

## Combination strategies for pharmacologic treatment of non-alcoholic steatohepatitis

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### Abstract

Non-alcoholic steatohepatitis (NASH) is defined as hepatic steatosis, inflammation, and hepatocyte injury with or without fibrosis. It has emerged as the second leading indication for liver transplantation with a rising death rate in the non-transplantable population. While there are many drugs in evaluation, currently no approved therapies are on the market for this condition. Given this importance, the Food and Drug Administration has provided formal guidance regarding drug development for stopping or reversing NASH or NASH associated fibrosis. The complex pathogenesis of NASH and its bidirectional relationship with metabolic syndrome has highlighted multiple drugs of interest that address metabolic, inflammatory, and fibrotic factors. A few promising liver specific targets include farnesoid X receptor agonists and peroxisome proliferator-activated receptor agonists. Previously studied drug classes such as glucagon-like peptide-1 analogs or sodium/glucose transport protein 2 inhibitors have also demonstrated ability to improve hepatic steatosis. Here we discuss current rationale, scientific work, and preliminary data in combining multiple drugs for the purposes of a multimodal attack on the pathogenesis of NASH. We highlight multiple Phase 2 and Phase 3 studies that demonstrate the potential to achieve a response rate higher than previously assessed monotherapies for this condition. Ultimately, one of these combination strategies may rise above in its safety and efficacy to become a part of a standardized approach to NASH.

**Key Words:** Non-alcoholic steatohepatitis; Fatty liver; Combination treatment; Drug therapy; Pharmacologic treatment; Clinical trials

**Core Tip:** Multimodal combination approaches targeting two or more molecular pathways contributing to steatohepatitis and liver fibrosis are needed to augment efficacy of novel investigational drug regimens to achieve non-alcoholic steatohepatitis (NASH) resolution and NASH fibrosis improvement.

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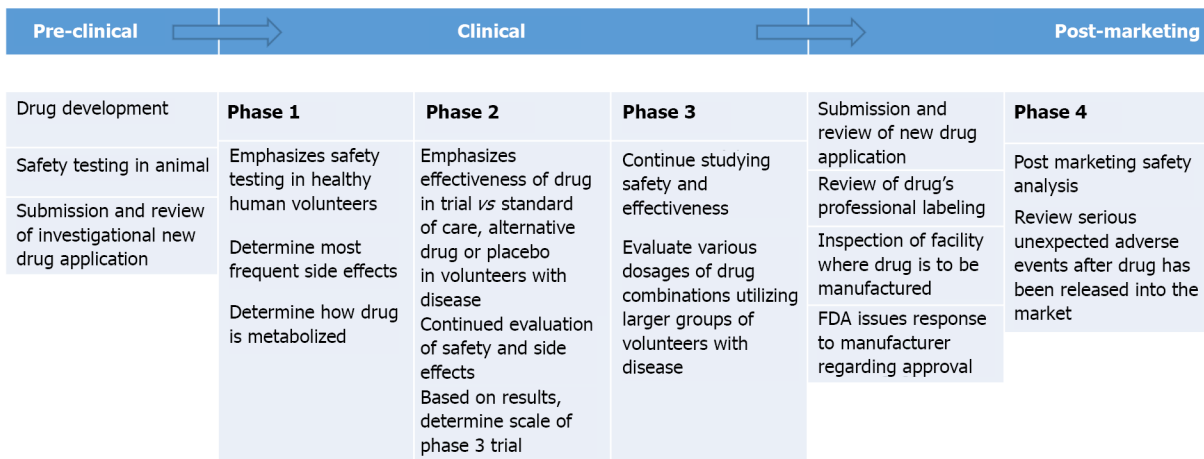
## INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is defined as the presence of  $\geq 5\%$  hepatic steatosis and inflammation with hepatocyte injury with or without fibrosis. Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of pathology encompassing hepatic steatosis, steatohepatitis (NASH), and liver fibrosis, and poses a significant challenge to the medical community as there are currently no Food and Drug Administration (FDA) approved therapies available on the market. The definition of NAFLD includes the lack of secondary causes of hepatic steatosis such as alcohol consumption, steatogenic medication or hereditary liver disease. With NAFLD-associated death rates on the rise and NASH emerging as the second most common indication for liver transplantation, there has been heightened urgency to target various disease pathways in NASH development with the hopes of controlling the global impact of this disease[1,2]. With this rising importance, the FDA has published formal guidance regarding drug development aimed at stopping or reversing NASH and NASH fibrosis. The current drug development pipeline contains many mono-therapeutic options which address a wide range of metabolic, inflammatory, and fibrosis target pathways associated with NASH pathogenesis.

