Journal of Translational Gastroenterology **2025** vol. 3(1) | 9–17
DOI: 10.14218/JTG.2024.00040

Review Article

Advances in Novel Drug Therapy for Metabolic Dysfunction-associated Steatohepatitis Cirrhosis

Syed Alishan Nasir[1], Anjali Mangla[2], Vikas Taneja[1], Triston Berger[1], Deep Pandya[3], Vikas Gupta[4] and Joseph K. Lim[4*]

[1]Norwalk Hospital, Department of Gastroenterology and Hepatology, Norwalk, CT, USA; [2]Yale University, Department of Neuroscience, New Haven, CT, USA; [3]Ruby L. Ruggles Biomedical Research Institute, Danbury, CT, USA; [4]Yale School of Medicine, Section of Digestive Diseases and Yale Liver Center, New Haven, CT, USA

Received: November 20, 2024 | **Revised:** February 05, 2025 | **Accepted:** February 18, 2025 | **Published online:** March 17, 2025

Abstract

Metabolic dysfunction-associated steatotic liver disease has emerged as a leading cause of chronic liver disease and cirrhosis in the Western world. With rising rates of obesity, the prevalence of metabolic dysfunction-associated steatohepatitis (MASH)-related cirrhosis is expected to increase. MASH is associated with chronic hepatic inflammation and progressive liver fibrosis, and significant research is focused on developing pharmacological therapies to reverse these downstream complications. Recent trials have explored various therapeutic targets across metabolic, inflammatory, and fibrogenic pathways aimed at decreasing liver triglycerides, inflammation, lipotoxicity, and fibrosis. Some of these drugs show promise in reversing biomarkers and/or histologic markers of steatohepatitis and fibrosis, although most have been primarily studied in non-cirrhotic patients. However, in the context of the significant unmet medical need of patients with MASH-associated cirrhosis, growing interest in targeting compensated cirrhosis has prompted renewed investment in numerous early clinical and late-stage programs evaluating novel investigational agents in this population. This review summarizes current therapies under evaluation in phase 2 and 3 clinical trials for MASH-related cirrhosis, highlighting drug mechanisms, outcomes, and future research directions.

Introduction

Hepatic steatosis, or the accumulation of fat within hepatocytes, is a phenomenon that has long been recognized, with descriptions dating back to the mid-1800s.[1] It was quickly associated with the consumption of alcohol and excessive calorie intake, both of which account for the vast majority of etiologies. As such, it was characterized as alcoholic versus non-alcoholic fatty liver disease in the late 1900s, with the latter being associated with overnutrition. As the global incidence of diabetes and obesity has risen, the prevalence of hepatic steatosis has similarly increased. The association of metabolic syndrome with hepatic steatosis has led to a shift in nomenclature, in which the presence of hepatic steatosis in the context of metabolic syndrome without alcohol consumption is termed metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease. The estimated worldwide prevalence of MASLD is at least 15–35%, projected to increase in tandem with obesity and diabetes.[2–4] Hepatic inflammation in the context of MASLD, histologically characterized by lobular inflammation and ballooning degeneration, is termed metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), and comprises roughly 20–25% of patients with MASLD.

The events that result in the development of MASH are complex and have been summarized in recent reports; however, persistent hepatocellular injury and progressive fibrosis can result in cirrhosis and associated complications such as hepatic decompensation and hepatocellular carcinoma. The prevalence of cirrhosis among patients with MASH is currently estimated at 2% and is expected to rise to 3% by 2050.[5] In the U.S., it is estimated that up to 4.5 million Americans may have advanced fibrosis or cirrhosis due to MASH.[6] In 2017, the lifetime cost for patients with MASH was estimated at $222.6 billion overall, with $95.4 billion attributed to those with advanced MASH. The total economic cost of MASH in Europe has been estimated at €8.5 to €19.5 billion.[7]

Due to the significant morbidity, mortality, and healthcare re-

Keywords: Metabolic dysfunction-associated steatotic liver disease; MASLD; Metabolic dysfunction-associated steatohepatitis; MASH; Liver cirrhosis; Fibrosis reversal; Clinical trials; Fibroblast growth factor 21; FGF21.

***Correspondence to:** Joseph K. Lim, Section of Digestive Diseases and Yale Liver Center, Yale School of Medicine, PO Box 208019, New Haven, CT 06250-8019, USA. ORCID: https://orcid.org/0000-0003-1126-8128. Tel: +1-203-737-6063, Fax: +1-203-785-7273, E-mail: joseph.lim@yale.edu.

How to cite this article: Nasir SA, Mangla A, Taneja V, Berger T, Pandya D, Gupta V, *et al*. Advances in Novel Drug Therapy for Metabolic Dysfunction-associated Steatohepatitis Cirrhosis. *J Transl Gastroenterol* 2025;3(1):9–17. doi: 10.14218/JTG.2024.00040.

source utilization associated with MASH, multiple investigational agents are under active evaluation in clinical trials, with the primary aim of MASH resolution and/or reversal of MASH-related fibrosis.[8] However, only a small proportion of these trials focus on patients with cirrhosis. In this manuscript, we summarize key investigational drug programs in phase 2 and/or 3 clinical trial development.

Evaluating clinical efficacy in patients with MASH cirrhosis

Until 2024, there were no approved treatments for MASH apart from lifestyle modifications and effective weight loss. Furthermore, clinical trials in MASH have primarily focused on evaluating outcomes in patients with F2 to F3 fibrosis. In this population, extensive crosslinking of collagen has not yet occurred, and there is potential for fibrosis reversal. In this context, the presence of advanced fibrosis drives hepatic outcomes, and the reversal of such fibrosis would be expected to lead to improvement.[9] Once fully established cirrhosis develops, particularly with mature collagen crosslinking and the development of portal hypertension, fibrosis reversal may be challenging to achieve. As such, the assessment of novel therapies in patients with compensated MASH cirrhosis is far more nuanced and may extend beyond histological endpoints (e.g., MASH resolution, fibrosis improvement). In its current guidance to the industry for the development of drugs for the treatment of MASH with compensated cirrhosis, the U.S. Food and Drug Administration (FDA) notes that "reversal of cirrhosis may not be feasible" and therefore "strongly recommends clinical outcome trials to support a marketing application" under the traditional rather than accelerated approval pathway. This could include a composite endpoint of time from randomization to the first of any outcome event, such as overt hepatic decompensation (e.g., spontaneous bacterial peritonitis, ascites, variceal hemorrhage, hepatic encephalopathy), worsening of the Model for End-Stage Liver Disease (MELD) score to ≥15, liver transplantation, or death from any cause. However, "histological improvements in fibrosis can be proposed and justified".[10]

