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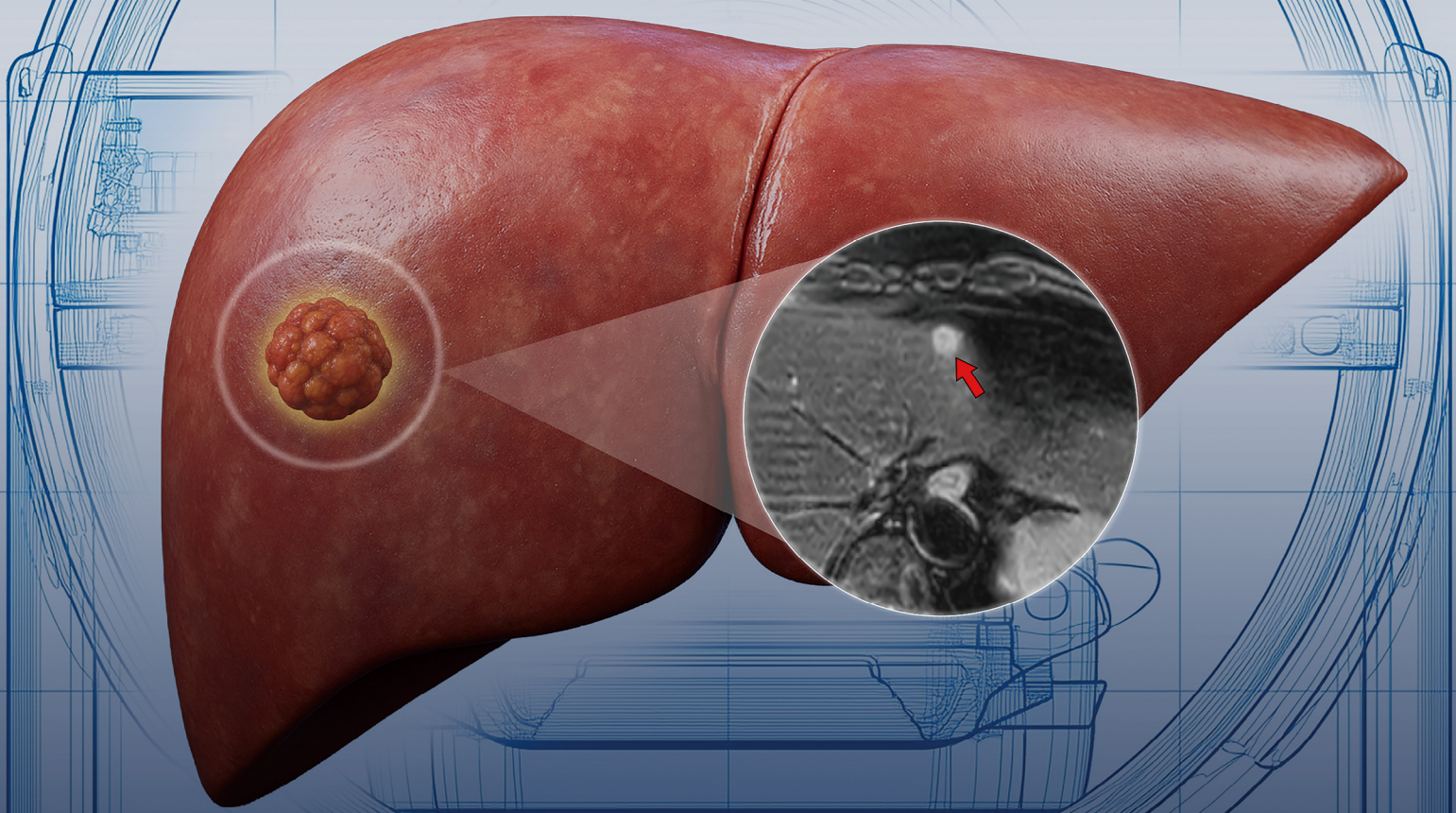

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Review

Prospects of late-stage development agents in the treatment of metabolic dysfunction-associated steatohepatitis

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a spectrum of pathology involving fatty liver disease that may progress to fibrosis, cirrhosis, hepatocellular carcinoma, and liver failure. The prevalence of MASLD and metabolic dysfunction-associated steatohepatitis (MASH) continues to increase, mirroring the rise in global prevalence of related comorbidities such as obesity and type 2 diabetes mellitus. Due to the alarming rise of these comorbidities, a greater proportion of the population is at risk for developing MASLD and MASH. As such, there has been a significant effort to develop effective therapies for MASLD and MASH. Recently, the U.S. Food and Drug Administration approved resmetirom, a selective thyroid hormone receptor-beta agonist, as the first treatment for patients with MASH. In India, the Drug Controller General of India approved saroglitazar, a dual peroxisome proliferator-activated receptor (PPAR) α/γ agonist, for the treatment of MASLD. Currently, we have various drug classes, including liver-specific therapies, in Phase 3 development with even more agents earlier in the pipeline. This review will discuss prospective therapies in later stages of development such as thyroid hormone receptor-beta agonists, PPAR agonists, glucagon-like peptide-1 receptor agonists, fibroblast growth factor 21 agonists, and fatty acid synthase inhibitors. **(Clin Mol Hepatol 2025;31:1167-1196)**

Keywords: MASH; NASH; Drug development in MASH; MASH treatment

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease worldwide, with an estimated prevalence of 30% of the global population.[1] It is linked to obesity and type 2 diabetes mellitus (T2DM), as MASLD is present in up to 70% of patients with T2DM.[2,3] Metabolic-associated steatotic liver begins as fatty liver disease associated with metabolic dysfunction and is defined as the presence of ≥5% hepatic steatosis without evidence of hepatocellular injury.[4] It may progress to metabolic dysfunction-associated steatohepatitis (MASH), characterized by the presence of ≥5% steatosis with lobular inflammation and hepatocellular injury due to accumulation of lipotoxic fat in the liver.[5] This damage can progress to scarring of the liver, called fibrosis. Stages of fibrosis in MASLD according to the nonalcoholic steatohepatitis (NASH) clinical research network (CRN) staging system are defined as: F1 (centrilobular pericellular fibrosis), F2 (centrilobular and periportal fibrosis), F3 (bridging fibrosis),

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and F4 (cirrhosis). Patients with MASH and F2–F4 fibrosis are at an increased risk for liver-related events and mortality and are categorized as at-risk MASH.[6]

Formerly known as nonalcoholic fatty liver disease (NAFLD), the disease's pathophysiology is now better understood, allowing the diagnosis to be changed from one of exclusion to one defined by steatosis in the presence of specific cardiometabolic criteria. Furthermore, due to the global prevalence of MASLD, there was an emphasis on the need for an affirmative and non-stigmatizing name. Therefore, the nomenclature for NAFLD was changed in favor of MASLD, and NASH in favor of MASH. The revised nomenclature addresses the overarching theme of steatotic liver disease and specifically delineates MASLD from other etiologies of steatosis.[7,8]

Globally, MASH is quickly becoming a major player in the realm of chronic liver disease with respect to morbidity and mortality. MASH continues to increase in prevalence and severity, dictating it as one of the major causes of chronic liver disease necessitating liver transplantation. In the U.S., MASH is currently the second leading cause of liver transplantation for males, and the leading cause for females.[9] A single-center cohort study in Turkey found that MASH has become the third leading cause of liver transplantation, following viral and alcohol-associated liver disease.[10] In the Asia-Pacific region, the prevalence of hepatocellular carcinoma (HCC) arising from MASLD is increasing and is expected to continue growing rapidly in the near future.[11] One study showed that in a hepatitis B-endemic area of South Korea, the proportion of MASLD-related HCC increased while HCC from prior or current hepatitis B infection decreased.[12] According to a 2019 study out of Yonsei University in South Korea, although Hepatitis B remains the globally predominant cause of liver cancer-related disease-adjusted life years and mortality, rates associated with MASLD/MASH have increased.[13]

While liver biopsy is the gold standard for disease staging, its limitations include invasiveness, sampling errors, and intra- and inter-observer variability. The two main non-invasive tests (NITs) are image-based elastography and serum biomarkers. Image-based elastography measures liver stiffness via vibration-controlled transient elastography (VCTE), shear wave ultrasound elastography, or magnetic resonance elastography.[14] Image-based elastography can also measure liver steatosis via transient elastography-based controlled attenuation parameter (CAP) and magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF). The FibroScan-aspartate transaminase (FAST) score is a score developed using VCTE-acquired measurements of liver stiffness and CAP as well as serum AST.[15] Serum biomarkers have been validated and are often used due to their easy accessibility.[14] Such biomarker tests include the fibrosis-4 (FIB-4) index and the enhanced liver fibrosis (ELF) score.[16,17] FIB-4 can easily be calculated using an algorithm based on age, alanine transaminase (ALT), AST and platelet count while ELF is a proprietary blood test that must be ordered. Several societies have issued recommendations on how to screen and stage patients for MASLD/MASH with many recommending FIB-4 as the screening tool followed by FibroScan and/or ELF for those indeterminate.[6,18,19] In September 2024, the Korean Association for the Study of the Liver (KASL) published clinical practice guidelines recommending NITs for initial assessment and monitoring of liver fibrosis in patients with chronic liver disease.[20] The choice of NIT should consider factors such as disease etiology, patient comorbidities, and availability of testing; for patients with MASLD, these guidelines suggested the FIB-4 as the first-line screening tool, with VCTE and magnetic resonance elastography for those with indeterminate FIB-4 results.[20] The other societies do not give specific guidance on the order of use of non-invasive modalities and leave the decision to the clinician.[21]

