOI PubMed
10. Mia C, Mahmoud BA, Abdelmalek MF. The liver in diabetes and metabolic syndrome. *Clin Liv Dis*. 2025;29:407-29. DOI PubMed
11. Najjar SM, Perdomo G. Hepatic insulin clearance: mechanism and physiology. *Physiology*. 2019;34:198-215. DOI PubMed PMC
12. Gastaldello A, Cusi K, Pettiti M, et al. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. *Gastroenterology*. 2007;133:496-506. DOI PubMed
13. Park G, Jung S, Wellen KE, Jang C. The interaction between the gut microbiota and dietary carbohydrates in nonalcoholic fatty liver disease. *Exp Mol Med*. 2021;53:809-22. DOI PubMed PMC
14. Mouries J, Brescia P, Silvestri A, et al. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. *J Hepatol*. 2019;71:1216-28. DOI PubMed PMC
15. Puengel T, Tacke F. Pharmacotherapeutic options for metabolic dysfunction-associated steatotic liver disease: where are we today? *Expert Opin Pharmacother*. 2024;25:1249-63. DOI PubMed
16. Administration U. S. FOOD & DRUG. FDA approves first treatment for patients with liver scarring due to fatty liver disease. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty->

- [liver-disease](#). [Last accessed on 22 Dec 2025].
17. Wegovy approved for MASH. *Nat Biotechnol*. 2025;43:1404. [DOI](#)
 18. Yale JF, Major-Pedersen A, Catarig AM, Jain R, Menzen M, Holmes P. Real-world safety profile of once-weekly semaglutide in people with type 2 diabetes: analysis of pooled data from the Semaglutide Real-world Evidence (SURE) programme. *Diabetes Obes Metab*. 2024;26:4429-40. [DOI](#) [PubMed](#)
 19. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. *Metabolites*. 2021;11:73. [DOI](#) [PubMed](#) [PMC](#)
 20. Harrison SA, Bedossa P, Guy CD, et al; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med*. 2024;390:497-509. [DOI](#) [PubMed](#)
 21. Newsome PN, Ambery P. Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver. *J Hepatol*. 2023;79:1557-65. [DOI](#) [PubMed](#)
 22. Sookoian S, Rotman Y, Valenti L. Genetics of metabolic dysfunction-associated steatotic liver disease: the state of the art update. *Clin Gastroenterol Hepatol*. 2024;22:2177-87.e3. [DOI](#) [PubMed](#) [PMC](#)
 23. Raverdy V, Tavaglione F, Chatelain E, et al. Data-driven cluster analysis identifies distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat Med*. 2024;30:3624-33. [DOI](#) [PubMed](#) [PMC](#)
 24. Jamialahmadi O, De Vincentis A, Tavaglione F, et al. Partitioned polygenic risk scores identify distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat Med*. 2024;30:3614-23. [DOI](#) [PubMed](#) [PMC](#)
 25. Gastaldelli A. Insulin resistance and reduced metabolic flexibility: cause or consequence of NAFLD? *Clin Sci*. 2017;131:2701-4. [DOI](#) [PubMed](#)
 26. Dongiovanni P, Stender S, Pietrelli A, et al. Causal relationship of hepatic fat with liver damage and insulin resistance in nonalcoholic fatty liver. *J Intern Med*. 2018;283:356-70. [DOI](#) [PubMed](#) [PMC](#)
 27. Fromenty B, Roden M. Mitochondrial alterations in fatty liver diseases. *J Hepatol*. 2023;78:415-29. [DOI](#) [PubMed](#)
 28. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology*. 2019;70:1913-27. [DOI](#) [PubMed](#)
 29. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology*. 1999;30:1356-62. [DOI](#) [PubMed](#)
 30. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology*. 2020;158:1611-25.e12. [DOI](#) [PubMed](#)
 31. Marino L, Kim A, Ni B, Celi FS. Thyroid hormone action and liver disease, a complex interplay. *Hepatology*. 2025;81:651-69. [DOI](#) [PubMed](#) [PMC](#)
 32. Harrison SA, Taub R, Neff GW, et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med*. 2023;29:2919-28. [DOI](#) [PubMed](#) [PMC](#)