Non-invasive tests for liver fibrosis have been widely adopted in clinical practice and include direct and indirect serum biomarker assays, as well as imaging-based elastography using ultrasound or magnetic resonance imaging (MRI). The enhanced liver fibrosis (ELF) score is generated through the measurement of three components of liver collagen biomatrix, and a decrease of 0.3 points or more in ELF score is associated with histologic improvement in liver fibrosis and may be predictive of differences in liver-related outcomes.[11,12] As such, a decrease in ELF score could potentially serve as an endpoint for these novel drugs in patients with cirrhosis.

Similarly, multiple imaging-based elastography tools have been validated for the assessment of liver fibrosis, including vibration-controlled transient elastography (VCTE), shear wave elastography, and magnetic resonance elastography. These imaging modalities can be used for liver stiffness measurement (LSM) in units of kilopascals. A decrease in LSM has been shown to reduce the risk of liver-related events,[13] and therefore, it may also serve as a viable trial endpoint.

As the disease progresses in patients with MASH cirrhosis, collagen accumulates within the extracellular matrix, disrupting the connections between hepatocytes and the sinusoids. This results in progressive restriction of sinusoidal flow, ultimately leading to portal hypertension.[14,8] A hepatic venous pressure gradient (HVPG) greater than 10 mm Hg results in clinically significant portal hypertension, which is associated with complications such as ascites, hepatic encephalopathy, and variceal hemorrhage. As such, there has been interest in evaluating direct and/or indirect measurement of HVPG as a clinical trial endpoint. Although this is attractive due to its strong association with clinical outcomes, a delta change in HVPG may be limited by the invasive nature of HVPG measurement, which typically requires transjugular or transvenous introduction of a catheter into the hepatic vein for measurement of free and wedged hepatic venous pressure, as well as intra-observer and inter-observer variability in measurement.

Clinical endpoints, including hepatic decompensation events, liver transplantation, and death, represent well-validated outcomes and would serve as acceptable trial endpoints for full approval in the traditional FDA regulatory pathway. However, due to the latency and variability of disease progression in patients with MASH fibrosis or cirrhosis, the use of clinical endpoints creates unique challenges, including the potential need for a larger sample size to ensure an adequate number of clinical events, a longer timeframe beyond one year to reach a primary endpoint, and careful patient selection to appropriately identify patients with compensated cirrhosis with or without portal hypertension and without prior hepatic decompensation events. Scores such as the MELD and Child-Pugh-Turcot have been extensively validated in predicting clinical outcomes in patients with cirrhosis. Therefore, a delta change in these markers may represent complementary measures for assessing the clinical efficacy of novel agents in patients with compensated MASH cirrhosis.

Therapeutic strategies and preliminary outcomes

There are currently ten drugs that have been studied in either phase 2 or phase 3 trials to assess their efficacy in patients with MASH cirrhosis. Table 1 summarizes these trials by drug, mechanism of action, trial design, and trial outcomes.

Farsenoid X activated receptor pathway

OCA is a synthetic derivative of chenodeoxycholic acid, an endogenous bile acid, and a highly selective agonist for the farnesoid X-activated receptor (FXR), a nuclear bile acid receptor and transporter. It was approved for the treatment of primary biliary cholangitis. FXR agonism has a spectrum of cell-type specific effects.[15,16] Activation within ileal enterocytes causes the release of fibroblast growth factor (FGF) 19, which then acts on hepatocytes to decrease bile acid synthesis. OCA has also demonstrated modulation of inflammatory cells and inhibition of hepatic stellate cell activation, thereby having direct anti-fibrotic effects.[17] Subsequent phase 3 studies of OCA in patients with MASH and F1-F3 fibrosis demonstrated a significant reduction in fibrosis by one stage or greater (12% placebo vs 23% OCA 25 mg over 18 months). However, it was not approved by the FDA due to an unfavorable benefit/risk balance. OCA was further studied in the REVERSE phase 3 clinical trial to assess histological improvement in fibrosis in adults with compensated cirrhosis due to MASH. In this trial, a cohort of 919 subjects treated with OCA 10–25 mg showed fibrosis improvement of one stage or greater at 18 months in 11.9% of subjects versus 9.9% in the placebo group (not statistically significant). Although OCA has demonstrated anti-fibrotic effects in patients with F2-F3 fibrosis, it remains uncertain if it can be safely combined with other novel therapies to enhance fibrosis reversal in patients with either fibrosis or cirrhosis (NCT03439254).[18]

Aldafermin (formerly known as NGM282) is an engineered analog of FGF19, a hormone that plays a key role in bile acid metabolism by acting downstream of FXR signaling.[16] Its mechanism