Initial management for MASLD includes abstinence from alcohol, vaccination for hepatitis A and B viruses, and risk factor modification for cardiovascular disease.[22-24] Treating obesity and T2DM is crucial for managing MASH, as these

Abbreviations:

ACC, acetyl-coenzyme A carboxylase; AI, artificial intelligence; CAP, controlled attenuation parameter; CRN, clinical research network; DALYs, disease-adjusted life years; ELF, enhanced liver fibrosis; EOD, every other day; FASN, fatty acid synthase; FAST, FibroScan-AST; Fc, fragment crystallizable; FDA, U.S. Food and Drug Administration; FGF21, fibroblast growth factor 21; FIB-4, fibrosis-4 index; FXR, farnesoid X receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HCC, hepatocellular carcinoma; KASL, Korean Association for the Study of the Liver; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NITs, non-invasive tests; PPAR, peroxisome proliferator-activated receptor; T2DM, type 2 diabetes mellitus; THR-β, thyroid hormone receptor-β; TZD, thiazolidinedione; VCTE, vibration-controlled transient elastography

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conditions drive hepatic inflammation and fat accumulation. Weight loss is the cornerstone of management for the majority of patients with MASLD.[25-28] Weight loss of ≥5% is associated with improvement in NAFLD activity score (NAS), whereas weight loss of ≥10% is associated with improvement in NAS, resolution of MASH, and regression of fibrosis.[28] Pharmacologic therapy can be used for weight loss in patients who are unable to achieve adequate weight loss with lifestyle modifications alone.

Given the largely unmet need for a treatment of MASH, the U.S. Food and Drug Administration (FDA) presented an accelerated pathway for drug approval in January 2021.[29,30] This pathway requires that sponsors demonstrate biopsy-defined histologic improvement in an at-risk MASH population or reduction of major adverse liver outcomes in a MASH population with compensated cirrhosis. Specifically, the FDA identified efficacy endpoints to support accelerated approval for at-risk MASH: (1) resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score, or (2) at least one stage improvement in liver fibrosis and no worsening of steatohepatitis, or (3) both resolution of steatohepatitis and improvement in fibrosis. Biopsy-defined histologic improvement is likely predictive of improved clinical outcomes for at-risk MASH (F2–F3). For compensated MASH cirrhosis (F4), improved clinical outcomes would be necessary for approval. If sponsors are able to demonstrate efficacy and safety via separate Phase 3 trials, they should be able to obtain approval for treatment of MASH with F2–F4 fibrosis.[5,30,31]

This review will discuss the pipeline of emerging pharmacologic therapies for MASLD/MASH that are currently in later stage clinical development. Table 1 summarizes the efficacy and safety and Table 2 addresses the mechanism of action of late-stage development agents currently being studied.

THERAPIES FOR MASH IN LATE-STAGE CLINICAL DEVELOPMENT

Thyroid hormone receptor-β agonists

Hypothyroidism, specifically intrahepatic hypothyroidism, was seen to drive lipotoxicity in preclinical models.[32] In humans, hypothyroidism and subclinical hypothyroidism have shown an association with MASH.[33,34] Thyroid hormones can stimulate metabolic activity via liver fatty acid β-oxidation and excretion of cholesterol and phospholipids into bile.[5] Impairment of thyroid hormone receptor-β (THR-β) function in humans, as seen in MASH, leads to reduced β-oxidation of fatty acids and ultimately lipotoxicity causing increased fibrosis.[32,35] THR-β agonists can therefore stimulate increased oxidation of fatty acids, resulting in a decreased lipotoxicity burden.[32] Selecting for hepatic THR-βs stimulates beneficial hepatic metabolic processes without cardiac side effects that are typically induced by THR-α.[5]

Resmetirom is an oral liver-specific, selective THR-β agonist. The MAESTRO-NASH trial (NCT03900429) recruited subjects with biopsy-proven F1b-F3 fibrosis across the USA, Australia, Europe, Canada, Israel, Mexico, and Puerto Rico.[36] Subjects were adults (≥18 years of age) with at least three of five cardiometabolic criteria for metabolic syndrome, CAP of >280 dB/m, and a liver-stiffness measurement of ≥8.5 kPa as assessed by prescreening VCTE.[35] Additional key inclusion criteria were biopsy-defined histologic evidence of MASH based on a NAS of 4 or more, with a score of 1 or more in each of the components (steatosis grade, lobular inflammation, liver cell injury).[35] Subjects were randomly assigned to resmetirom 80 mg, 100 mg, or placebo daily. There were two primary endpoints measured at 52 weeks: (1) resolution of MASH (measured as a reduction of the NAS by ≥2 points) with no worsening of fibrosis and (2) reduction of fibrosis by at least one stage with no worsening of the NAS.[35] MASH resolution with no worsening of fibrosis was achieved by 25.9% of subjects in the 80 mg resmetirom arm, and 29.9% of subjects in the 100 mg resmetirom arm, compared with 9.7% of subjects in the placebo arm.[35] Reduction of fibrosis by at least one stage with no worsening of the NAS was seen by 24.2% of subjects in the 80 mg arm and 25.9% of subjects in the 100 mg arm, compared with 14.2% of subjects in the placebo arm.[35] The most frequent adverse events reported in this study were diarrhea and nausea. Serious adverse events were similar across the 80 mg, 100 mg, and placebo arms at 10.9%, 12.7%, and 11.5%, respectively.[35] In the 80 mg treatment arm, the most common serious adverse events were infections including coronavirus disease 2019 (COVID-19), musculoskeletal and connective tissue disorders. In the 100 mg arm, the most com-

mon serious adverse events were classified as injury, poisoning, and procedural complications. In the placebo group, the most common serious adverse events were infections including COVID-19, gastrointestinal disorders, and cardiac disorders.[35] Serious adverse events considered by investigators to be related to the trial regimen occurred in two subjects in the 80 mg treatment arm and one in the placebo arm.[35] Minor weight reductions were noted in all treatment arms with no significant difference between arms.[35] In March 2024, the U.S. FDA approved resmetirom as the first treatment for patients with MASH with moderate-to-advanced liver fibrosis (F2 to F3 fibrosis) under the accelerated approval pathway. MAESTRO-NASH remains ongoing and is capturing long-term clinical outcomes data. Concurrently, there is a second outcomes trial, MAESTRO-NASH-OUTCOMES (NCT05500222), in subjects with well-compensated MASH cirrhosis and it is evaluating progression to liver decompensation events with resmetirom versus placebo.[37,38]

VK2809, another oral THR-β agonist, recently completed the Phase 2b VOYAGE study (NCT04173065) in subjects with at least 8% liver fat, as measured by MRI-PDFF, and biopsy-proven F1–F3 fibrosis.[39] The study successfully achieved the primary endpoint by demonstrating statistically significant reductions of liver fat content compared with placebo.[40,41] In the treatment arms receiving 5 mg and 10 mg every other day (EOD), VK2809 demonstrated statistically significant improvements in MASH resolution in 63% (P=0.009) and 75% (P<0.0001), respectively, compared with 29% for placebo.[41,42] In all treatment cohorts, 44% of patients treated with VK2809 experienced resolution of MASH and ≥1 point reduction in fibrosis (P<0.01) compared with 19.5% for placebo.[41] At 52 weeks, 75% of subjects treated with 10 mg VK2809 EOD achieved resolution of NASH with no worsening of fibrosis compared with 29% for placebo (P<0.0001).[41] Additionally, 56.8% of subjects treated with 10 mg VK2809 EOD demonstrated >1 stage fibrosis improvement with no worsening of NASH compared with 34.1% for placebo (P<0.0497).[41] Subjects treated with VK2809 experienced significant reductions in plasma lipids after 52 weeks, thus suggesting that therapy can reduce cardiovascular risk in patients with MASH fibrosis.[41] VK 2809 was well-tolerated over the 52-week treatment phase. Treatment-emergent adverse events were comparable between subjects in the treatment (29%) and placebo (34%) groups.[41] The majority (94%) of treatment related adverse events among subjects receiving VK2809 were reported as mild or moderate, with rates of nausea, diarrhea, stool frequency, and vomiting that were similar among treatment arms and placebo.[43] Furthermore, VK2809 demonstrated excellent GI tolerability, with rates of nausea, vomiting, diarrhea, and stool frequency that were similar among treated subjects and placebo.[43] Phase 3 development is currently being planned.