 33. Harrison SA, Bashir MR, Guy CD, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2019;394:2012-24. [DOI](#) [PubMed](#)
 34. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316:1289-97. [DOI](#) [PubMed](#)
 35. National Guideline Centre (UK). Non-alcoholic fatty liver disease: assessment and management. London: National Institute for Health and Care Excellence (NICE); 2016. [PubMed](#)
 36. Loomba R, Neuschwander-Tetri BA, Sanyal A, et al; NASH Clinical Research Network. Multicenter validation of association between decline in MRI-PDFF and histologic response in NASH. *Hepatology*. 2020;72:1219-29. [DOI](#) [PubMed](#) [PMC](#)
 37. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81:492-542. [DOI](#) [PubMed](#)
 38. Nouredin M, Charlton MR, Harrison SA, et al. Expert panel recommendations: practical clinical applications for initiating and monitoring resmetirom in patients with MASH/NASH and moderate to noncirrhotic advanced fibrosis. *Clin Gastroenterol Hepatol*. 2024;22:2367-77. [DOI](#) [PubMed](#)
 39. Loomba R, Neutl J, Bernard D, et al. LBP-20-VK2809, a novel liver-directed thyroid receptor beta agonist, significantly reduces liver fat with both low and high doses in patients with non-alcoholic fatty liver disease: a phase 2 randomized, placebo-controlled trial. *J Hepatol*. 2019;70:e150-1. [DOI](#)
 40. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014;155:1280-90. [DOI](#) [PubMed](#)
 41. Barritt AS 4th, Marshman E, Nouredin M. Review article: role of glucagon-like peptide-1 receptor agonists in non-alcoholic steatohepatitis, obesity and diabetes-what hepatologists need to know. *Aliment Pharmacol Ther*. 2022;55:944-59. [DOI](#) [PubMed](#) [PMC](#)
 42. Armstrong MJ, Hull D, Guo K, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *J Hepatol*. 2016;64:399-408. [DOI](#) [PubMed](#) [PMC](#)
 43. Liuzzo G, Patrono C. Weekly Journal Scan: The ESSENCE of metabolic risk: targeting metabolic dysfunction-associated steatohepatitis with semaglutide. *Eur Heart J*. 2025;46:3505-7. [DOI](#) [PubMed](#)
 44. Armstrong MJ, Gaunt P, Aithal GP, et al; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic

- steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387:679-90. DOI PubMed
45. Newsome PN, Buchholtz K, Cusi K, et al; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2021;384:1113-24. DOI PubMed
46. Sanyal AJ, Newsome PN, Kliers I, et al; ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med*. 2025;392:2089-99. DOI PubMed
47. Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841-51. DOI PubMed
48. Chen VL, Morgan TR, Rotman Y, et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology*. 2025;81:312-20. DOI PubMed
49. Loomba R, Abdelmalek MF, Armstrong MJ, et al; NN9931-4492 investigators. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8:511-22. DOI PubMed PMC
50. Alkhouri N, Charlton M, Gray M, Noureddin M. The pleiotropic effects of glucagon-like peptide-1 receptor agonists in patients with metabolic dysfunction-associated steatohepatitis: a review for gastroenterologists. *Expert Opin Investig Drugs*. 2025;34:169-95. DOI PubMed
51. Qin W, Yang J, Ni Y, et al. Efficacy and safety of once-weekly tirzepatide for weight management compared to placebo: an updated systematic review and meta-analysis including the latest SURMOUNT-2 trial. *Endocrine*. 2024;86:70-84. DOI PubMed PMC
52. Soni H. Peptide-based GLP-1/glucagon co-agonists: a double-edged sword to combat diabetes. *Med Hypotheses*. 2016;95:5-9. DOI PubMed
53. Loomba R, Hartman ML, Lawitz EJ, et al; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med*. 2024;391:299-310. DOI PubMed
54. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet*. 2021;398:583-98. DOI PubMed
55. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol*. 2022;10:393-406. DOI PubMed