Table 1. Completed phase 2 and 3 trials in subjects with MASH cirrhosis

Drug name	Sponsor	Mechanism	Trial Identifiers	Sample Size	Primary endpoint	Phase	Results
Obetichoic Acid (OCA)	Alfasigmna/ Intercept Pharmaceuticals	Farsenoid X Receptor (FXR) Agonist	REVERSE (NCT03439254)	919 (Placebo: 313; OCA 10 mg: 296; OCA 10 mg titrated to 25 mg: 310)	Reversal of fibrosis by ≥1 stage without worsening MASH	3	Primary endpoint not established by intervention group. Fibrosis improvement: 11.9% OCA 10 mg titrated to 25 mg vs. 11.1% OCA 10 mg vs. 9.9% placebo
Selonsertib (SEL)	Gilead Sciences	Small molecule ASK1 inhibitor	STELLAR-4 (NCT03053063)	877 (Placebo: 172; SEL 6 mg: 351; SEL 18 mg: 354)	Reversal of fibrosis by ≥1 stage without worsening MASH at week 48	3	Did not meet primary end point. Fibrosis improvement without worsening: 14.4% SEL 18 mg vs. 12.8% SEL 18 mg vs. 12.8% placebo
Simtuzumab (SIM)	Gilead Sciences	Monoclonal antibody targeting LOXL2	NCT01672879	258 (Placebo: 85; SIM 200 mg: 87; SIM 700 mg: 86)	Reduction in hepatic venous pressure gradient (HVPG)	2b	Did not meet efficacy endpoint. Change in HVPG: −0.1 SIM 200 mg vs. 0.0 SIM 700 mg vs. −0.1 placebo
Semaglutide	Novo Nordisk	GLP-1 receptor agonist	NCT03987451	71 (Placebo: 24; Semaglutide 2.4 mg: 47)	Reversal of fibrosis by ≥1 stage without worsening MASH at week 48	2	Did not significantly improve fibrosis or achieve MASH resolution over placebo. Fibrosis improvement: 10.6% semaglutide vs. 29.2% placebo
Aldafermin	NGM Biopharmaceuticals	FGF19 analog	ALPINE-4 (NCT04210245)	160 (Placebo: 56; Aldafermin 0.3 mg: 7; Aldafermin 1 mg: 42; Aldafermin 3 mg: 55)	Reversal of fibrosis as measured by reduced ELF score	2b	ELF reduction: −0.2 aldafermin 3 mg vs. 0.2 aldafermin 1 mg vs. 0.3 placebo
BMS-986263	Bristol-Meyers Squibb	HSP47 inhibitor	NCT04267393	124 (Placebo: 40; BMS-986263 45 mg QW: 42; BMS-986263 90 mg QW: 42)	Reversal of fibrosis by ≥1 stage at week 12	2	Lack of short term efficacy of treatment. Fibrosis improvement: 12.2% BMS-986263 45 mg QW vs. 7.1% BMS-986263 90 mg QW vs. 20.5% placebo
Efruxifermin (EFX)	Akero Therapeutics	FGF21 mimic	SYMMETRY (NCT05039450)	182	Reversal of fibrosis by ≥1 stage without worsening MASH	2b	Week 36 data shows a promising trend towards fibrosis improvement. Fibrosis improvement: 22% EFX 28 mg vs. 14% EFX 50 mg vs. 10% placebo. MASH resolution: 67% EFX 28 mg vs. 60% EFX 50 mg vs. 26% placebo
Combination therapy Selonsertib (SEL) + Cilofexor (CILO) + Firsocostat (FIR)	Gilead Sciences	ASK1 inhibitor, FXR receptor agonist	ATLAS (NCT03449446)	392 (Placebo: 39; SEL: 39; FIR: 40; CILO: 40; SEL + FIR: 79; SEL + CILO: 77; FIR + CILO: 78)	Reversal of fibrosis by ≥1 stage without worsening MASH	2b	FIR + CILO showed promising fibrosis improvement, NAS reduction, and liver function tests. Fibrosis improvement: 20.9% FIR + CILO vs. 19.1% SEL + CILO vs. 15.5% SEL + FIR vs. 28.6% SEL vs. 12.1% FIR vs. 11.8% CIL
Emricasan	Histogen/ Conatus	Caspase inhibitor	ENCORE-PH (NCT02960204)	263 (Placebo: 67; Emricasan 5 mg: 65; Emricasan 25 mg: 65; Emricasanan 50 mg: 66)	Reduction in hepatic venous pressure gradient (HVPG)	2	HVPG change: -.70 Emricasan 50 mg vs -.81 Emricasan 25 mg vs -.48 Emricasan 5 mg vs. −0.18 placebo
Belapectin	Galectin Therapeutics Inc.	Galectin-3 inhibitor	NCT02462967	162 patients with NASH-related cirrhosis and portal hypertension	Reduction in hepatic venous pressure gradient (HVPG) at week 26.	2b	HVPG Change: No significant difference between treatment and placebo; the 2 mg/kg group showed −0.28 mm Hg vs. +0.10 mm Hg in placebo (p = 1.0), and the 8 mg/kg group showed −0.25 mm Hg vs. placebo (p = 1.0)

of action involves binding to and activating the FGF receptor 4 on hepatocytes, which results in the downregulation of bile acid synthesis through inhibition of cholesterol 7α-hydroxylase, the enzyme responsible for converting cholesterol into bile acids in the liver.[17] Aldafermin was studied in patients with compensated MASH cirrhosis in the ALPINE 4 trial,[13] in which participants were randomly assigned to receive either aldafermin 1 mg, 3 mg, or placebo. The primary endpoint was the change from baseline ELF score to ELF score at week 48 of treatment. The aldafermin 3 mg group experienced a mean decrease in ELF score of 0.5 at week 48, and histological fibrosis improvement of one stage or greater without worsening steatohepatitis was achieved in 20%, 16%, and 13% of patients in the 3 mg, 1 mg, and placebo groups, respectively. Additional studies may be needed to further examine the potential effect of aldafermin on histological fibrosis endpoints and/or clinical outcomes in patients with MASH-related cirrhosis.

Apoptosis signal-regulating kinase 1 inhibitor

Selonsertib is an apoptosis signal-regulating kinase 1 (ASK1) inhibitor and a member of the mitogen-activated protein kinase family that activates the JNK and p38 mitogen-activated protein kinase pathways in conditions of oxidative stress and proinflammatory cytokine exposure.[19] Animal model studies in ASK1 gene knockout models have shown no effect on liver weight, triglyceride content, and steatohepatitis in mice fed with high-calorie diets compared to those fed regular diets. Subsequent studies showed that inhibition of ASK1 reduced cell death and hepatic fibrosis.[20,21] In 2016, Selonsertib was studied in a phase 2 protocol that examined a cohort of patients with biopsy-proven MASH and F2-F3 fibrosis. This trial revealed significant histological improvement in MASH activity score and reduction in fibrosis, supporting the development of a phase 3 program, which evaluated Selonsertib in F3 fibrosis (STELLAR-3) and compensated cirrhosis (STELLAR-4, NCT03053063).[22,23] The primary efficacy endpoint was the proportion of patients with ≥1-stage improvement in fibrosis without worsening of NASH at week 48; however, no anti-fibrotic effect was seen in patients enrolled in either STELLAR-3 (F3) or STELLAR-4 (cirrhosis).