Peroxisome proliferator-activated receptor agonists

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that are activated by dietary fatty acids and act to regulate gene expression of lipid metabolism, energy balance, inflammation, and atherosclerosis.[44-46] There are three PPAR subtypes (PPAR-α, PPAR-β/δ, and PPAR-γ) that regulate different pathways involved in the development of MASLD (Fig. 1).[45] PPAR-α, primarily expressed in the liver and brown adipose tissue, modulates genes involved in fatty acid transport, activation, and oxidation, thereby increasing hepatic degradation of fatty acids.[44] PPAR-α agonists such as fibrates, are used to treat hypertriglyceridemia.[47] PPAR-β/δ, expressed ubiquitously, modulates expression of genes involved in thermogenesis, and its activation stimulates fatty acid oxidation and reduces lipogenesis, thereby improving hepatic steatosis.[44] PPAR-γ, expressed in adipose tissue and macrophages, promotes adipogenesis and storage of lipids.[46,48] PPAR-γ agonists, such as the thiazolidinedione (TZD) class, are used for treatment of type 2 diabetes.[47] Activation of PPAR-α and PPAR-β/δ enhances fatty acid metabolism, reduces triglyceride levels and increases high-density lipoprotein (HDL), while activation of PPAR-γ increases insulin sensitivity and reduces fibrosis.[44,49] Dual- and pan-PPAR agonists are expected to be more efficacious in MASLD/MASH treatment than subtype-specific PPAR agonists.[47]

Lanifibranor is an oral pan-PPAR (PPAR-α, PPAR-β/δ, and PPAR-γ) agonist. The Phase 2b NATIVE trial (NCT03008070) achieved its primary endpoint of decreasing, by at least 2 points, the activity portion of the steatosis activity fibrosis (SAF) score[50] without worsening fibrosis.[51,52] Most (94%) of the study participants in the NATIVE study were White, consistent with the location of study site (U.S.,

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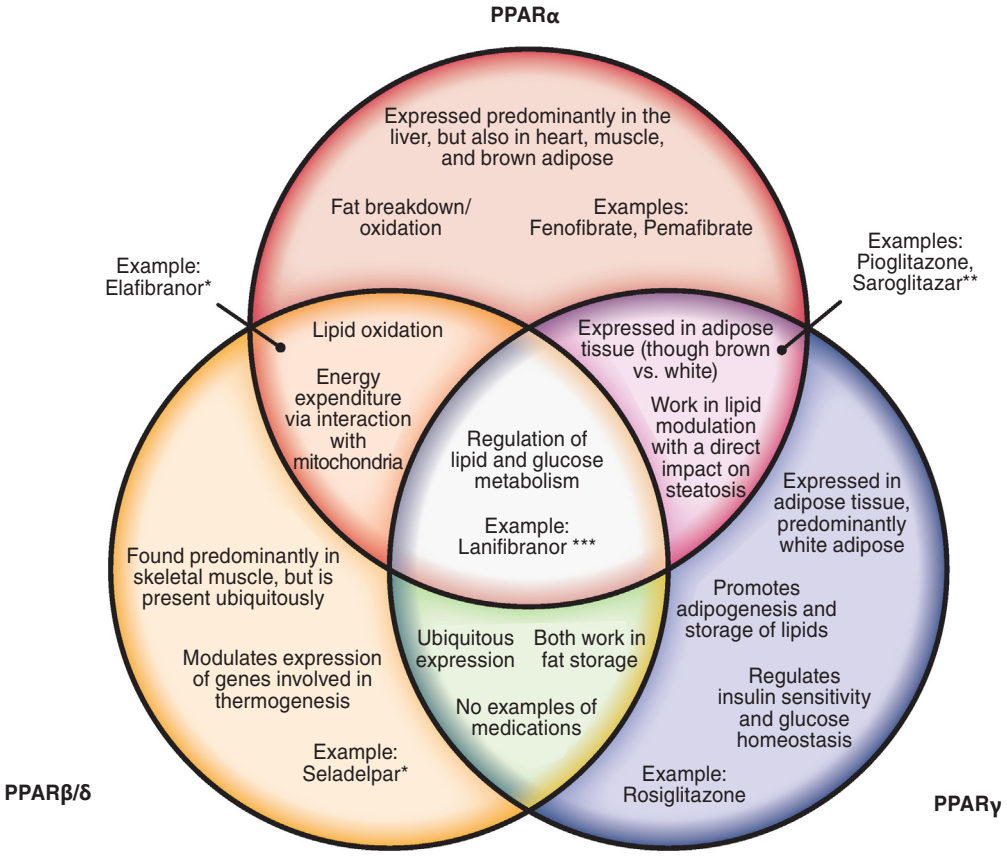

Figure 1. *No longer investigated for MASLD/MASH, but currently second line for PBC. **Approved for MASLD/MASH treatment in India. ***Currently undergoing Phase 3 (NATiV3). MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor

Canada, Australia, Europe, and Mauritius).[51] Subjects were adults with noncirrhotic MASH based on a SAF scoring, of whom 42% had T2DM and a mean body mass index (BMI) of 33 kg/m^2, and 33.6% had significant or advanced fibrosis.[51] Subjects were randomized into one of three treatment arms: 800 mg lanifibranor, 1,200 mg lanifibranor, or placebo. The percentage of subjects that achieved the primary endpoint (a decrease of at least 2 points in the activity part of the SAF score without worsening of fibrosis) was significantly higher in the treatment arms compared with the placebo arm; 48% of the 800 mg arm, 55% of the 1,200 mg arm, and 33% of the placebo arm.[51] Additionally, many secondary endpoints were achieved as well. Resolution of MASH without worsening of fibrosis was seen in 39% of subjects in the 800 mg arm and 49% of subjects in the 1,200 mg arm, compared to 22% of subjects in the placebo arm. Improvement of fibrosis without worsening of MASH was seen in 34%, 48%, and 29% of subjects in the 800 mg, 1,200 mg, and placebo arms, respectively.[51] Resolution of MASH with improvement in fibrosis was seen in 25% and 35% of subjects in the 800 mg and 1,200 mg treatment arms, respectively, compared to 9% in the placebo group.[51] The adverse events reported more frequently with lanifibranor compared with placebo were nausea, diarrhea, peripheral edema, anemia, and weight gain. Most adverse events were mild or moderate in severity.[51] At week 24, lanifibranor was associated with a mean increase of body weight from baseline of 2.6% in the 800 mg arm and 3.1% in the 1,200 mg arm compared with a mean decrease of body weight from baseline of 0.2% in the placebo arm.[51] An ongoing Phase 3 trial, NATiV3 (NCT04849728), is evaluating efficacy and safety of lanifibranor in subjects with F2–F3 stages of fibrosis.[53]

Saroglitazar is an oral dual-PPAR agonist with activity on the PPAR-α and PPAR-γ subtypes. EVIDENCES II (CTRI/2015/10/006236) and EVIDENCES IV (NCT03061721) are

completed Phase 3 and Phase 2 studies, respectively, that demonstrated efficacy and safety in subjects with MASLD.[54-58] The Phase 3 study EVIDENCES II was conducted at 10 sites in India to determine efficacy and safety of saroglitazar 4 mg compared with placebo in subjects with biopsy proven MASH with fibrosis stages F1–F3 and a NAS of ≥4 with a score of at least 1 in each component.[59] The primary endpoint was histological improvement of NASH. This was achieved, as there was a significantly higher proportion of subjects with a decrease of ≥2 in NAS among at least 2 of the NAS components without worsening fibrosis.[54] Most adverse events were mild and moderate. The most commonly reported adverse events were flatulence, dyspepsia, and abdominal pain.[59] Saroglitazar appears to be weight neutral, although there was some minor weight loss in both saroglitazar and placebo arms.[59] EVIDENCES IV was a randomized controlled double-blind Phase 2 study that demonstrated that saroglitazar significantly improved liver enzymes, liver fat content, insulin resistance, and atherogenic dyslipidemia in subjects with MASLD/MASH.[57] The study enrolled subjects across 20 U.S. sites. Inclusion criteria were adults 18–75 years of age, BMI of at least 25 kg/m^2, and imaging-proven MASLD or biopsy-proven MASH.[57] The primary efficacy endpoint measured percentage change in serum ALT at week 16 compared to baseline. This was achieved in all treatment arms (saroglitazar 1 mg, 2 mg, and 4 mg), with ALT reduction ranging from –25.5% to –45.8% compared with 3.4% in the placebo arm.[57] The most frequently reported adverse events related to treatment in the saroglitazar treatment arms were diarrhea, cough, abdominal pain, and bronchitis. Notably, saroglitazar was approved for treatment of MASH by the Drug Controller General of India in March 2024. It is currently undergoing further development in India under the EVIDENCES XI (NCT05872269) trial to assess safety and efficacy in subjects with MASLD and comorbidities. EVIDENCES X (NCT05011305) is an ongoing Phase 2b study evaluating efficacy and safety in subjects with MASH. The study is enrolling subjects in U.S., Argentina and Turkey.