The pathophysiology of NASH is based on a bidirectional relationship between type 2 diabetes mellitus (T2DM), hypertension, obesity and dyslipidemia—or metabolic syndrome. This relationship contributes to excess free fatty acids generated from lipolysis and de novo lipogenesis in the liver, which creates lipotoxic species which induce oxidative stress, inflammasome activation, and fibrinogenesis[3]. Liver specific targets aimed at decreasing histologic inflammation or fibrosis such as farnesoid X receptor (FXR) agonists or peroxisome proliferator-activated receptor (PPAR) agonists are currently being evaluated for the treatment of NASH. These are in addition to drug classes such as glucagon-like peptide-1 (GLP-1) agonists and sodium/glucose transport protein 2 inhibitors that were initially approved for treatment of diabetes but have demonstrated the ability to decrease liver fat content[4,5]. While individually these agents have shown promise in early trials, there has been growing interest in pursuing a multimodal combination approach targeting two or more molecular targets/pathways responsible for NASH and NASH-associated liver fibrosis, particularly in context of modest effects of single agent strategies on histologic endpoints, with fewer than 50% of patients achieving either NASH resolution or fibrosis improvement of one stage or greater[6]. Therefore, this mini review will succinctly summarize the current efforts to examine combination strategies of drugs which may further augment therapeutic response in patients with NASH.

## FDA APPROVAL PATHWAY

The FDA generally has two pathways for drug approval. The traditional pathway focuses on clinical benefit endpoints (*i.e.*, morbidity and mortality) and requires long term data. A brief review is provided in [Figure 1](#). The accelerated approval pathway is intended to expedite the process for serious medical conditions with unmet needs. This pathway relies on short term surrogate markers that would reliably predict long term clinical outcomes to support drug approval. To inform clinical trial design for investigational drugs under evaluation for NASH, industry guidance was issued by the FDA in 2018 with a focus on patients with non-cirrhotic NASH with stage 2-3 liver fibrosis[7]. Although histologic endpoints were reinforced as required for assessment of surrogate endpoints for NASH and liver fibrosis, the agency encouraged the development and validation of noninvasive biomarkers in clinical trials to accelerate drug development. NASH was defined as a NAFLD activity score (NAS) greater than or equal to 4 with at least 1 point each in inflammation and ballooning degeneration, plus a NASH Clinical Research Network fibrosis score greater than stage 1 fibrosis but less than stage 4 for enrollment in these trials. Lastly, the primary regulatory endpoints required to support accelerated approval include: (1) NASH resolution on histology (NAS less than 4 with individual components scores of 0 for



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Figure 1 Flow diagram of standard Food and Drug Administration drug approval process.

ballooning degeneration and 0-1 for inflammation) without worsening fibrosis; (2) Improvement in liver fibrosis greater than or equal to one stage without worsening NASH; or (3) NASH resolution and improvement in fibrosis by one stage or greater. Clinical benefit for these drugs was defined as superiority to placebo in delayed disease progression measured by a composite endpoint including progression to cirrhosis, hepatic decompensation, change in MELD score, liver transplantation, or all-cause mortality.

## DRUGS IN DEVELOPMENT—PHASE 2

Key phase 2 trials for NASH therapeutics are summarized in Table 1. In brief, one major class being pursued is fibroblast growth factor 21 (FGF21) agonists such as pegbelfermin. FGF21 is endogenously produced by the liver and has a pleiotropic effect on metabolism that may benefit patients with NASH. Endogenous FGF21 concentrations are elevated as much as 10-fold in patients with obesity, NAFLD or NASH, leading to the hypothesis that these may represent an FGF21-resistant state which may benefit from exogenous stimulation to improve insulin sensitivity and lipid metabolism[8]. GLP-1 is an incretin hormone made by intestinal cells post prandially for which receptors are predominantly in the pancreas, adipose tissue and brain. It regulates plasma glucose by stimulating glucose release and inhibiting glucagon secretion. GLP-1 agonists have previously shown to improve hepatic steatosis, decrease liver inflammation, and ameliorate insulin resistance in murine models of fatty liver disease. Semaglutide and liraglutide have shown promising results with statistically significant NASH improvement or resolution compared to placebo[9,10]. Norursodeoxycholic acid is an orally administered side chain-shortened homologue of ursodeoxycholic acid that undergoes hepatic enrichment with hepatoprotective, anti-inflammatory, and antifibrotic activity. It has shown significant reduction of serum alanine aminotransferase (ALT) within 12 wk of treatment when compared with placebo, encouraging further investigation[11]. Aldafermin is an analogue of fibroblast growth factor 19 (FGF19) which regulates bile acid metabolism and fat storage in the liver. FGF19 levels are lower in patients with NAFLD and insulin resistance. Activation of the FGF19 pathway has been shown to improve insulin sensitivity and liver steatosis. In a 24-wk placebo-controlled trial, the aldafermin group experienced a significant reduction in absolute liver fat content compared with placebo ( $P = 0.002$ ) and fibrosis improvement of at least 1 stage (38% vs 18%,  $P = 0.10$ )[12]. The currently ongoing phase 2b ALPINE 4 study is designed to assess the efficacy, safety and tolerability of this agent (NCT04210245).