Galectin-3 inhibitor pathway

Belapectin is an investigational drug that targets galectin-3, a carbohydrate-binding protein implicated in liver fibrosis and inflammation. Galectin-3 contributes to fibrogenesis in liver disease by promoting macrophage activation and hepatic stellate cell activity, leading to collagen deposition and fibrosis development.24 By inhibiting galectin-3, belapectin represents an attractive approach to targeting fibrosis and portal hypertension. In a phase 2b randomized controlled trial, subjects received biweekly infusions of Belapectin at 8 mg/kg, 2 mg/kg, or placebo over 52 weeks.[24] The primary endpoint, delta change in HVPG, was not statistically different between groups: −0.28 mm Hg, −0.25 mm Hg, and +0.10 mm Hg, respectively. However, a subgroup analysis revealed that belapectin demonstrated a significant decrease in HVPG and incidence of new varices among patients without baseline esophageal varices. These findings have supported the ongoing NAVIGATE phase 3 trial, which examines the impact of belapectin on the development of varices in MASH cirrhosis NCT04365868.

Fibroblast growth factor analogues

FGF21 is a stress-induced hormone primarily produced by the liver and adipose tissue. Its signaling is limited to tissues that express the β-klotho co-receptor, including the liver, where FGF21 can have paracrine effects. Stressed hepatocytes release FGF21, which protects hepatocytes from lipotoxicity, increases fatty acid oxidation, and modulates stellate and Kupffer cells, resulting in decreased inflammation and fibrosis.[25] Efruxifermin is a long-acting FGF21 analogue, formed by a modified sequence of native human FGF21 fused to the Fc region of human immunoglobulin G1. Mutations in the FGF21 moiety in efruxifermin increase its half-life in humans to more than three days and enhance its binding affinity to the obligate co-receptor.[26] In a phase 2a study involving patients with F1–F3 MASH, efruxifermin significantly reduced liver fat, markers of liver injury and fibrosis, and resulted in an improvement in glucose and lipid parameters.[27] Notably, 50% of patients with F2 or F3 MASH experienced a two-stage reversal of fibrosis after only 16 weeks of treatment. Based on these results, efruxifermin was studied in the phase 2b SYMMETRY trial, which enrolled subjects with compensated cirrhosis due to MASH.(NCT03976401) Participants were randomized to 50 mg weekly, 28 mg weekly, or placebo. The primary endpoint of ≥1 stage improvement in fibrosis without worsening of MASH was achieved in 24%, 22%, and 14% of subjects at 24 weeks of treatment, and 39%, 29%, and 15% of subjects at 96 weeks of treatment. Although these differences were not statistically significant at 24 weeks, the 24% placebo-adjusted delta at 96 weeks was statistically significant ($p < 0.01$). Significant improvement was also observed on the MASH resolution endpoint with efruxifermin at 24 weeks (60–63% vs. 26% placebo) and 96 weeks (55–59% vs. 18% placebo). Efruxifermin is currently under evaluation in the phase 3 SYNCHRONY trial, which includes both a real-world and outcomes protocol in patients with compensated MASH cirrhosis.

Glucagon-like peptide 1 analogues

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have emerged as a promising drug class with demonstrated weight loss benefits in patients with obesity and type 2 diabetes mellitus. This has been associated with significant improvements in metabolic, cardiovascular, and renal outcomes.[3,28] GLP-1RAs were first evaluated in the treatment of steatohepatitis in a phase 2 randomized controlled trial, which revealed that liraglutide was associated with improvement in steatohepatitis, although no impact on fibrosis was observed.[29] Newer GLP-1RAs have shown greater efficacy for weight loss and were subsequently studied in the context of MASH. A phase 2 study of semaglutide found that 41.6% of patients treated with semaglutide achieved MASH resolution, compared to 18.3% in the placebo group; however, no improvement in fibrosis was observed.[30] In the context of these findings, a phase 2 trial evaluated the effect of semaglutide 2.4 mg weekly for 48 weeks in subjects with compensated MASH cirrhosis, but no improvement was observed in MASH resolution or fibrosis improvement between the semaglutide and placebo groups.[31] An additional phase 2 trial examined the combination of semaglutide with cilofexor (FXR agonist) and/or firsocostat (acetyl-CoA carboxylase inhibitor) to assess efficacy in patients with non-cirrhotic MASH fibrosis. This study revealed a significant decrease in liver steatosis on MRI-proton density fat fraction (PDFF) and non-invasive fibrosis markers, including LSM and ELF, and has supported an ongoing protocol in subjects with MASH cirrhosis.[32]

Other pathways

Other drugs studied for MASLD-related cirrhosis have shown limited promise. Lysyl oxidase-like 2 (LOXL2) is a secreted enzyme

that plays a key role in tissue fibrosis by cross-linking collagen and elastin. In murine models of pulmonary and hepatic fibrosis, an inhibitory antibody targeting LOXL2 demonstrated prevention and reversal of liver fibrosis.[33] Simtuzumab is a humanized monoclonal antibody that inhibits LOXL2 and has been tested for its ability to reverse and/or halt fibrosis. A phase 2b clinical trial[34] examined the role of simtuzumab in patients with compensated cirrhosis, with primary endpoints being a change in baseline HVPG at week 96 and time to the first liver-related event (variceal bleeding, ascites, hepatic encephalopathy, liver transplantation, or a 2-point increase in the Child-Pugh-Turcot score) or death. Simtuzumab was not associated with a significant reduction in HVPG or liver-related events.