Pioglitazone is an oral TZD therapy approved in many countries for the treatment of T2DM. It acts as a selective PPAR-γ agonist. The PIVENS trial (NCT00063622) evaluated efficacy and safety of pioglitazone compared with vitamin E and placebo in non-diabetic subjects, with the primary outcome defined as an improvement of histologic findings as measured by the NAS without worsening fibrosis.[60,61] While vitamin E was associated with significantly greater improvement of MASH, pioglitazone did not reach the primary endpoint.[60] Pioglitazone did demonstrate an improvement in insulin resistance; however, it was also associated with significant weight gain.[60] The AIM 2 trial (NCT04501406) is an ongoing Phase 2a trial evaluating pioglitazone in adults with T2DM and biopsy-confirmed MASH. While the accepted dose of pioglitazone for the treatment of T2M is 30 mg to 40 mg daily, this study aims to evaluate the efficacy of pioglitazone 15 mg daily on liver histology compared with placebo.[62] In another Phase 2 trial (NCT01068444), pioglitazone therapy for 24 weeks improved steatosis by 46.7% compared to 11.1% with placebo in an Asian population with biopsy-proven MASH.[63,64] This study, conducted in Taiwan, evaluated 90 subjects with fibrosis ranging from F0 to F4, of whom 23% had T2DM.[63] At the current time, the ongoing pioglitazone studies are smaller, investigator-initiated studies and not designed for health authority approval.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced by L-cells of the small and large intestines.[65,66] Ingestion of nutrients stimulates the secretion of GLP-1 which binds to GLP-1 receptors expressed in various tissues, such as pancreatic beta cells, pancreatic ducts, kidney, lung, heart, skin, immune cells, and central nervous cells.[65,66] In the pancreas, GLP-1 stimulates insulin secretion by beta cells and downregulates glucagon secretion by alpha cells. Furthermore, GLP-1 acts on the central nervous system at the level of the hypothalamus and brainstem to reduce food intake and body weight.[65] As the liver lacks GLP-1 receptor expression, the effect of GLP-1 agonists on MASH is likely related to indirect, extrahepatic beneficial effects on weight and insulin resistance, as well as reductions in metabolic dysfunction, lipotoxic effects, and inflammation.[65,67] Currently, GLP-1 receptor agonists are approved in many countries for the treatment of T2DM and obesity. This drug class has garnered significant attention due to its strong ability to decrease weight and improve cardiovascular outcomes.

Semaglutide is a GLP-1 receptor agonist approved for treatment of both T2DM and obesity in numerous countries

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Table 1. Primary efficacy and key safety results for agents in later stage development for MASH

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Resmetirom	Thyroid hormone receptor-β (THR-β) agonist	Oral	MAESTRO-NASH (NCT03900429)[35,36]	n=966	80 mg daily, 100 mg daily	MASH resolution (achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the nonalcoholic fatty liver disease activity score (NAS) by ≥2 points) with no worsening of fibrosis • 25.9% (80 mg) [*P*<0.001] • 29.9% (100 mg) [*P*<0.001] • 9.7% placebo	F1B–F3	38.5% of the 80 mg and 41.5% of the 100 mg treatment groups experienced ≥1 adverse event attributed to resmetirom, compared with 27.4% attributed to placebo. Most frequent adverse events were gastrointestinal (diarrhea: 27% in 80 mg and 33.4% in 100 mg treatment groups, 15.6% placebo; nausea: 22.0% in 80 mg and 18.9% in 100 mg treatment groups, 12.5% in placebo). 0.6% of the 80 mg and 0% of the 100 mg treatment groups experienced ≥1 serious adverse event attributed to resmetirom, compared with 0.3% attributed to placebo.
			MAESTRO-NASH-OUTCOMES (NCT05500222)[37]	n=700*	80 mg daily	Improvement (reduction) in fibrosis by at least one stage with no worsening of the NAS • 24.2% (80 mg) [*P*<0.001] • 25.9% (100 mg) [*P*<0.001] • 14.2% placebo Any event of all-cause mortality, liver transplant, ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage, and confirmed increase of MELD score from <12 to ≥ 15 due to liver disease	F4 (cirrhosis)	

Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
VK2809	THR-β agonist	Oral	VOYAGE (NCT04173065)[39,41]	n=248†	1 mg daily, 2.5 mg daily, 5 mg EOD, 10 mg EOD	Relative change in liver fat content (assessed by MRI-PDFF) from baseline to week 12 in subjects treated with VK2809 compared to the change in subjects treated with placebo. • –37.5% (1 mg daily) [*P*=0.082] • –48.1% (2.5 mg daily) [*P*<0.0001] • –42.5% (5 mg EOD) [*P*<0.0001] • –55.1% (10 mg EOD) [*P*<0.0001] • –5.4% placebo Resolution of MASH (assessed by biopsy) with no worsening of fibrosis at 52 weeks • 71.4% (1 mg daily) [*P*<0.05] • 65.4% (2.5 mg daily) [*P*<0.01] • 63.0% (5 mg EOD) [*P*<0.01] • 75.0% (10 mg EOD) [*P*<0.001]	F1–F3	94% of treatment related adverse events among patients receiving VK2809 were reported as mild or moderate. Rates of nausea, diarrhea, stool frequency, and vomiting were similar between VK2809-treated and placebo-treated groups.

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Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Lanifibranor	Peroxisome proliferator-activated receptor (PPAR) agonist	Oral	NATIVE (NCT03008070)[51,52]	n=247	800 mg daily, 1,200 mg daily	Decrease of at least 2 points in the steatosis activity fibrosis activity (SAF-A) with no worsening of the clinical research network fibrosis Score (CRN-F) at week 24 • 48% (800 mg) [*P*=0.07] • 55% (1,200 mg) [*P*=0.007] • 33% placebo	F2–F3	30% of the 800 mg and 28% of the 1,200 mg treatment groups experienced ≥1 adverse event attributed to lanifibranor, compared with 23% attributed to placebo.
			NATiV3 (NCT04849728)[53]	n=1,000*	800 mg daily, 1,200 mg daily	Resolution of MASH and improvement of fibrosis at week 72, defined by NASH CRN scores for ballooning of 0 and inflammation of 0 to 1, and fibrosis score ≥1 stage decrease compared to baseline.	F2–F3	The most frequent adverse events were diarrhea (10% 800 mg group, 12% 1,200 mg group, 1% placebo), fatigue (4% 800 mg group, 13% 1,200 mg group, 10% placebo), nausea (10% 800 mg group, 8% 1,200 mg group, 4% placebo), and weight gain (10% 800 mg group, 8% 1,200 mg group, and 0% placebo). No subjects in the 800 mg or 1,200 mg treatment groups experienced serious adverse events related to lanifibranor, compared with 2% attributed to placebo.

Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Saroglitazar	PPAR agonist	Oral	EVIDENCES II (CTRI/2015/10/006236)[54,55]	n=102	4 mg daily	Histological improvement of MASH without worsening of fibrosis • 52.3% (4 mg) [*P*=0.0427] • 23.5% placebo	F1–F3	Majority of adverse events were mild (38.2% in the treatment group and 32.4% in placebo) or moderate (14.7% in the treatment group and 17.6% in placebo). The most common reported treatment emergent adverse events were flatulence (7.4% treatment group, 17.6% placebo), dyspepsia (8.8% treatment group, <5.9% placebo), and abdominal pain (7.4% treatment group, 14.7% placebo).
			EVIDENCES IV (NCT030-61721)[56,57]	n=106	1 mg daily, 2 mg daily, 4 mg daily	Percentage change from baseline in serum ALT levels at week 16 in the saroglitazar groups as compared to the placebo group • –25.5% (1 mg) [*P*<0.001] • –27.7% (2 mg) [*P*<0.001] • –45.8% (4 mg) [*P*<0.001] • 3.4% placebo	N/A	No serious adverse events were attributed to saroglitazar treatment. Adverse events related to study drug were reported in 15.4% subjects in 1 mg group, 8.0% subjects in the 2 mg group, and 32.1% subjects in the placebo group.
			EVIDENCES X (NCT050-11305)	n= 240*	2 mg daily, 4 mg daily	Resolution of steatohepatitis with no worsening of fibrosis at week 52	F2–F3	The most frequently reported adverse events related to treatment in the treatment groups were diarrhea (3 subjects), cough (3 subjects), abdominal pain (2 subjects) and bronchitis (2 subjects). No severe adverse events were considered related to treatment.

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Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Pioglitazone	PPAR agonist	Oral	PIVENS (NCT00063622)[60,61]	n=247	30 mg daily	Improvement in NAS defined by change in standardized scoring of liver biopsies at baseline and after 96 weeks of treatment • 34% (30 mg) [*P*=0.04] • 43% (vitamin E 800 IU) [*P*<0.001] • 19% placebo	N/A	Hypoglycemia was noted in 18.8% of subjects in the pioglitazone group, compared to 9.6% in the vitamin E group and 9.5% in the placebo group. 4.7% of subjects in the vitamin E group experienced new-onset diabetes compared to 0% in the pioglitazone and placebo groups.
			AIM 2 (NCT04501406)[62]	n=166*	15 mg daily	The proportion of pioglitazone-treated patients relative to placebo achieving an improvement of ≥2 points in NAS without an increase in fibrosis stage at week 72.	F1–F3	3.8% of subjects in the pioglitazone group experienced weight gain ≥20% from baseline in the pioglitazone group compared with 0% in the vitamin E and placebo groups. There were 19 severe adverse events (2 in the pioglitazone group, 7 in the vitamin E group, and 10 in the placebo group).

Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Semaglutide	Glucagon-like peptide-1 (GLP-1) receptor agonist	SC injection	ESSENCE (NCT04822181)[68-70]	n=800	2.4 mg weekly	Resolution of steatohepatitis and no worsening of liver fibrosis • 62.9% (2.4 mg) (95% CI 21.1–36.2, *P*<0.001) • 34.3% placebo Improvement in liver fibrosis and no worsening of steatohepatitis • 36.8% (2.4 mg) (95% CI 7.5–21.3, *P*<0.001) • 22.4% placebo	F2–F3	Adverse events were seen in 86.3% of the treatment group compared with 79.7% of the placebo group. Serious adverse events were present in 13.4% of both the treatment and placebo groups. Adverse events leading to trial discontinuation were present in 2.6% of the treatment group compared with 3.3% of the placebo group. Most common adverse events in the treatment group were nausea (36.3%), diarrhea (26.9%), and constipation (18.6%). The most common adverse events in the placebo group (excluding COVID-19) were nausea (13.2%), diarrhea (12.2%), and constipation (8.4%).

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Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Survodutide	Glucagon and GLP-1 receptor dual agonist	SC injection	(NCT04771273, EudraCT 2020-002723-11)[74-76]	n=293	2.4 mg weekly, 4.8 mg weekly, 6.0 mg weekly	Percentage of patients with histological improvement of MASH (NAS reduction of 2 or more points) with no worsening of fibrosis after 48 weeks of treatment • 47% (2.4 mg) [+] • 62% (4.8 mg) [+] • 43% (6.0 mg) [+] • 14% placebo [+] [*P*<0.001 for the quadratic dose-response curve as best-fitting model]	F1–F3	The most common adverse events were nausea (63% of 2.4 mg group, 68% of 4.8 mg group, 66% of 6 mg group, and 23% of placebo), diarrhea (41% of 2.4 mg group, 56% of 4.8 mg group, 50% of 6 mg group, and 23% of placebo), vomiting (37% of 2.4 mg group, 46% of 4.8 mg group, 50% of 6 mg group, and 4% of placebo), and constipation (21% of 2.4 mg group, 17% of 4.8 mg group, 26% of 6 mg group, and 15% of placebo). Adverse events considered related to treatment or placebo were seen in 82% of the 2.4 mg group, 82% of the 4.8 mg group, 81% of the 6 mg group, and 49% in placebo. Serious adverse events considered related to treatment or placebo were seen in 1% of the 2.4 mg group and 0% in the 4.8 mg treatment group, 6 mg treatment group, and placebo.

Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Tirzepatide	Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor dual agonist	SC Injection	SYNERGY-NASH (NCT04166773)[77,78]	n=190	5 mg weekly, 10 mg weekly, 15 mg weekly	Resolution of MASH without worsening of fibrosis at 52 weeks • 44% (5 mg) [*P*<0.001] • 56% (10 mg) [*P*<0.001] • 62% (15 mg) [*P*<0.001] • 10% placebo At least one stage improvement in fibrosis without worsening of MASH (secondary endpoint) • 55% (5 mg) [95% CI 5–46] • 51% (10 mg) [95% CI 1–42] • 51% (15 mg) [95% CI 1–42] • 30% placebo	F2–F3	Adverse events were noted in 91% of the 5 mg group, 94% of the 10 mg group, 92% of the 15 mg group, and 83% of the placebo group. The most common adverse events were nausea (36% of the 5 mg group, 34% of the 10 mg group, 44% of the 15 mg group, and 12% of placebo), diarrhea (32% of the 5 mg group, 36% of the 10 mg group, 27% of the 15 mg group, and 23% of placebo), decreased appetite (19% of the 5 mg group, 21% of the 10 mg group, 23% of the 15 mg group, and 2% of placebo), and constipation (23% of the 5 mg group, 19% of the 10 mg group, 15% of the 15 mg group, and 6% of placebo). Serious adverse events were seen in 11% of the 5 mg group, 9% of the 10 mg group, 0% of the 15 mg group, and 6% of the placebo group.

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Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Efruxifermin	Fibroblast growth factor 21 (FGF21) agonists	SC injection	HARMONY (NCT04767529)[82,86]	n=128	28 mg weekly, 50 mg weekly	Improvement in fibrosis of at least 1 stage and no worsening of MASH, based on analyses of baseline and week 24 biopsies • 39% (28 mg) [*P*=0.025] • 41% (50 mg) [*P*=0.036] • 20% placebo	F2–F3	Treatment- or placebo-related adverse events were noted in 75% of the 28 mg group, 81% of the 50 mg group, and 49% of placebo. The most common adverse events were diarrhea (40% of the 28 mg group, 40% of the 50 mg group, and 19% of placebo), nausea (28% of the 28 mg group, 42% of the 50 mg group, 23% of placebo), injection site erythema (20% of the 28 mg group, 20% of the 50 mg group, and 19% of placebo), and increased appetite (20% of the 28 mg group, 23% of the 50 mg group, and 5% of placebo).
			SYNCHRONY histology (NCT06215716, CTRI/2023/11/060385)[91,92]	n=1,000*	28 mg weekly, 50 mg weekly	Resolution of MASH and a ≥1 stage improvement in fibrosis	F2–F3	
			SYNCHRONY Real-World (NCT06161571, CTRI/2024/01/061246)[93,94]	n=700*	50 mg weekly	Extent of exposure, number of participants with adverse events, number of participants with adverse events by severity, and number of participants with clinically significant changes in clinical assessments at 52 weeks	F2–F3	
			SYMMETRY (NCT05039450)[87]	n=200*	28 mg weekly, 50 mg weekly	Proportion of patients with ≥1 stage improvement in fibrosis (per NASH CRN score) from baseline with no worsening steatohepatitis at 36 weeks	F4 (cirrhosis)	Four total treatment-emergent serious adverse events arose in the 50 mg treatment group (9%), of which one, ulcerative esophagitis, was considered therapy-related (2%). No serious adverse events were noted in the other treatment groups or placebo group.

Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Pegozafermin	FGF21 agonists	SC injection	ENLIVEN (NCT04929483)[95,96]	n=222	15 mg weekly, 30 mg weekly, 44 mg EOW	Improvement of fibrosis staging by 1 or more with no worsening of MASH • 22% (15 mg) [95% CI −9 to 38] • 26% (30 mg) [*P*=0.009] • 27% (44 mg every 2 weeks) [*P*=0.008] • 7% placebo MASH resolution without worsening of fibrosis • 37% (15 mg) [95% CI 10–59] • 23% (30 mg) [95% CI 9–33] • 26% (44 mg every 2 weeks) [95% CI 10–37] • 2% placebo	F2–F3	Adverse events related to therapy or placebo were noted in 48% of the 15 mg weekly group, 54% of the 30 mg weekly group, 42% of the 44 mg every other week group, and 29% of the placebo group. The most frequent adverse events were nausea (19% of the 15 mg group, 32% of the 30 mg group, 19% of the 44 mg group, and 9% of placebo), diarrhea (24% of the 15 mg group, 19% of the 30 mg group, 14% of the 44 mg group, and 6% of placebo), injection-site erythema (14% of the 15 mg group, 15% of the 30 mg group, 5% of the 44 mg group, and 4% of placebo), increased appetite (10% of the 15 mg group, 14% of the 30 mg group, 7% of the 44 mg group, and 1% of placebo), and vomiting (5% of the 15 mg group, 14% of the 30 mg group, 4% of the 44 mg group, and 3% of placebo).
			ENLIGHTEN-Fibrosis (NCT06318169)[97]	n=1,050*	30 mg weekly, 44 mg EOW	Improvement of fibrosis ≥1 stage without worsening of MASH at week 52 MASH resolution without worsening of fibrosis at week 52 Fibrosis regression	F2–F3	
			ENLIGHTEN-Cirrhosis (NCT06419374)[98]	n=762*	30 mg weekly	Time to first occurrence of disease progression as measured by composite of protocol-specified clinical events	F4 (cirrhosis)	One serious adverse event of acute pancreatitis in the 44 mg group was related to pegozafermin therapy. No adverse events with a severity above grade 3 or deaths were reported.

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Table 1. Continued

Agent	Target/class	Mode of delivery	Study name (clinical trial ID)	Total number of subjects	Doses tested	Primary endpoints (dose) [*P*-value] vs. placebo	Stage of fibrosis	Reported safety summary
Denifanstat	Fatty acid synthase (FASN) inhibitor	Oral	FASCINATE-2 (NCT0-4906421)[102-104]	n=168	50 mg daily	Histological improvement (≥2 points improvement) in NAS with ≥1 point improvement in ballooning or inflammation at week 52 • 38% (50 mg) [*P*=0.0035] • 16% placebo Resolution of MASH and a ≥2 point improvement in NAS with no worsening of liver fibrosis (by NASH CRN fibrosis score). • 26% (50 mg) [*P*=0.0173] • 11% placebo	F2–F3	Adverse events related to denifanstat were seen in 46% of subjects, while adverse events related to placebo were seen in 36%. The most common adverse events were COVID-19 (17% of denifanstat group and 11% of the placebo group), dry eye (9% of denifanstat group and 14% of placebo), and reversible hair thinning (19% of denifanstat group and 4% of placebo) Serious adverse events were seen in 12% and 5% of the denifanstat and placebo groups, respectively.

CI, confidence interval; COVID-19, coronavirus disease 2019; EOD, every other day; EOW, every other week; MASH, metabolic dysfunction-associated steatohepatitis; NASH, non-alcoholic steatohepatitis; SC, subcutaneous.