FXR agonists, which bind to the transcription factor FXR to help regulate bile acid metabolism are in multiple phases of clinical trial investigation. The FXR agonist tropifexor has demonstrated a robust and dose-dependent decrease in ALT, hepatic fat fractionation, and body weight with good safety and tolerability after 12 wk of treatment in a phase 2 trial[13]. The PPAR $\alpha$ ,  $\beta/\delta$  and  $\gamma$ , play a central role in the regulation of glucose and lipid metabolism and of the inflammatory and fibrogenic pathways which contribute to NASH pathogenesis. Lanifibranor (IVA337), a pan-PPAR agonist, combines pharmacological effects that could improve fatty acid oxidation, dyslipidemia, and insulin sensitivity, and has demonstrated anti-inflammatory, antifibrotic and hepatoprotective effects in preclinical models and phase 1/2 trials. TVB-2640 is an orally bioavailable, first-in-class fatty acid synthase (FASN) inhibitor. FASN is a key enzyme in the de novo lipogenesis pathway that is responsible for the synthesis of excess fat and activation of fibrogenic and inflammatory mechanisms in the liver of patients with NASH. TVB-2640 demonstrated significant improvement in several NASH endpoints in the FASCINATE-1 trial as

Table 1 Phase 2 trials in non-alcoholic steatohepatitis

Trial name/NCT number	Manufacturer	Drugs	Mechanism of action	Enrollment (targeted)	Study arms	Duration	Primary or relevant end point(s)	Results/SE
NCT03976401	Akero Therapeutics	AKR-001	FGF 21 receptor agonist	80	(1) AKR-001 50 mg QD; and (2) Placebo	112	Change in liver fat fraction measured by MRI-PDFF	Ongoing
NCT04541186	89bio	BIO89-100	FGF 21 receptor agonist	90	(1) BIO89-100 (QW or every 2 wk); and (2) Placebo	112	Change in various lab parameters TG, LDL, HDL, fasting glucose. Change in liver fat fraction measured by MRI-PDFF	Ongoing
NCT02097277	Bristol-Myers Squibb	Pegbelfermin (BMS-986036)	FGF 21 receptor agonist	120	(1) Pegbelfermin 1 mg QD; (2) Pegbelfermin 5 mg QD; (3) Pegbelfermin 20 mg QD; (4) Pegbelfermin 20 mg weekly; and (5) Placebo	84	Safety, tolerability, and change in HbA1c. Change in insulin sensitivity, lipids, adiponectin, and disease progression biomarkers	No significant effects of pegbelfermin versus placebo on HbA1c. Pegbelfermin 20 mg/d significantly improved high-density lipoprotein cholesterol and triglycerides. Most frequent adverse events were injection-site bruising and diarrhea
NCT01237119	Novo Nordisk	Liraglutide	GLP-1analogue	52	(1) Liraglutide 1.8 mg SC QD; and (2) Placebo	336	Resolution of NASH without worsening fibrosis	39% who received liraglutide and underwent end-of-treatment liver biopsy had resolution of definite non-alcoholic steatohepatitis compared with 9% in placebo ( $P = 0.019$ ). Side effects diarrhea and loss of appetite
NCT02970942	Novo Nordisk	Semaglutide	GLP-1 analogue	320	(1) Semaglutide 0.1 mg SC QD; (2) Semaglutide 0.2 mg SC QD; (3) Semaglutide 0.4 mg SC QD; and (4) Placebo	504	Resolution of NASH without worsening fibrosis. Improvement in fibrosis, LFTs, A1c level	NASH resolution was achieved in 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group ( $P < 0.001$ for semaglutide 0.4 mg <i>vs</i> placebo). Side effects including nausea, constipation, and vomiting which was higher in the 0.4-mg group
2013-004605-38	Dr Falk Pharma GmbH	Norursodeoxycholic acid	homologue of ursodeoxycholic acid, undergoes hepatic enrichment with hepatoprotective, anti-inflammatory, and antifibrotic activity	198	(1) 500 mg norursodeoxycholic acid QD; (2) 1500 mg norursodeoxycholic acid QD; and (3) Placebo	112	Change in ALT levels	Dose-dependent reduction in ALT with norursodeoxycholic acid versus placebo, with a significant effect in the 1500 mg group ( $P < 0.0001$ ). Side effects included headache, gastrointestinal disorders, and infections
COHORT 4/NCT02443116	NGM Biopharmaceuticals	Aldafermin	Analog of fibroblast growth factor 19, inhibits bile acid synthesis and regulates metabolic homeostasis	78	(1) aldafermin 1 mg QD; and (2) Placebo	168	Improvement in liver fibrosis of greater or equal to one stage with no worsening of NASH	Aldafermin group with higher rate of liver fat content reduction compared to placebo (7.7% <i>vs</i> 2.7%, $P = 0.02$ ). Aldafermin produced significantly greater decrease in bile acids, liver enzymes. Fibrosis improvement without worsening NASH higher in aldafermin group (38% <i>vs</i> 18%, $P = 0.10$ ). NASH resolution without worsening fibrosis higher in aldafermin group (24% <i>vs</i> 9%, $P = 0.20$ ). Side effects include diarrhea, headache, abdominal distention and peripheral edema