Emricasan is a first-in-class small molecule pan-caspase inhibitor that has been examined as a potential anti-fibrotic agent for liver disease.[35] Lipotoxicity within the liver can activate caspases, resulting in hepatocyte apoptosis and the release of inflammatory cytokines such as interleukin 1 and interleukin 18, supporting the hypothesis that caspase inhibition may be associated with anti-inflammatory and anti-fibrotic effects beneficial for MASH-associated fibrosis. This was further supported in mouse models and early human studies, which revealed a decrease in HVPG by 3.7 mm Hg.[36,37] A phase 2 placebo-controlled trial randomized subjects with biopsy-proven steatohepatitis and F1–F3 fibrosis to emricasan 50 mg, 5 mg, or placebo for 72 weeks. No significant difference in histologic fibrosis improvement was found.[38] The ENCORE-PH phase 2b trial randomized patients with biopsy-proven cirrhosis and baseline HVPG ≥ 12 mm Hg to twice-daily oral emricasan (5 mg, 25 mg, 50 mg) or placebo for 48 weeks.[39] The primary endpoints for this study were reduction in HVPG, development of liver-related events, and changes in fibrosis biomarkers. No improvement was demonstrated in HVPG or liver-related events.

BMS-986263 is a retinoid-conjugated lipid nanoparticle delivering small interfering RNA designed to inhibit the synthesis of heat shock protein 47.[40] Heat shock protein 47 is a collagen-specific chaperone, helping to correct the triple-helix formation of procollagen within the endoplasmic reticulum. Conjugation with retinoids enhances targeted delivery to hepatic stellate cells. Based on early studies that demonstrated robust improvement in fibrosis in animal models,[41,42] BMS-986263 was studied in a phase 2 randomized controlled trial in patients with hepatitis C-associated cirrhosis who achieved sustained virological response. They were randomized to receive BMS-986263 45 mg or 90 mg weekly or placebo for 12 weeks. The primary endpoint (>1 stage fibrosis improvement at week 12) was achieved in 21%, 17%, and 13% of subjects, respectively. These findings supported further examination of BMS-986263 in a phase 2 trial in subjects with MASH-associated cirrhosis. No significant reduction in HVPG or liver-related events was observed in the BMS-986263-treated patients versus placebo. (NCT04267393).

Therapies being studied in clinical trials

While certain drugs have already been studied, ongoing trials continue to assess the efficacy of others for patients with MASH cirrhosis. Table 2 highlights these drugs, their mechanisms of action, and their current trials.

The NAVIGATE study is a phase 2b/3, randomized, double-blind, placebo-controlled clinical trial assessing belapectin's potential to prevent esophageal varices in patients with MASH and Child-Pugh A cirrhosis without esophageal varices. Participants are randomized in a 2:1 ratio to receive belapectin 2 mg/kg or placebo intravenously every two weeks for 78 weeks (primary outcome) or 156 weeks (secondary outcomes). The primary endpoint is the proportion of patients who develop new esophageal varices, as confirmed by endoscopy. Secondary endpoints include the development of ascites requiring hospitalization, hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization), all-cause mortality, or the need for liver transplant. This study will demonstrate the effectiveness of belapectin in preventing decompensation in patients with MASH cirrhosis.

The phase 3 MAESTRO-NASH-Outcomes trial is an event-driven, randomized controlled trial in which a cohort of 700 patients with MASH cirrhosis is randomized in a 3:1 ratio to receive resmetirom 80 mg daily or placebo for a duration of two to three years. The trial will be evaluated based on the primary endpoint of time to a composite clinical outcome, including liver-related events (e.g., ascites, hepatic encephalopathy, variceal bleeding), liver transplant, or all-cause mortality.

Survodutide has been evaluated in a phase 1 trial, which was a two-stage, open-label study assessing its safety, pharmacokinetics, and efficacy in compensated or decompensated MASH-related cirrhosis. In the initial phase, all 41 participants received a 0.3 mg dose, showing consistent pharmacokinetics in patients with and without cirrhosis, suggesting that no dose adjustments are needed for patients with cirrhosis. In the second phase, participants were administered weekly subcutaneous doses starting at 0.3 mg, titrated to 6.0 mg over 24 weeks, and maintained for four additional weeks, permitting assessment of dose tolerability and efficacy. At week 28, significant reductions were noted in key liver and metabolic parameters such as liver fat content, measured by MRI with PDFF, in patients with cirrhosis compared to those without. Additionally, LSM, measured by MRI elastography, as well as ELF scores, also showed a decrease. Given these findings, survodutide represents a potential therapeutic target in the treatment of MASH cirrhosis.

Pegozafermin is a specifically engineered glycoPEGylated analog of FGF21. FGF21 is an endogenous hormone involved in multiple metabolic pathways, including regulating glucose and lipid metabolism and energy expenditure. Pegozafermin has direct anti-fibrotic and anti-inflammatory properties, as well as metabolic effects such as reduced triglyceride levels, and improvement in insulin sensitivity and glycemic control. ENLIGHTEN-Cirrhosis is a phase 3, randomized, double-blind, placebo-controlled trial examining the efficacy and safety of pegozafermin for the treatment of MASH in 760 patients with compensated cirrhosis (F4), who will be randomized 1:1 to receive either pegozafermin 30 mg subcutaneously weekly or placebo. The primary endpoint is time to the first event of disease progression, based on a composite of protocol-specified clinical events, and the proportion of participants achieving fibrosis regression. Key secondary endpoints include the proportion of participants who develop clinically significant portal hypertension, change from baseline in enhanced liver fibrosis (ELF) score, and change from baseline in fibroscan VCTE.

WAYFIND is a phase 2, randomized, double-blind, double-dummy, placebo-controlled 72-week study evaluating the safety and efficacy of semaglutide and the fixed-dose combination of cilofexor and firsocostat, alone and in combination, in 457 subjects with compensated cirrhosis due to MASH. The primary outcome is the percentage of participants who achieve ≥1-stage improvement in fibrosis according to the NASH Clinical Research Network classification, without worsening of MASH in participants treated with safety and efficacy of semaglutide + cilofexor/firsocostat versus placebo.