56. Parlati L, Régnier M, Guillou H, Postic C. New targets for NAFLD. *JHEP Rep*. 2021;3:100346. DOI PubMed PMC
57. Sanyal AJ, Bedossa P, Fraessdorf M, et al. A phase 2 randomized trial of survodutide in MASH and Fibrosis. *N Engl J Med*. 2024;391:311-9. DOI PubMed
58. Chiang CH, Jaroenlapnopparat A, Colak SC, et al. Glucagon-like peptide-1 receptor agonists and gastrointestinal adverse events: a systematic review and meta-analysis. *Gastroenterology*. 2025;169:1268-81. DOI PubMed
59. Sanyal AJ, Kaplan LM, Frias JP, et al. Triple hormone receptor agonist retetritide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat Med*. 2024;30:2037-48. DOI PubMed PMC
60. Lefere S, Puengel T, Hundertmark J, et al. Differential effects of selective- and pan-PPAR agonists on experimental steatohepatitis and hepatic macrophages^{*}. *J Hepatol*. 2020;73:757-70. DOI PubMed
61. Francque SM, Bedossa P, Ratziu V, et al; NATIVE Study Group. A randomized, controlled trial of the Pan-PPAR agonist lanifibranor in NASH. *N Engl J Med*. 2021;385:1547-58. DOI PubMed
62. Barb D, Kalavalapalli S, Godinez Leiva E, et al. Pan-PPAR agonist lanifibranor improves insulin resistance and hepatic steatosis in patients with T2D and MASLD. *J Hepatol*. 2025;82:979-91. DOI PubMed
63. Pharma Inventiva. Inventiva announces positive results from the Phase II, LEGEND, Proof-of-Concept study combining lanifibranor with empagliflozin in patients with MASH/NASH and T2D. Available from: <https://inventivapharma.com/wp-content/uploads/2024/03/Inventiva-PR-Results-LEGEND-EN-03-18-2024.pdf>. [Last accessed on 12 Dec 2025].
64. Tillman EJ, Rolph T. FGF21: an emerging therapeutic target for non-alcoholic steatohepatitis and related metabolic diseases. *Front Endocrinol*. 2020;11:601290. DOI PubMed PMC
65. Kaufman A, Abuqayyas L, Denney WS, Tillman EJ, Rolph T. AKR-001, an Fc-FGF21 analog, showed sustained pharmacodynamic effects on insulin sensitivity and lipid metabolism in type 2 diabetes patients. *Cell Rep Med*. 2020;1:100057. DOI PubMed PMC
66. Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non- alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat Med*. 2021;27:1262-71. DOI PubMed
67. Harrison SA, Ruane PJ, Freilich B, et al. A randomized, double- blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. *JHEP Rep*. 2023;5:100563. DOI PubMed PMC
68. Harrison SA, Frias JP, Neff G, et al; HARMONY Study Group. Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol*. 2023;8:1080-93. DOI PubMed
69. Noureddin M, Rinella ME, Chalasani NP, et al. Efruxifermin in compensated liver cirrhosis caused by MASH. *N Engl J Med*. 2025;392:2413-24. DOI PubMed
70. Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. *NEJM*. 2023;389:998-1008. DOI PubMed PMC

71. Loomba R, Kowdley KV, Rodriguez J, et al. Efimosfermin alpha (BOS -580), a long-acting FGF21 analogue, in participants with phenotypic metabolic dysfunction-associated steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet Gastroenterol Hepatol*. 2025;10:734-45. DOI PubMed
72. Loomba R, Bedossa P, Grimmer K, et al. Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: a multicentre, double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol*. 2024;9:1090-100. DOI PubMed
73. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut*. 2024;73:691-702. DOI PubMed
74. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221-32. DOI PubMed
75. Hovingh GK, Klausen IC, Heggen E, et al. Resmetirom (MGL-3196) in patients with heterozygous familial hypercholesterolemia. *J Am Coll Cardiol*. 2022;79:1220-2. DOI PubMed
76. Nouredin M. MASH clinical trials and drugs pipeline: an impending tsunami. *Hepatology*. 2025;82:1325-40. DOI PubMed