ALPINE 4/NCT04210245	NGM Biopharmaceuticals	Aldafermin	Analog of fibroblast growth factor 19, inhibits bile acid synthesis and regulates metabolic homeostasis	72	(1) Aldafermin 0.3 mg QD; (2) Aldafermin 1 mg QD; (3) Aldafermin 3 mg; and (4) Placebo	168	Improvement in liver fibrosis of greater or equal to one stage with no worsening of NASH	Ongoing
FLIGHT-FXR/NCT02855164	Novartis Pharmaceutical	Tropifexor	FXR agonist	152	(1) TXR 140 g QD; (2) TXR 200gr QD; and (3) Placebo	84	Changes in liver fat fraction, liver enzymes, body weight	End point achieved in TXR 800 mg <i>vs</i> 1200 mg <i>vs</i> Placebo (51% <i>vs</i> 55% <i>vs</i> 34%, $P = 0.001$ ). Side effects include mild pruritus and increase in LDL
NATIVE/NCT03008070	Inventiva	Lanifibranor	PPAR agonist	247	(1) Lanifibranor 800 mg QD; (2) Lanifibranor 1200 mg QD; and (3) Placebo	168	Responder analysis based on the improvement of the SAF activity score	L800 mg <i>vs</i> 1200 mg <i>vs</i> Placebo (51% <i>vs</i> 55% <i>vs</i> 34%) $P = 0.0015$ . SE weight gain, peripheral edema
FASCINATE-1/NCT03938246	Sagimet Biosciences Inc	TVB-2640	FASN inhibitor	99	(1) TVB2640 25 mg QD; (2) TVB2640 50 mg; and (3) Placebo	84	Change in hepatic fat fraction from baseline in subjects with NASH by proton-density fat fraction by magnetic resonance imaging	Dose-dependent relative changes in liver fat by MRI-PDFF were -28.2% with 50 mg ( $P < 0.005$ <i>vs</i> placebo), -9.6% with 25 mg, and +4.5% with placebo. 30% relative reduction in liver fat at week 12 were 61% ( $P < 0.001$ <i>vs</i> placebo)
NCT02856555	Gilead Sciences	Firsocostat	Acetyl-coenzyme A carboxylase Inhibitor	126	(1) Firsocostat 20 mg QD; (2) Firsocostat 5 mg QD; and (3) Placebo	84	Safety and tolerability. Secondary end point efficacy (NASH improvement without fibrosis)	Decrease of at least 30% from baseline in MRI-PDFF occurred in 48% of patients with 20 mg ( $P = 0.004$ ), 23% given 5 mg ( $P = 0.43$ ), and 15% given placebo. SE cause, abdominal pain, diarrhea
VOYAG/LBP20	Viking therapeutics	VK2809	Thyroid beta receptor agonist, selectively cleaved in hepatic tissue	45	(1) VK2809 5 mg QD; (2) VK2809 10 mg QOD; (3) VK280910 mg QD; and (4) Placebo	84	Safety, tolerability and efficacy in reducing liver fat content and LDL	< Liver fat content was 8.7% for 5 mg QD ( $P = 0.0014$ ) <i>vs</i> 8.9% 10 mg QOD ( $P = 0.013$ ) <i>vs</i> 10.6% for 10 mg QD ( $P = 0.0030$ ), <i>vs</i> 1.1% for placebo. 70% in VK2809 therapy showed a $\geq 50\%$ . Reduction in MRI-PDFF ( $P = 0.014$ )
NCT02912260	Madrigal Pharmaceuticals	Resmetirom (MGL-3196)	Selective thyroid hormone receptor- $\beta$ agonist	125	(1) Resmetirom 80 mg QD; and (2) Placebo	252	Change in liver fat fraction measured by MRI-PDFF	80 mg <i>vs</i> placebo reduction of hepatic fat at week 12 (-32.9% <i>vs</i> -10.4%; $P < 0.0001$ ) and week 36 (-37.3% <i>vs</i> -8.5%; $P < 0.0001$ )
NCT02784444	Cirius Therapeutics	MSDC-0602K	Insulin sensitizer designed to preferentially target the mitochondrial pyruvate carrier with direct binding to the transcriptional factor PPAR $\gamma$	392	(1) MSDC-0602K 62.5 mg QD; (2) MSDC-0602K 125 mg QD; (3) MSDC-0602K 250 mg QD; and (4) Placebo	364	Hepatic histological and activity score improvement in either ballooning or lobular inflammationNo increase in fibrosis stage at 12 mo	Primary end point placebo 29.7%, <i>vs</i> 62.5 mg 29.8%, <i>vs</i> 125 mg 32.9% <i>vs</i> 250 mg 39.5% (95% CI: 0.44–1.81) (95% CI: 0.60–2.48), (95% CI: 0.83–3.27)