Efinopegdutide (MK-6024) is a dual GLP-1 receptor and glucagon receptor agonist being studied as part of a phase 1a trial for

Table 2. Ongoing phase 2 and 3 trials in subjects with MASH cirrhosis

Drug Name	Sponsor	Mechanism	Trial Identifiers	Sample Size	Primary Endpoint	Phase	Completion Date (estimate)
Resmetirom	Madrigal Pharmaceuticals, Inc.	Thyroid hormone receptor beta (THR-β) agonist	MAESTRO-NASH-OUTCOMES, NCT05500222	700 (estimated) randomized to 80mg Resmetirom vs Placebo	Composite clinical outcome events including: ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage, liver transplant, increase in MELD score from <12 to ≥15, all-cause mortality	3	01/2027
Belapectin	Galectin Therapeutics Inc.	Galectin-3 inhibitor	NAVIGATE, NCT04365868	357 Randomized to 2mg/kg dose, 4mg/kg dose, or placebo. After 78 weeks patients will be switched to optimal dose	New-onset esophageal varices at Week 78	2b/3	12/2024
Efruxifermin (EFX)	Akero Therapeutics, Inc	Fc-Fibroblast Growth Factor 21 (Fc-FGF21) fusion protein analogue	SYMMETRY, NCT05039450	200 Randomized to EFX 28mg, EFX 50mg, or placebo.	Reversal of fibrosis by ≥1 stage without worsening MASH at week 36	2b	04/2024
Efruxifermin (EFX)	Akero Therapeutics, Inc	Fc-Fibroblast Growth Factor 21 (Fc-FGF21) fusion protein analogue	SYNCHRONY, NCT06528314	1,150 (estimate). Randomized to EFX 50mg or placebo	Disease progression (measured by composite of protocol-specified events) over five-year time frame. Cohort 1: Reversal of fibrosis by ≥1 stage without worsening MASH steatohepatitis at 96 weeks	3	10/2029
Pegozafermin	89bio, Inc.	FGF21 analog	ENLIGHTEN, NCT06419374	762 (estimated). Randomized to Pegozafermin or placebo	Reversal of fibrosis by ≥1 stage at Month 24. Time to disease progression based on composite clinical events through Month 60	3	08/2031
Survodutide	Boehringer Ingelheim	Glucagon/Glucagon-like peptide-1 (GLP-1) dual agonist	LIVERAGE – Cirrhosis, NCT06632457	1,590 (estimated). Randomized to Survodutide or placebo	Time to first composite clinical event including hepatic decompensation, worsening of MELD to ≥15, progression to CSPH, liver transplant, all-cause mortality	3	06/2029
Efinopegdutide	Merck Sharp & Dohme LLC	Glucagon/Glucagon-like peptide-1 (GLP-1) dual agonist	MK-6024-017, NCT06465186	80 (estimated)	Decrease in liver fat content (LFC) on MRI-PDFF at Week 28	2	05/2026

efficacy and safety in compensated MASH cirrhosis. The primary outcome is a change in MRI-estimated PDFF. Secondary outcomes include changes from baseline in iron-corrected T1 (ct1), enhanced liver fibrosis (ELF), and LSM assessed by VCTE. A study to test whether avenciguat (BI 685509), alone or in combination with empagliflozin, improves portal pressures in compensated cirrhosis caused by viral hepatitis or MASH was terminated early.

Limitations

Our review uniquely focuses on summarizing therapeutic modalities that have been studied within the context of MASLD-related cirrhosis. It has important limitations, including the exclusion of studies examining the larger group of investigational agents in clinical trials for subjects with F2-F3 fibrosis. Additionally, this review only encompasses drugs that have been publicly reported on ClinicalTrials.gov, with formal reports of study design and/or trial results as of November 2024, and is subject to publication bias due to the exclusion of unreported studies or trial results.

Conclusions

MASH-associated cirrhosis is increasingly prevalent among patients with MASLD and is associated with substantial morbidity and mortality due to hepatic decompensation, hepatocellular carcinoma, major adverse cardiovascular events, and all-cause mortality. The unique challenges of this population require novel, differentiated approaches to drug development and support an independent regulatory framework for rational clinical trial endpoints. These endpoints should include a combination of histologic outcomes (MASH resolution and/or fibrosis improvement of one stage or greater), liver-related events (hepatic decompensation, worsening MELD score), and both liver-related and all-cause mortality. Recent clinical trial history in MASH cirrhosis has been sobering due to multiple failures in a growing "graveyard" of drug development. These setbacks highlight both the difficulty in achieving statistically significant fibrosis improvements in this population and the urgent need for innovative approaches targeting liver fibrosis and portal hypertension. Previous programs in the F4 population have failed for several reasons, including weak potency in liver-directed effects on fibrosis, short trial duration below the threshold required to observe histologic benefits, inadequate validation in phase 2 due to small sample sizes, absence of placebo controls, reliance on subgroup analyses, intrinsic variability in the placebo arm response rate, and methodological limitations in study population, endpoint selection, and trial design. Current ongoing phase 2 and 3 trials evaluating novel agents such as THR-beta receptor agonists, galectin-3 inhibitors, FGF21 analogues, GLP-1/glucagon receptor agonists, and novel combination approaches offer hope for future advances in drug therapy for patients with MASH cirrhosis.

Based on available data, FGF21 analogues appear to be best positioned to demonstrate efficacy in the compensated cirrhosis population on the fibrosis endpoint (reversal of F4 to F3 or less) due to their potent direct antifibrotic properties, mediated through inhibition of stellate cell activation, as well as indirect antifibrotic effects through significant decreases in liver triglycerides, inflammation, and lipotoxicity. The recent report of 96-week data from the phase 2 SYMMETRY trial (ClinicalTrials.gov; ID NCT05039450) revealed that 39% of subjects in the efruxifermin 50 mg dose arm achieved fibrosis reversal (versus 15% in the placebo arm), marking the first demonstration of histologic cirrhosis reversal in a randomized controlled trial to date. Future studies with efruxifermin and pegozafermin will further clarify the potential role of FGF21 analogs in the F4 population. Future advances in drug development for MASH cirrhosis will require further exploration of novel two- or three-agent combination approaches with metabolic, anti-inflammatory, and anti-fibrotic mechanisms that may enhance synergy on MASH and fibrosis endpoints. There will also be a need for further validation of histologic and biomarker endpoints, such as elastography or ELF, which may serve as surrogate endpoints for accelerated approval, separate from clinical outcomes.