*Estimated enrollment as per ClinicalTrials.gov. †Actual enrollment as per ClinicalTrials.gov.

including U.S., Canada, UK, Europe, UAE, South Korea, China, Japan, and Brazil. The large, multicenter Phase 3 ESSENCE trial (NCT04822181) is underway in the U.S., Canada, Mexico, Puerto Rico, Argentina, Brazil, UK, Europe, Israel, South Africa, Asia, and Australia.[68] This study is evaluating 1,200 subjects with biopsy-defined MASH and F2–F3 fibrosis, in which subjects received either once-weekly subcutaneous semaglutide 2.4 mg or placebo. While the study length is 240 weeks, the primary endpoints were achieved at a planned interim analysis at 72 weeks of the first 800 participants.[69,70] MASH resolution without worsening of fibrosis was observed in 62.9% of subjects compared with 34.3% placebo (P<0.001). Reduction of fibrosis by ≥1 stage without worsening of MASH was achieved by 36.8% of subjects compared with 22.4% of placebo (P<0.001). Combined resolution of MASH and improvement of fibrosis was achieved by 32.7% of subjects treated with semaglutide compared with 16.1% treated with placebo (P<0.001).[69,70] Furthermore, as expected, there were improvements in body weight and cardiometabolic parameters observed in the Phase 3 study, with a mean change in body weight of –10.5% with semaglutide compared with –2.0% with placebo (P<0.001).[69,70] Semaglutide exhibited an acceptable safety profile with primarily gastrointestinal adverse events (nausea, vomiting, constipation, abdominal pain) most prevalent during the dose escalation phase (first 20 weeks). Serious adverse events from semaglutide use, such as gallbladder-related disorders and pancreatitis, have been described among the large body of evidence for semaglutide in other indications. Gallbladder-related disorders in the ESSENCE trial were noted in 20 (2.5%) of the treatment arm and 6 (1.5%) of the placebo group.[69] Acute pancreatitis was noted in three (0.4%) subjects in the treatment arm compared with two (0.5%) in the placebo group.[69] A smaller study (NCT05813249) was recently completed at Zagazig University in Egypt, assessing a primary endpoint of improved hepatic steatosis measured by CAP with oral and injectable semaglutide compared with pioglitazone and/or vitamin E; however, results have not been published yet.[71] Furthermore, a Phase 2 trial (NCT03987451) concluded that semaglutide 2.4 mg once weekly was well tolerated and did not raise any new safety concerns in patients with compensated MASH cirrhosis;[72] however, it did not significantly improve fibrosis or achieve resolution of MASH in these patients.[73]

Survodutide is a glucagon and GLP-1 receptor dual agonist. The double-blind, placebo-controlled Phase 2 trial was completed in December 2023 with promising results. The GLP-1 receptor agonist mechanism is similar to that of semaglutide; however, this medication is also an agonist on the hepatic glucagon receptors thereby increasing lipolysis, metabolism, and mobilization of hepatic fatty deposits.[74] The Phase 2 study (NCT04771273, EudraCT 2020-002723-11) included 293 subjects with biopsy-confirmed MASH and F1–F3 fibrosis who were randomized to receive weekly subcutaneous injections of survodutide (2.4 mg, 4.8 mg, 6.0 mg) or placebo.[75,76] The primary endpoint demonstrated an improvement in MASH without worsening of fibrosis in 47% of the 2.4 mg arm, 62% in the 4.8 mg arm and 43% in the 6.0 mg arm compared with 14% in the placebo arm.[74] The secondary endpoint yielded a reduction in liver fat content by at least 30% in 63% of the 2.4 mg arm, 67% of the 4.8 mg arm and 57% of the 6.0 mg arm compared to 14% in the placebo arm. Another secondary endpoint measuring improvement in fibrosis by at least one stage was seen in 34% of the 2.4 mg arm, 36% of the 4.8 mg arm, and 34% of the 6.0 mg arm compared to 22% in placebo arm. The safety profile was similar to semaglutide with adverse events including nausea, vomiting, and diarrhea.[74] These results are promising and support Phase 3 development.

Tirzepatide is a glucose-dependent insulinotropic polypeptide and GLP-1 receptor dual agonist with approval for both weight loss and T2DM in multiple countries including U.S., UK, Europe, and China. The multicenter, double-blind, randomized placebo-controlled SYNERGY-NASH trial (NCT04166773) was completed in January 2024.[77] A total of 190 subjects from the U.S., Europe, Israel, Japan, and Mexico with biopsy confirmed MASH and F2–F3 fibrosis were randomly assigned to weekly subcutaneous injections of 5 mg, 10 mg, 15 mg or placebo for 52 weeks.[78] The primary endpoint, resolution of MASH without worsening fibrosis, was seen in 44% of the 5 mg arm, 56% of the 10 mg arm and 62% of the 15 mg arm in comparison to 10% of placebo with P-value <0.001. The secondary endpoint, at least one stage improvement in fibrosis without worsening of MASH, was seen in 55% of the 5 mg arm, 51% of the 10 mg arm, and 51% of the 15 mg arm in comparison to 30% of placebo. Adverse events were prominently gastrointestinal in origin (nausea, diarrhea, constipation, de-

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creased appetite) and present in 92% of subjects, including in the placebo arm.[78] Notably, tirzepatide has shown to induce substantial weight reduction in placebo-controlled trials in subjects with T2DM, obesity, or both.[79-81] Consistent with these prior findings, the SYNERGY-NASH trial demonstrated mean reduction in body weight of 10.7%, 13.3%, and 15.6% in the 5 mg, 10 mg, and 15 mg treatment arms, respectively, compared with 0.8% in the placebo group.[81] Based on these promising results, a Phase 3 program is being considered.

Fibroblast growth factor 21 agonists

Fibroblast growth factor 21 (FGF21) is a stress-induced endocrine hormone that plays a crucial role in the regulation of metabolism of lipid, glucose, and energy.[82-84] While multiple cell types (white and brown adipocytes, skeletal muscle cells, cardiac myocytes, and pancreatic beta cells) generate FGF21, the liver is the major FGF21-producing organ.[83] FGF21 prevents hepatocyte death, inflammation, and fibrosis by increasing mitochondrial capacity and inducing antioxidant pathways during times of metabolic stress.[82] FGF21 analogs act on various components in the pathogenesis of MASH by clearing hepatic lipids, protecting hepatocytes from stress and apoptosis, and inhibiting differentiation of cells that ultimately cause fibrosis.[85] Given that circulating FGF21 can be used as a predictor of metabolic diseases, FGF21-related therapies are being explored to assuage such metabolic diseases through their activity in regulating glucose and lipid metabolism.[83]

Efruxifermin is a long-acting engineered fusion protein made by linking the fragment crystallizable (Fc) region of human immunoglobulin to FGF21. It is subcutaneously administered once weekly.[5,82] The Phase 2b HARMONY study (NCT04767529) was conducted at 41 U.S. sites.[82,86] The HARMONY study recruited adults 18–75 years of age with biopsy-confirmed MASH (defined as a NAS of 4 or higher with scores of 1 or higher in each of the categories) and histological stage F2–F3 fibrosis.[82] The primary endpoint was the proportion of subjects with improvement of fibrosis by at least 1 stage without worsening of MASH based on biopsies at 24 weeks compared with baseline.[82] Most subjects (92%) were White, and a significant proportion (41%) were Hispanic or Latino.[82] Treatment arms consisted of efruxifermin 28 mg weekly, efruxifermin 50 mg weekly, and placebo.[82] Both doses met primary histologic endpoints; 39% of the 28 mg efruxifermin arm and 41% of the 50 mg efruxifermin arm had improvement in fibrosis of at least 1 stage compared with 20% in the placebo arm.[82] MASH resolution without worsening of fibrosis was seen in 47% of subjects in the 28 mg treatment arm and 76% of subjects in the 50 mg treatment arm compared with 15% of subjects in the placebo group.[82] The most frequently reported adverse events related to efruxifermin were diarrhea and nausea.[82] The efruxifermin 50 mg arm had a mean decrease from baseline body weight of 2.9 kg; however, this was not statistically different from placebo group, which had a mean decrease from baseline body weight of 2.3 kg.[82] Another trial, SYMMETRY (NCT05039450), is an ongoing Phase 2b study in the U.S., Mexico, and Puerto Rico evaluating the safety and efficacy of efruxifermin in subjects with current or previous T2DM and compensated cirrhosis due to MASH.[87] Its primary endpoint is the proportion of patients with ≥1 stage improvement in fibrosis (per NASH CRN score) from baseline with no worsening steatohepatitis at 36 weeks. At 36 weeks, biopsies showed statistically significant resolution of MASH in 63% and 60% of the subjects in the 28 mg and 50 mg treatment cohorts, respectively, compared with 26% in the placebo group.[88] Primary analysis at 96 weeks demonstrated regression of F4 fibrosis, with 21% of subjects in the 25 mg treatment arm and 29% of subjects in the 50 mg treatment arm experiencing fibrosis improvement of ≥1 stage and no worsening of MASH, compared with 11% in the placebo group.[89] These results suggest a durable response with longer treatment, as patients who had reduction in fibrosis at week 36 appeared to maintain their response at week 96, with additional new responses observed at week 96.[89] Recruitment into the global Phase 3 SYNCHRONY program is underway. SYNCHRONY Histology (NCT06215716, CTRI/2023/11/060385) is investigating efruxifermin in subjects with MASH and F2-F3 fibrosis, while SYNCHRONY Real-World (NCT06161571, CTRI/2024/01/061246) is investigating efruxifermin in subjects with F1-F3 MASH or MASLD.[90-94]