FGF: Fibroblast growth factor; MRI-PDFF: Magnetic resonance imaging with proton density fat fraction; GLP-1: Glucagon-like peptide-1; FXR: Farnesoid X receptor; PPAR: Peroxisome proliferator-activated receptor; FASN: Fatty acid synthase.

summarized in Table 1[14]. Firsocostat (GS-0976) is an inhibitor of ACC (acetyl-coenzyme A carboxylase) which catalyzes de novo lipogenesis in the liver. In a randomized placebo-controlled trial, firsocostat 20 mg decreased hepatic steatosis and surrogate markers of fibrosis[15]. VK2809 is a small

molecule prodrug of a potent thyroid beta receptor agonist which has demonstrated favorable effects on lipid metabolism and biomarkers of hepatic steatosis and steatohepatitis in a phase 2 trial, supporting its potential role in patients with NASH[16]. MSDC-0602K is a novel insulin sensitizer designed to preferentially target the mitochondrial pyruvate carrier while minimizing direct binding to the transcriptional factor PPAR $\gamma$ . MSDC-0602K did not demonstrate statistically significant effects on primary and secondary histologic endpoints in a phase 2 trial, but favorable effects on liver cell injury and glucose metabolism support further investigation for in patients with type 2 diabetes[17].

## DRUGS IN DEVELOPMENT—PHASE 3

Novel investigational agents which have completed are undergoing evaluation in phase 3 trials are summarized in **Table 2**. Obeticholic acid, an FXR agonist, has been shown to improve the histological features of NASH, with fibrosis improvement in 23% of patients treated with Obeticholic acid compared with 12% in placebo group[18]. Elafibranor, a PPAR agonist, improves liver enzymes, lipids, glucose levels, and markers of systemic inflammation and is being tested in a phase 3 study (NCT02704403)[19]. Aramchol inhibits steroyl-CoA desaturase 1, a key enzyme in hepatic lipogenesis that converts saturated fatty acids into monounsaturated fatty acid. In the phase 2b ARREST trial, aramchol demonstrated liver fat reduction, biochemical improvement, NASH resolution and fibrosis reduction in a dose response pattern[20]. It has since been included in an ongoing phase 3 trial to test its safety and efficacy (NCT04104321). Cenicriviroc is an oral, dual antagonist of C-C motif chemokine receptor (CCR) types 2 and 5. It has shown anti-inflammatory and anti-fibrotic properties, which are mediated by CCR types 2 and 5 (CCR2/CCR5) blockade. In a randomized double-blind phase 2b study of 289 subjects, cenicriviroc was associated with a statistically significant improvement in NASH fibrosis of one stage or greater *vs* placebo (20% *vs* 10%;  $P = 0.02$ )[21]. A phase 3 randomized, double-blind, placebo-controlled trial (AURORA) is currently ongoing with evaluation of 2000 adults with NASH who are treated with cenicriviroc or placebo for 52 wk[22]. Resmetirom is a liver-directed, orally active, selective thyroid hormone receptor- $\beta$  agonist designed to improve NASH by increasing hepatic fat metabolism and reducing lipotoxicity. In a phase 2b study, resmetirom treated patients showed a relative reduction of hepatic fat compared with placebo with statistically significant NASH resolution *vs* placebo[23], and is currently under evaluation in a phase 3 registration trial (NCT03900429). GR-MD-02 (belapectin), is an inhibitor of galectin 3 that reduces liver fibrosis and portal hypertension. In a phase 2 trial, belapectin was safe but not associated with significant reduction in hepatic venous pressure gradient (HVPG) or fibrosis. However, in a subgroup analysis of patients without esophageal varices, 2 mg/kg belapectin reduced HVPG and development of varices, suggesting a possible benefit in patients with NASH cirrhosis without esophageal varices[24]. In the phase 3 NAVIGATE trial, the safety and efficacy of belapectin is under evaluation with primary clinical endpoints of development of varices and event-free survival (NCT04365868).

## COMBINATION THERAPEUTICS

The rationale of combining two or more strategies for NASH therapy aims to augment rates of NASH resolution and NASH fibrosis improvement. By targeting the development of steatohepatitis, liver fibrosis as well as controlling metabolic syndrome, we may achieve response rates higher than 32% as seen currently *via* trials of drugs as monotherapy[6]. **Table 3** is a collection of studies currently underway, and some completed, that evaluate multidrug regimens for the treatment of NASH. FXR agonists, which regulate bile acid metabolism, are one major class of drugs incorporated in many of these trials. Obeticholic acid, a promising drug in this class, has demonstrated the dose-dependent ability to improve liver fibrosis and steatohepatitis in NASH patients with stage F2/F3 fibrosis based on initial and secondary analysis of the REGENERATE trials[18,25]. Cilofexor, another FXR agonist, has been tested in combination with firsocostat, an ACC inhibitor and selonsertib, an ASK1 inhibitor, in the phase 2b ATLAS study that demonstrated improvements in liver enzymes, fibrosis, NAS score on histology and improvements in liver elastography in the cilofexor/firsocostat group compared to placebo[26]. Ongoing studies with tropifexor include combinations with cenicriviroc and LYS0006 with early results still pending and waiting to be reviewed.