Drug development for MASH with F2-F3 fibrosis has been extensively summarized in multiple recent reviews. Therefore, this concise review aimed to provide a focused summary and interpretation of drug development for MASH cirrhosis and may help inform clinicians, patients, investigators, and industry partners on current progress and future directions in research for this important population.

Acknowledgments

None.

Funding

The authors received no funding for the preparation of this manuscript.

Conflict of interest

JKL received research contracts (to institution) from Gilead, Intercept, Inventiva, Novo Nordisk, Pfizer, and Viking. SAN, AM, VT, TB, DP, and VG report no conflicts of interest.

Author contributions

Manuscript concept and design (JKL, SAN), acquisition of data (SAN, AM, VT, TB, DP, VG, JKL), analysis and interpretation (SAN, AM, VT, TB, DP, VG, JKL), drafting of the manuscript (SAN, AM, VT, TB, DP), critical revision of the manuscript for important intellectual content (VG, JKL), and manuscript supervision (JKL). All authors have approved the publication of this manuscript.

References

[1] Ayonrinde OT. Historical narrative from fatty liver in the nineteenth century to contemporary NAFLD - Reconciling the present with the past. JHEP Rep 2021;3(3):100261. doi:10.1016/j.jhepr.2021.100261, PMID:34036255.

[2] Harrison SA, Loomba R, Dubourg J, Ratziu V, Noureddin M. Clinical Trial Landscape in NASH. Clin Gastroenterol Hepatol 2023;21(8):2001–2014. doi:10.1016/j.cgh.2023.03.041, PMID:37059159.

[3] European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary. Diabetologia 2024;67(11):2375–2392. Erratum in: Diabetologia. 2024;67(11):2608. doi: 10.1007/s00125-024-06258-6doi:10.1007/s00125-024-06196-3, PMID:38869512.

[4] Huby T, Gautier EL. Immune cell-mediated features of non-alcoholic steatohepatitis. Nat Rev Immunol 2022;22(7):429–443. doi:10.1038/s41577-021-00639-3, PMID:34741169.

[5] Le P, Tatar M, Dasarathy S. Projection of the clinical burden of NAFLD in US adults from 2020-2050: A modeling study. Proceedings of the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting, Boston, MA, USA; 2023.