Pegozafermin is another subcutaneous long-acting Fc-FGF21 fusion protein. The most recent data come from the Phase 2b ENLIVEN study (NCT04929483), in which subjects with biopsy-confirmed NASH and fibrosis staged F2–F3 received 15 mg pegozafermin weekly, 30 mg pegozafermin weekly, 44 mg pegozafermin every 2 weeks, or

Table 2. Therapeutic classes of agents in Phase 3 development including mechanism of action and other approved indications

Therapeutic class	Mechanism of action for treatment of MASH	Drugs in development	Other approved indications within class (approved for indication in at least one country)
Thyroid hormone receptor-β (THR-β) agonists	Stimulates liver-targeted increased oxidation of fatty acids.	Resmetirom VK2809	Resmetirom has approval for the treatment of MASH in individuals with moderate to advanced fibrosis (consistent with F2–F3 fibrosis).
Peroxisome proliferator-activated receptor (PPAR) agonists	PPAR-α modulates genes involved in fatty acid transport, activation, and oxidation, increasing hepatic degradation of fatty acids. PPAR-β/δ stimulates fatty acid oxidation and reduces lipogenesis, improving hepatic steatosis. PPAR-γ promotes adipogenesis, storage of lipids, insulin sensitivity, and reduction of adipokines that can induce insulin resistance.	Lanifibranor (pan-PPAR) Saroglitazar (PPAR-α and PPAR-γ) Pioglitazone (PPAR-α and PPAR-γ)	Fibrates (e.g., fenofibrate, gemfibrozil, pemafibrate; PPAR-α agonists) have approvals for treatment of hyperlipidemia, specifically hypertriglyceridemia. Thiazolidinediones (e.g., pioglitazone, rosiglitazone; PPAR-α and PPAR-γ agonist, PPAR-γ agonist, respectively) have approvals for treatment of T2DM. Saroglitazar (PPAR-α and PPAR-γ agonist) has approvals for the treatment of diabetic dyslipidemia. Chiglitazar (pan-PPAR agonist) is approved for the treatment of T2DM in China.
Glucagon-like peptide-1 (GLP-1) receptor agonists	Stimulates insulin secretion by pancreatic beta cells and downregulates glucagon secretion by pancreatic alpha cells. Acts on central nervous system to reduce food intake and thus lowers body weight.	Semaglutide Survodutide (glucagon and GLP-1 receptor agonist) Tirzepatide (GIP and GLP-1 receptor agonist)	Semaglutide has approvals for the treatment of T2DM and weight loss. It is also indicated in the reduction of risk of major adverse cardiovascular events in patients with established cardiovascular disease who are overweight or obese. Tirzepatide has approvals for the treatment of T2DM, weight loss and sleep apnea in adults with obesity.
Fibroblast growth factor 21 (FGF21) agonists	Increases insulin sensitivity of peripheral tissues, inhibiting release of free fatty acids by adipocytes that would ultimately be taken up by hepatocytes. Allows insulin to better promote uptake of chylomicrons (containing dietary fat from the GI tract) and VLDL (secreted by hepatocytes). Increases capacity of antioxidant pathways to protect hepatocytes against stress and cell death. Inhibits differentiation of hepatic stellate cells into collagen secreting myofibroblasts.	Efruxifermin Pegozafermin	None

GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; T2DM, type 2 diabetes mellitus; VLDL, very low density lipoprotein.

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placebo weekly or every 2 weeks.[95,96] The study had two primary histologic endpoints at 24 weeks: (1) improvement of fibrosis staging by 1 or more with no worsening of MASH and (2) MASH resolution without worsening of fibrosis. Both primary endpoints were met.[95] The study included adults 21–75 years of age with biopsy-confirmed MASH defined as F2–F3 fibrosis and a NAS of at least 4, with at least 1 point in each category, and excluded those with cirrhosis or uncontrolled type 2 diabetes.[95] The trial was conducted at 61 U.S. sites. 94% of the subjects identified as White, and 38% identified as Hispanic or Latino.[95] Improvement of fibrosis was seen in 22% of the 15 mg pegozafermin arm, 26% in the 30 mg pegozafermin arm, and 27% in the 44 mg pegozafermin arm compared with 7% in the pooled placebo arm.[95] Resolution of MASH was seen in 37% in the 15 mg pegozafermin arm, 23% in the 30 mg pegozafermin arm, and 26% in the 44 mg pegozafermin arm compared with 2% in the placebo arm.[95] The most frequent adverse events were nausea, diarrhea, and injection-site erythema.[95] In the ENLIVEN study, pegozafermin treatment was associated with a decrease in serum triglycerides and an increase in HDL cholesterol; however, no significant effect on body weight was observed.[95] Two Phase 3 trials are underway evaluating the efficacy and safety of pegozafermin in subjects with MASH and fibrosis in the ENLIGHTEN-Fibrosis study (NCT06318169) as well as efficacy and safety in subjects with compensated cirrhosis due to MASH in the ENLIGHTEN-Cirrhosis study (NCT06419374).[97,98]

Fatty acid synthase inhibitors

Fatty acid synthase (FASN) is involved in the synthesis of palmitate, a saturated 16-carbon fatty acid, via conversion of acetyl-CoA and malonyl-CoA from simple dietary sugars.[99] Elevated levels of palmitate have been linked to inflammation and hepatic fibrosis and may be a significant factor in the progression of MASH.[56-58]

Denifanstat is an oral FASN inhibitor that recently completed the FASCINATE-2 Phase 2b study (NCT04906421) and successfully achieved its primary and secondary endpoints. The international, multicenter study assessed the efficacy and safety of 50 mg denifanstat vs placebo in subjects with F2–F3 MASH by targeting three significant drivers of the disease: fat accumulation, inflammation, and fibrosis. The primary endpoints at 52 weeks were (1) a ≥2-point decrease in NAS with ≥1 point improvement in ballooning or inflammation or (2) MASH resolution with a ≥2-point reduction in NAS without worsening of fibrosis. Thirty eight percent (38%) of denifanstat-treated subjects achieved a ≥2-point reduction in NAS without worsening fibrosis compared to 16% in the placebo arm. Additionally, 26% denifanstat-treated subjects achieved MASH resolution and a ≥2-point reduction in NAS without worsening of fibrosis compared with 11% in the placebo arm.[100-104] Notably, denifanstat showed a significant improvement in fibrosis regression by ≥1 stage, particularly in F3 subjects (49% vs. 13% placebo, P=0.0032).[102,103] Secondary endpoints included improvement of fibrosis without worsening of steatohepatitis as well as MASH resolution without worsening of fibrosis.[103] Denifanstat also showed improvements in several non-invasive metrics, including liver fat, FAST score, ALT, AST, and LDL.[102] At 52 weeks of treatment, the treatment arm experienced reduction of liver fat by 31.0% compared with 10.0% in the placebo group, as measured by MRI-PDFF (P=0.0008).[103] Denifanstat rapidly reduced tripalmitin, a biomarker of *de novo* lipogenesis, as early as 4 weeks into treatment. Tripalmitin will be investigated as a potential biomarker of response to denifanstat therapy.[102] Denifanstat was generally well tolerated. Treatment-related adverse events were reported by 45.5% of subjects in the denifanstat arm vs. 35.7% of subjects in the placebo arm. Serious adverse events were seen in 11.6% and 5.4% of the denifanstat and placebo arms, respectively. The most common adverse events were COVID-19 (17% of denifanstat arm and 10.7% of the placebo arm), dry eye (8.9% of denifanstat arm and 14.3% of placebo arm), and reversible hair thinning (18.8% of denifanstat arm and 3.6% of placebo arm).[102] There were no treatment-related serious adverse events or deaths in the FASCINATE-2 study.[103] Phase 3 planning is currently underway.

DISCUSSION

While MASLD and MASH are increasingly prevalent in communities around the world, the number of emerging therapies provides some solace. In traversing the landscape of therapies for MASH, recent victories offer optimism against the background of numerous failed therapies.

This past decade has seen significant efforts and resources invested into the development of therapies that have fallen short. The increase in therapies targeting MASLD and MASH is driven by a combination of its rising global prevalence and growing awareness of its health impacts. Previous attempts failed due to challenges in addressing the multifactorial nature of MASLD, poor study design, suboptimal efficacy and issues with safety and tolerability.