By now it is well known that features of metabolic syndrome increase the risk of developing NAFLD. Type 2 diabetes, specifically, is a risk factor for NASH and its presence increases the risk of progression of NASH fibrosis[27,28]. Therefore, some of the ongoing trials in combination therapy for NASH include semaglutide, pioglitazone or licogliflozin; from drug classes that traditionally have been utilized for the management of T2DM. In one randomized, placebo controlled trial in patients with biopsy proven NASH, a GLP-1 analog, liraglutide, was associated with greater improvement in steatohepatitis and lower progression of fibrosis[9]. A proof-of-concept trial is currently underway including semaglutide along with cilofexor and firsocostat. Licogliflozin, which has shown benefit in lowering liver fat content, is being studied as part of a combination trial with tropifexor in the ELIVATE trial.

Table 2 Phase 3 trials in non-alcoholic steatohepatitis

Trial name/NCT number	Manufacturer	Drugs	Mechanism of action	Enrollment (targeted)	Study arms	Duration (weeks)	Primary or relevant end point(s)	Results
REGENERATE/NCT02548351	Intercept Pharmaceuticals	Obeticholic acid	Farnesoid X receptor agonist	2480	(1) Obeticholic acid 10 mg QD; (2) Obeticholic acid 25 mg QD; and (3) Placebo	72-378	Fibrosis improvement ( $\geq 1$ stage) with no worsening of NASH, or NASH resolution with no worsening of fibrosis	Fibrosis improvement endpoint- (12%) placebo, (18%) obeticholic acid 10 mg, (23%) obeticholic acid group 25 mg. Safety most common adverse event was pruritus
RESOLVE-IT/NCT02704403	Genfit	Elafibranor	PPAR agonist	2157	(1) Elafibranor 120 mg QD; and (2) Placebo	72-216	Change in fibrosis. Change in histologic score of NASH	ongoing
ARMOR/NCT0410432	Galmed pharmaceuticals	Aramchol	SCD-1 inhibitor	247	(1) Aramchol 600 mg QD; (2) Aramchol 400 mg qd; and (3) Placebo	364	(1) Evaluate the safety and efficacy as measured with % change in the liver triglycerides concentration; and (2) Safety	Ongoing
AURORA/NCT03028740	Tobira Therapeutics	Cenicriviroc	Dual antagonist of CCR types 2 and 5	2000	(1) Cenicriviroc 150 mg; and (2) Placebo	364	(1) Proportion of subjects with $\geq 1$ -stage improvement in liver fibrosis and no worsening of steatohepatitis at month 12 relative to screening; and (2) Safety	Ongoing
MAESTRO-NASH/NCT03900429	Madrigal Pharmaceuticals	Resmetirom	Selective thyroid hormone receptor- $\beta$ agonist	2000	(1) resmetirom 80 mg QD; (2) resmetirom 100 mg QD; and (3) Placebo	364	NASH resolution, with at least a 2-point reduction in NAS (NASH Activity Score-biopsy), and with no worsening of fibrosis. Secondary end p. (1) Liver fibrosis improvement of at least one stage, with no worsening of NASH; and (2) Lowering of LDL-cholesterol	Ongoing
NAVIGATE/NCT04365868	Galectin Therapeutics	GR-MD-02 (belapectin)	Inhibitor of galectin 3	1010	(1) Belapectin 2 mg/kg intravenously (IV) every other week; (2) Belapectin 4 mg/kg intravenously (IV) every other week; and (3) Placebo	504	Development of new esophageal varices at 78 weeks in the belapectin group Cumulative incidence rate of decompensations and event-free survival by time to first cirrhosis related clinical event	Ongoing

PPAR: Peroxisome proliferator-activated receptor; SCD-1: Steroyl-CoA desaturase 1; CCR: C-C motif chemokine receptor

Numerous trials have already established the benefit of pioglitazone in improving inflammation and fibrosis in patients with biopsy proven NASH and therefore it is included as recommended management for a select group of patients according to the most recent American Association for the Study of Liver Diseases guidelines on NAFLD[29].