[6] Lee ECZ, Anand VV, Razavi AC, Alebna PL, Muthiah MD, Siddiqui MS,

et al. The Global Epidemic of Metabolic Fatty Liver Disease. Curr Cardiol Rep 2024;26(4):199–210. doi:10.1007/s11886-024-02025-6, PMID:38376745.
[7] Younossi ZM, Mangla KK, Chandramouli AS, Lazarus JV. Estimating the economic impact of comorbidities in patients with MASH and defining high-cost burden in patients with noncirrhotic MASH. Hepatol Commun 2024;8(8):e0488. doi:10.1097/HC9.0000000000000488, PMID:39037377.
[8] Xie Z, Li Y, Cheng L, Huang Y, Rao W, Shi H, Li J. Potential therapeutic strategies for MASH: from preclinical to clinical development. Life Metab 2024;3(5):loae029. doi:10.1093/lifemeta/loae029, PMID:39872142.
[9] Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, *et al*. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology 2020;158(6):1611–1625.e12. doi:10.1053/j.gastro.2020.01.043, PMID:32027911.
[10] Loomba R, Ratziu V, Harrison SA, NASH Clinical Trial Design International Working Group. Expert Panel Review to Compare FDA and EMA Guidance on Drug Development and Endpoints in Nonalcoholic Steatohepatitis. Gastroenterology 2022;162(3):680–688. doi:10.1053/j.gastro.2021.10.051, PMID:34822801.
[11] Day JW, Rosenberg WM. The enhanced liver fibrosis (ELF) test in diagnosis and management of liver fibrosis. Br J Hosp Med (Lond) 2018;79(12):694–699. doi:10.12968/hmed.2018.79.12.694, PMID:30526098.
[12] Rinella ME, Lieu HD, Kowdley KV, Goodman ZD, Alkhouri N, Lawitz E, et al. A randomized, double-blind, placebo-controlled trial of aldafermin in patients with NASH and compensated cirrhosis. Hepatology 2024;79(3):674–689. doi:10.1097/HEP.0000000000000607, PMID:37732990.
[13] Gawrieh S, Vilar-Gomez E, Wilson LA, Pike F, Kleiner DE, Neuschwander-Tetri BA, et al. Increases and decreases in liver stiffness measurement are independently associated with the risk of liver-related events in NAFLD. J Hepatol 2024;81(4):600–608. doi:10.1016/j.jhep.2024.05.008, PMID:38762169.
[14] Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. JAMA 2023;329(18):1589–1602. doi:10.1001/jama.2023.5997, PMID:37159031.
[15] Krupa KN, Nguyen H, Parmar M. Obeticholic Acid. StatPearls 2024;Treasure Island, FLStatPearls Publishing.
[16] Adorini L, Trauner M. FXR agonists in NASH treatment. J Hepatol 2023;79(5):1317–1331. doi:10.1016/j.jhep.2023.07.034, PMID:37562746.
[17] Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145(3):574–82.e1. doi:10.1053/j.gastro.2013.05.042, PMID:23727264.
[18] Zhao J, Li B, Zhang K, Zhu Z. The effect and safety of obeticholic acid for patients with nonalcoholic steatohepatitis: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2024;103(7):e37271. doi:10.1097/MD.0000000000037271, PMID:38363900.
[19] Takenaka S, Fujisawa T, Ichijo H. Apoptosis signal-regulating kinase 1 (ASK1) as a therapeutic target for neurological diseases. Expert Opin Ther Targets 2020;24(11):1061–1064. doi:10.1080/14728222.2020.1821648, PMID:32930624.
[20] Ogier JM, Nayagam BA, Lockhart PJ. ASK1 inhibition: a therapeutic strategy with multi-system benefits. J Mol Med (Berl) 2020;98(3):335–348. doi:10.1007/s00109-020-01878-y, PMID:32060587.
[21] Schuster-Gaul S, Geisler LJ, McGeough MD, Johnson CD, Zagorska A, Li L, et al. ASK1 inhibition reduces cell death and hepatic fibrosis in an Nlrp3 mutant liver injury model. JCI Insight 2020;5(2):123294. doi:10.1172/jci.insight.123294, PMID:31996485.
[22] Younossi ZM, Stepanova M, Lawitz E, Charlton M, Loomba R, Myers RP, et al. Improvement of hepatic fibrosis and patient-reported outcomes in non-alcoholic steatohepatitis treated with selonsertib. Liver Int 2018;38(10):1849–1859. doi:10.1111/liv.13706, PMID:29377462.
[23] Harrison SA, Wong VW, Okanoue T, Bzowej N, Vuppalanchi R, Younes Z, et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials. J Hepatol 2020;73(1):26–39. doi:10.1016/j.jhep.2020.02.027, PMID:32147362.
[24] Chalasani N, Abdelmalek MF, Garcia-Tsao G, Vuppalanchi R, Alkhouri N, Rinella M, et al. Effects of Belapectin, an Inhibitor of Galectin-3, in Patients With Nonalcoholic Steatohepatitis With Cirrhosis and Portal Hypertension. Gastroenterology 2020;158(5):1334–1345.e5. doi:10.1053/j.gastro.2019.11.296, PMID:31812510.
[25] Harrison SA, Rolph T, Knott M, Dubourg J. FGF21 agonists: An emerging therapeutic for metabolic dysfunction-associated steatohepatitis and beyond. J Hepatol 2024;81(3):562–576. doi:10.1016/j.jhep.2024.04.034, PMID:38710230.
[26] Harrison SA, Ruane PJ, Freilich B, Neff G, Patil R, Behling C, et al. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. JHEP Rep 2023;5(1):100563. doi:10.1016/j.jhepr.2022.100563, PMID:36644237.
[27] Harrison S. A., Ruane P.J., Freilich B.L. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2a trial. Nat Med 2021;27:1262–1271. doi:10.1038/s41591-021-01425-3, PMID:34239138.
[28] Mariam Z, Niazi SK. Glucagon-like peptide agonists: A prospective review. Endocrinol Diabetes Metab 2024;7(1):e462. doi:10.1002/edm2.462, PMID:38093651.
[29] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387(10019):679–690. doi:10.1016/S0140-6736(15)00803-X, PMID:26608256.
[30] Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med 2021;384(12):1113–1124. doi:10.1056/NEJMoa2028395, PMID:33185364.
[31] Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, et al. 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(6):511–522. doi:10.1016/S2468-1253(23)00068-7, PMID:36934740.
[32] Alkhouri N, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, et al. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial. J Hepatol 2022;77(3):607–618. doi:10.1016/j.jhep.2022.04.003, PMID:35439567.
[33] Barry-Hamilton V, Spangler R, Marshall D, McCauley S, Rodriguez HM, Oyasu M, et al. Allosteric inhibition of lysyl oxidase-like-2 impedes the development of a pathologic microenvironment. Nat Med 2010;16(9):1009–1017. doi:10.1038/nm.2208, PMID:20818376.
[34] Harrison SA, Abdelmalek MF, Caldwell S, Shiffman ML, Diehl AM, Ghalib R, et al. Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis. Gastroenterology 2018;155(4):1140–1153. doi:10.1053/j.gastro.2018.07.006, PMID:29990488.
[35] Linton SD, Aja T, Armstrong RA, Bai X, Chen LS, Chen N, et al. First-in-class pan caspase inhibitor developed for the treatment of liver disease. J Med Chem 2005;48(22):6779–6782. doi:10.1021/jm050307e, PMID:16250635.
[36] Barreyro FJ, Holod S, Finocchietto PV, Camino AM, Aquino JB, Avagnina A, et al. The pan-caspase inhibitor Emricasan (IDN-6556) decreases liver injury and fibrosis in a murine model of non-alcoholic steatohepatitis. Liver Int 2015;35(3):953–966. doi:10.1111/liv.12570, PMID:24750664.
[37] Garcia-Tsao G, Fuchs M, Shiffman M, Borg BB, Pyrsopoulos N, Shetty K, et al. Emricasan (IDN-6556) Lowers Portal Pressure in Patients With Compensated Cirrhosis and Severe Portal Hypertension. Hepatology 2019;69(2):717–728. doi:10.1002/hep.30199, PMID:30063802.
[38] Harrison SA, Goodman Z, Jabbar A, Vemulapalli R, Younes ZH, Freilich B, et al. A randomized, placebo-controlled trial of emricasan in patients with NASH and F1-F3 fibrosis. J Hepatol 2020;72(5):816–827. doi:10.1016/j.jhep.2019.11.024, PMID:31887369.
[39] Garcia-Tsao G, Bosch J, Kayali Z, Harrison SA, Abdelmalek MF, Lawitz E, et al. Randomized placebo-controlled trial of emricasan for non-alcoholic steatohepatitis-related cirrhosis with severe portal hypertension. J Hepatol 2020;72(5):885–895. doi:10.1016/j.jhep.2019.12.010,

PMID:31870950.
[40] Qosa H, de Oliveira CHMC, Cizza G, Lawitz EJ, Colletti N, Wetherington J, et al. Pharmacokinetics, safety, and tolerability of BMS-986263, a lipid nanoparticle containing HSP47 siRNA, in participants with hepatic impairment. Clin Transl Sci 2023;16(10):1791–1802. doi:10.1111/cts.13581, PMID:37654022.
[41] Sato Y, Murase K, Kato J, Kobune M, Sato T, Kawano Y, et al. Resolution of liver cirrhosis using vitamin A-coupled liposomes to deliver siRNA against a collagen-specific chaperone. Nat Biotechnol 2008;26(4):431–442. doi:10.1038/nbt1396, PMID:18376398.
[42] Lawitz EJ, Shevell DE, Tirucherai GS, Du S, Chen W, Kavita U, et al. BMS-986263 in patients with advanced hepatic fibrosis: 36-week results from a randomized, placebo-controlled phase 2 trial. Hepatology 2022;75(4):912–923. doi:10.1002/hep.32181, PMID:34605045.