While the presentation of MASLD may look similar in many patients, the disease is highly heterogenous; its variability arises from numerous diverse underlying metabolic factors, genetic predispositions, and environmental influences.[105,106] These factors, such as dietary patterns, insulin sensitivity, alcohol consumption, play a role in disease progression and response to treatment.[105,106] Furthermore, genetic variability plays an important role in pathogenesis; genetically-driven MASLD can have a distinct metabolic profile from metabolically-driven MASLD in a similar fashion to how genetically-driven lipodystrophy has a distinct circulating lipid profile compared with insulin resistance.[105]

Many of these upcoming therapies encounter significant limitations with respect to treatment of diverse populations. The studied cohorts of the MAESTRO-NASH, NATIVE, EVIDENCES IV, Phase 2 semaglutide, Phase 2 survodutide, SYNERGY-NASH, HARMONY, and ENLIVEN trials were comprised of 87.5%, 93.9%, 85.8%, 77.5%, 70.0%, 86.3%, 92.2%, and 93.7% White subjects, respectively.[35,51,57,67,74,78,82,95] This lack of diversity can lead to gaps in understanding the impact of genetic, metabolic, and environmental factors on drug efficacy and safety in non-White populations. Thus, the results of these studies may not be generalizable to other racial and ethnic groups. This underscores the importance of more inclusive and representative research in a disease that affects a global population. Specific considerations should be made in future studies to prioritize Hispanic populations given the higher prevalence of the PNPLA3 gene variant associated with increased risk and severity of MASLD in this group.[4,107]

Earlier studies for MASLD/MASH therapies also failed due to suboptimal study design. Such studies failed to acknowledge heterogenous patient populations and relied on surrogate endpoints rather than hard clinical outcomes.[105] Many MASH studies were 1-year in duration with histologic endpoints that did not have any preliminary data on histologic efficacy. Other studies may have started registrational trials with insufficient demonstration of therapy efficacy from small Phase 2 trials.[105]

Safety and tolerability remain another issue in the development of effective therapies. Research for treatment of MASH with obeticholic acid, a farnesoid X receptor (FXR) agonist that was once the frontrunner for FDA approval in the US, has since been discontinued due to concerns with its side effect profile, most notably pruritus and dyslipidemia.[108] Exploration of various drugs in therapeutic classes listed above has also been discontinued due to failure to meet their primary efficacy endpoints. Such drugs include elafibranor (a PPAR agonist), liraglutide (a GLP-1 receptor agonist), selonsertib (an ASK1 inhibitor), and cenicriviroc (a dual CCR2/CCR5 antagonist). Additionally, study design may have factored into the success of early trials; in the Phase 2b GOLDEN study, elafibranor did not meet its primary outcome, likely due to the high placebo response rate. This was due to the inclusion of subjects with a NAS of 3.[109] Furthermore, the pathophysiology of MASH is multifaceted, as it involves metabolic, inflammatory, and fibrotic processes.

Future perspectives

Although many agents have not been successful, there are many new agents in earlier stage development. Table 3 lists some that are in Phase 2b and beyond around the globe. Therapies with mechanisms of action that only target a single pathway may not address sufficient components of the disease. This makes it difficult for a single agent to achieve significant clinical benefit and supports the rationale for combination therapies.

Combination therapies present a promising area of exploration in the frontier of MASLD/MASH management by potentially addressing the multilayered nature of the disease. By using agents with different mechanisms, the hope is to target multiple pathways involved in disease progression to sustain more significant clinical benefits, enhance overall efficacy, and provide more comprehensive management. Furthermore, combination therapies may introduce agents to mitigate unfavorable side effects of other agents. One notable combination therapy being studied is cilofexor with firsocostat. Cilofexor is a nonsteroidal FXR agonist that inhibits lipogenesis, gluconeogenesis, and bile acid synthesis. Firsocostat is an inhibitor of hepatic acetyl-coen-

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Table 3. Agents in earlier stage development and/or large investigator-initiated research

Drug class/MOA	Drug name	Study name (NCT)	Study phase	Study countries
Thyroid hormone receptor β (THR-β) agonist	ALG-055009	HERALD* (NCT06342947)[116]	2a	USA
Fibroblast growth factor 21 (FGF21) analogue	Efimosfermin alfa	NCT04880031[117,118*]	2a	USA
Acetyl-CoA carboxylase (ACC) inhibitor	Firsocostat* Clesacostat*	NCT02856555[119] NCT03248882[120]	2 2a	USA USA, Australia, Canda, Poland, Taiwan
Mitochondrial uncoupler	HU6	NCT04874233[121]	2a	USA
Diacylglycerol-O-acyltransferase 2 (DGAT2) antisense inhibitor	ION224 Ervogastat	NCT04932512[122] NCT04321031[120*]	2b 2	USA, Puerto Rico USA, Europe, Canada, China, Hong Kong, India, Japan, Korea, Puerto Rico, Taiwan
17-β hydroxysteroid dehydrogenase 13 minimizer	ARO-HSD (GSK4532990)	HORIZON (NCT05583344)[123]	2b	USA, Argentina, Australia, Canada, Europe, India, Japan, Korea, Mexico, Panama, Puerto Rico, UK
Modified bile acid	Nor-ursodeoxycholic acid	NCT05083390[124]	2b	Austria
Deuterium-modified thiazolidinedione	PXL065	NCT04321343[125]	2b	USA
Glucagon-like peptide 1 and glucagon dual receptor dual agonist	Pemvidutide	IMPACT[126] (NCT05989711)	2b	USA, Australia, Puerto Rico
Sodium-glucose cotransporter-2 inhibitor	Dapagliflozin	DEAN[127,128] (NCT03723252)	3	China
Modified fatty acid derivative	Icosabutate	ICONA[129] (NCT04052516)	2b	USA, Puerto Rico

*Currently being investigated as part of combination therapy.

zyme A carboxylase that reduces hepatic de novo lipogenesis. Individually, Phase 2 trials showed that both therapies were well tolerated and led to decreased hepatic steatosis in NASH patients.[110,111] When combined, a Phase 2 trial showed that although these therapies did not achieve their primary endpoint, they demonstrated reduced MASH activity and improvement of fibrosis compared to monotherapy with either agent.[112] Both agents were associated with increases in serum lipids alone and in combination.[110-112] This combination was further studied with the addition of semaglutide. A Phase 2 trial that observed the safety and tolerability of semaglutide with cilofexor and/or firsocostat demonstrated that the combinations were well tolerated, but effects on lipid profile were mixed.[113] This draws similarities to how combination therapies revolutionized the treatment of hepatitis C infection, which led to unprecedented cure rates and improved long-term patient outcomes.

Healthy weight loss through conventional methods such as lifestyle modifications centered around modest caloric deficit and cardiovascular exercise continues to be the foundation of MASLD/MASH management. An observational, prospective study of 293 subjects with histologically proven MASH in Havana, Cuba demonstrated a clear association between the magnitude of weight loss through lifestyle change and improvement in liver histology.[28] In subjects with ≥5% weight loss, 58% achieved MASH resolution, and 82% had a ≥2-point reduction in their NAS. In subjects with ≥10% weight loss, 100% experienced improvement from baseline NAS, 90% achieved resolution of MASH, and 45% had regression of fibrosis.[28] Despite its clear benefits for MASLD/MASH, lifestyle modification for weight loss can be particularly challenging for patients as it requires significant effort to enact sustained behavioral changes and overcome long-standing habits. Bariatric sur-

gery offers a highly effective option for sustained weight loss in patients with obesity and risk factors for MASLD/MASH. A multicenter, randomized trial of 288 subjects with obesity (BMI 30–55 kg/m^2) and histologically confirmed MASH showed that bariatric surgery was more effective than lifestyle interventions and optimized medical therapy in achieving histological resolution of MASH; resolution was 3.60 times greater in subjects who underwent Roux-en-Y gastric bypass and 3.67 times greater in subjects who underwent sleeve gastrectomy compared with lifestyle modification (both P<0.0001).[114]

In addition to new therapies, the advent of artificial intelligence (AI) has the potential to revolutionize the evaluation of MASH pathology in clinical research. AI tools offer the promise of precise, reproducible, and scalable assessments of histology, with the goal of reducing variability and enhancing reliability of endpoint analysis in MASH therapy trials. The ARCON study is the open-label cohort of the Phase 3 ARMOR study that evaluated fibrosis reduction in MASLD with Aramchol, a stearoyl-CoA desaturase-1 inhibitor, compared with placebo (NCT04104321, EudraCT 2019-002073-56). Notably, the primary endpoint of this study was to compare the analysis of fibrosis improvement utilizing conventional histopathology-based methods compared with AI-assisted digital pathology.[115] Safety and efficacy of the drug were secondary endpoints. AI digital pathology had greater sensitivity to fibrosis change when compared with conventional histology analysis by a pathologist.[115] This advancement has the potential to accelerate drug development and provide more proficiency in the evaluation of therapeutic efficacy in future therapy trials.

In conclusion, with many promising mono- and combination therapies in development, we hope to see efficacy and safety data that can be compared to therapies in late-stage development. There is potential for emerging therapies and technology to contribute to the effort to provide effective regimens to transform the landscape of MASH care.

Authors' contributions

All authors: Literature collection, data interpretation, writing of manuscript, revision of manuscript, final approval of manuscript.

Conflicts of Interest

Dr. Lawitz is a Researcher for 89Bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, Astrazeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cour Pharmaceuticals, Corcept Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NGM Biopharmaceuticals Inc., Northsea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, Zydus Pharmaceuticals.

Dr. Lawitz is a Speaker for Abbvie, Gilead Sciences, Intercept, Novo Nordisk, and Madrigal.

Dr. Lawitz is a Consultant for 89Bio Inc., Astrazeneca, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly and Company, Inventiva, Merck & Co., Novo Nordisk Inc., Organovo, Regeneron, and Sagimet Biosciences.

The remaining authors have no conflicts of interest to disclose.

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