Aside from the ability to decrease inflammation and fibrosis in NASH, allowing treatment with lower doses of various drugs in combination or improvement the side effect profile are two alternate motives for pursuing combination therapy. In Wister rat models for NASH, one group was able to demonstrate a synergistic therapeutic effect on inflammation and oxidative stress from combining elafibranor and obeticholic acid at lower doses than with each drug in monotherapy[30]. FXR agonists have been shown to increase low density lipoprotein (LDL) cholesterol concentrations. In the CONTROL study, the

Table 3 Multidrug regimens for the treatment of non-alcoholic steatohepatitis

Trial name/NCT number	Phase	Manufacturer	Drugs	Mechanism of action	Enrollment (targeted)	Study arms	Duration (weeks)	Primary or relevant end point(s)
NCT02781584 (Proof of Concept)	1	Gilead Sciences	Selonsertib, firsocostat, cilofexor, fenofibrate, icosapent ethyl	(1) Selonsertib-selective ASK1 inhibitor; (2) Firsocostat-ACC inhibitor; (3) Cilofexor-FXR agonist; (4) Fenofibrate-PPAR agonist; and (5) Icosapent ethyl-under investigation	220	(1) Selonsertib; (2) Firsocostat; (3) Cilofexor; (4) Selonsertib + cilofexor; (5) Selonsertib + firsocostat; (6) Firsocostat + cilofexor; (7) Firsocostat (cirrhotic patients); (8) Cilofexor (cirrhotic patients); (9) Selonsertib + firsocostat + cilofexor; (10) Firsocostat + fenofibrate 48 mg; (11) Firsocostat + fenofibrate 145 mg; and (12) Icosapent ethyl + firsocostat + cilofexor	12	(1) Adverse events; (2) Serious adverse events; and (3) Lab abnormalities
ATLAS/NCT03449446	2	Gilead Sciences	Selonsertib, firsocostat, cilofexor	(1) Selonsertib-selective ASK1 inhibitor; (2) Firsocostat-ACC inhibitor; and (3) Cilofexor-FXR agonist	395	(1) Selonsertib + firsocostat + placebo; (2) Selonsertib + cilofexor + placebo; (3) Firsocostat + cilofexor + placebo; (4) Selonsertib + placebo + placebo; (5) Firsocostat + placebo + placebo; (6) Cilofexor + placebo + placebo; and (7) 3 placebos	48	(1) Adverse events; (2) Lab abnormalities; and (3) Improvement of $\geq 1$ -stage in fibrosis without worsening of NASH
NCT03987074	2	Gilead Sciences, Novo Nordisk	Cilofexor, semaglutide, firsocostat	(1) Semaglutide-GLP-1 agonist; (2) Firsocostat-ACC inhibitor; and (3) Cilofexor-FXR agonist	109	(1) Semaglutide; (2) Firsocostat + semaglutide; (3) Semaglutide + cilofexor 30 mg; (4) Semaglutide + cilofexor 100 mg; and (5) Semaglutide + firsocostat + cilofexor	24	(1) Adverse events; (2) Serious adverse events; and (3) Lab abnormalities
ELIVATE/NCT04065841	2	Novartis	Tropifexor, licoglitflozin	(1) Tropifexor-FXR agonist; and (2) Licoglitflozin-SGLT1/2 inhibitor	380	(1) Tropifexor + licoglitflozin; (2) Tropifexor + placebo; (3) Licoglitflozin + placebo; and (4) 2 placebos	48	(1) Improvement of $\geq 1$ -stage in fibrosis without worsening of NASH; and (2) Resolution of NASH without worsening fibrosis
NCT03776175	2A	Pfizer	PF-05221304, PF-06865571	(1) PF-05221304-ACC inhibitor; and (2) PF-06865571 - DGAT 2 inhibitor	99	(1) ACC inhibitor + placebo; (2) DGAT2 inhibitor + placebo; (3) ACC inhibitor + DGAT2 inhibitor; and (4) 2 placebos	6	Improvement in fat fraction
TANDEM/NCT03517540	2	Novartis, Allergan	Tropifexor, cenicriviroc	(1) Tropifexor-FXR agonist; and (2) Cenicriviroc-CCR2/CCR5 inhibitor	193	(1) Tropifexor; (2) Cenicriviroc; (3) Tropifexor dose 1 + cenicriviroc; and (4) Tropifexor dose 2 + cenicriviroc	48	(1) improvement in fibrosis; and (2) Resolution of steatohepatitis
CONTROL/NCT02633956	2	Intercept Pharmaceuticals	Obeticholic acid, atorvastatin	(1) Obeticholic acid-FXR agonist; and (2) Atorvastatin-HMG-CoA reductase inhibitor	84	(1) Obeticholic acid 5 mg/10 mg/25 mg + atorvastatin 10 mg/20 mg; and (2) Placebo + atorvastatin 10 mg/20 mg	16	(1) Change in LDL concentration; (2) Change in LDL particle size; and (3) Change in LDL particle concentration
NCT04235205	2	Albireo Pharma	Elobixibat, cholestyramine	(1) Elobixibat-IBAT inhibitor; and (2) Cholestyramine-bile acid binding resin	100	(1) Elobixibat + cholestyramine; (2) Elobixibat + placebo; (3) Placebo + cholestyramine; and (4) 2 placebos	16	(1) Change in liver fat fraction measured by MRI-PDFF; and (2) Change in fibrosis measured by MRE
PUVENAFLD/NCT04198805	2	DSM Nutritional Products	Vitamin E, omega-3 fatty acid	(1) Vitamin E-scavenging reactive oxidation species; and (2) Omega 3 FA-competing with omega 6 for cyclooxygenase and lipoxygenase-mediated	200	(1) Vitamin E + placebo; (2) Omega-3 fatty acid + placebo; (3) Omega 3-fatty acid + vitamin E; and (4) 2 placebos	24	(1) Change in liver fat fraction measured by MRI-PDFF; (2) Change in liver enzymes; and (3) FIB-4 scores



NEXSCOT/NCT04147195	2	Novartis	LYS006, tropifexor	inflammatory eicosanoid production, forming anti-inflammatory compounds (1) Tropifexor-FXR agonist; and (2) LYS006-leukotriene A4 hydrolase inhibitor	250	(1) LYS006; and (2) LYS006 + tropifexor	21	(1) Change in ELF score; and (2) Change in liver fat fraction measured by MRI-PDF
NCT02466516	2	Gilead Sciences	Selonsertib, simtuzumab	(1) Selonsertib-selective ASK1 inhibitor; and (2) Simtuzumab-lysyl oxidase-like 2 inhibitor	72	(1) Selonsertib 6 mg; (2) Selonsertib 18 mg; (3) Selonsertib 6 mg + simtuzumab; (4) Selonsertib 18 mg + simtuzumab; and (5) Simtuzumab	24	(1) Adverse events; (2) Serious adverse events; (3) Lab abnormalities; and (4) Number of participants who prematurely discontinued study due to adverse events
NCT01703260	2	AstraZeneca	Roflumilast, pioglitazone	(1) Roflumilast-phosphodiesterase 4 inhibitor; and (2) Pioglitazone-PPAR agonist	16	(1) Roflumilast + pioglitazone; (2) Roflumilast + placebo; and (3) Pioglitazone + placebo	20	(1) Change in liver enzymes; and (2) Change in liver fat fraction measured by MRI-PDF

ASK1: Apoptosis signal-regulating kinase-1; ACC: Acetyl-coenzyme A carboxylase; FXR: Farnesoid X receptor; PPAR: Peroxisome proliferator-activated receptor; GLP-1: Glucagon-like peptide-1; SGLT: Sodium/glucose transport protein; DGAT: Diacylglycerol acyltransferase; CCR: C-C motif chemokine receptor; IBAT: Ileal bile acid transporter.

authors were able to lower the LDL concentration below baseline with the addition of atorvastatin[31]. In a separate phase 2, proof-of-concept trial, fenofibrate was tested in combination with the ACC inhibitor, firsocostat, to help lower triglyceride levels[32].

## CONCLUSION

In this concise review, we have discussed numerous possible therapeutic options for cessation or reversal of NASH and associated fibrosis. It is clear that NASH and particularly NASH fibrosis or cirrhosis is a leading topic garnering much interest in the study of liver diseases today, which would be appropriate considering the clinical impact. Although some of the above targets may seem promising, there are still a few concerns regarding study of this particular topic. Firstly, it is evident by reviewing the endpoints of each of the studies listed above that there is much heterogeneity. This is partly because the gold standard of liver biopsy to prove effectiveness in this endeavor is cumbersome, costly, and generally not favored by patients. The use of surrogates for liver fibrosis and resolution including markers of turnover, inflammation, or non-invasive assessments of liver scarring have not universally been agreed upon in the use of clinical trials. Secondly, for those studies that have utilized liver biopsies are part of their endpoint assessment, there can be considerable inter-observer variability in interpretation of liver biopsy specimens, assuming they are of adequate quality. Additionally, it is apparent that many of the study developers use magnetic resonance imaging with proton density fat fraction for assessment of liver fat content while there are additional tools such as the controlled attenuation parameter of transient elastography systems which might be more acceptable as a point of

care test. Lastly, endoscopic and surgical bariatrics represent an emerging area of therapeutic development for the management of obesity in context of NASH. In one prospective study of 180 patients, bariatric surgery was associated with NASH resolution in 84% of patients with improvement in fibrosis in 70% of patients at the 5 year mark after surgery[33]. Separately, in a 6 mo multi-center study of 85 patients with T2DM undergoing duodenal mucosal resurfacing, not only did their A1c improve, but so did their ALT levels and FIB-4 scores hinting at the possible insulin sensitizing, lipid lowering, anti-inflammatory and antioxidant effects of this procedure[34]. In conclusion, more effective treatments for NASH are urgently needed, and combination pharmacotherapy represents among the most promising approaches in development.

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## FOOTNOTES

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