Review Article

Future Pharmacotherapy for Non-alcoholic Steatohepatitis (NASH): Review of Phase 2 and 3 Trials

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Abstract

Non-alcoholic steatohepatitis (NASH) results from inflammation and hepatocyte injury in the setting of hepatic steatosis. Non-alcoholic steatohepatitis increases the risk of progression to liver fibrosis and cirrhosis, and is the most rapidly growing etiology for liver failure and indication for liver transplantation in the USA. Weight loss and lifestyle modification remain the standard first-line treatment, as no USA Food and Drug Administration-approved pharmacotherapy currently exists. The past decade has seen an explosion of interest in drug development targeting pathologic pathways in non-alcoholic steatohepatitis, with numerous phase 2 and 3 trials currently in progress. Here, we concisely review the major targets and mechanisms of action by class, summarize results from completed pivotal phase 2 studies, and provide a detailed outline of key active studies with trial data for drugs in development, including obeticholic acid, elafibranor, cenicriviroc and selonsertib.
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Introduction

Non-alcoholic steatohepatitis (NASH), a subcategory of non-alcoholic fatty liver disease (NAFLD), is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury.[1] Approximately one-quarter of the world's population has NAFLD, with estimates of the prevalence of NASH ranging from 1.5% to 6.45%.[2] In the USA, this translates into an estimated $103 billion annual economic burden.[3]

NASH is currently the second leading etiology of cirrhosis among adults awaiting liver transplantation in the USA,[4] and is expected to soon represent the leading indication for liver transplantation.[5] There are currently no USA Food and Drug Administration (FDA) approved medications for the treatment of NASH. Current management is primarily focused on promoting weight loss through lifestyle interventions. Weight loss medications, bariatric surgery and bariatric endoscopy represent attractive future approaches for NASH, although there is limited prospective data to support their role in clinical practice, and they are not presently endorsed by the American Association for the Study of Liver Diseases.[1]

In the last decade, the number of clinical trials of pharmacotherapies for the treatment of NASH has significantly increased. Several systematic reviews and meta-analyses have been conducted to aggregate data from published studies.[6–8] Therapies investigated with questionable benefit have included metformin, thiazolidinediones, vitamin E and pentoxifylline. However, the heterogeneity of study design and inclusion criteria, modest cohort sizes, differences in reported outcomes (e.g., histologic characteristics), lack of fibrosis improvement, and uncertain long-term benefits and safety have limited interpretation of their therapeutic safety and efficacy. In this context, a growing cohort of clinical development programs evaluating novel pharmacotherapeutic agents for NASH has emerged, primarily focused on demonstrating improvement in histologic characteristics of NASH, including steatosis, steatohepatitis and fibrosis. The aim of this paper is to briefly summarize the targets for these future pharmacotherapies, with a focus on agents in phase 2 and 3 trials.

Methods

We searched ClinicalTrials.gov in May 2017 for phase 2 or 3 interventional studies that were open for enrollment or active but not enrolling and contained the phrase "non-alcoholic steatohepatitis". Pediatric studies were not included. We did not include trials for nutritional supplements. When there were discrepancies between ClinicalTrials.gov and published materials (e.g., conference abstract), we used the information from the published materials.

Key targets and mechanisms of action

Drugs in trials for NASH are designed to attenuate lipotoxicity, whether by reducing lipid accumulation or by reducing downstream pathways that lead to hepatocyte injury, death and, in some, cirrhosis. Many drugs in phase 3 trials and those with results from phase 2 trials target lipid metabolism, inflammation or the formation of fibrous connective tissue within the liver (Fig. 1). Examples of agents that target lipid metabolism

Keywords: Fatty liver; Non-alcoholic steatohepatitis; Clinical trials; Pharmacotherapy; Obeticholic acid.

Abbreviations: CCR, C-C motif chemokine receptor; CVC, cenicriviroc; FDA, USA Food and Drug Administration; FGF, fibroblast growth factor; FXR, farnesoid X nuclear receptor; GLP, glucagon-like peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; NCT, national clinical trial number; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor.

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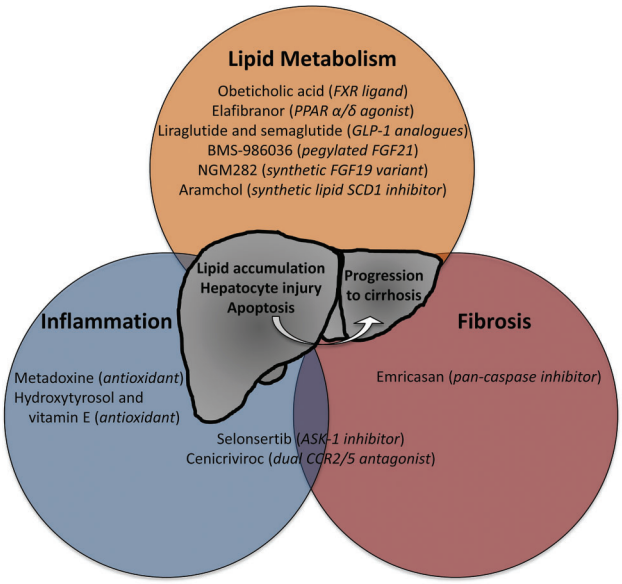

Fig. 1. Key targets for drugs in phase 2 and phase 3 clinical trials.

include farnesoid X nuclear receptor (FXR) agonists, fibroblast growth factor (FGF) variants and peroxisome proliferator-activated receptor (PPAR) agonists.

FXR is a bile acid receptor[9] that regulates lipid and glucose metabolism.[10] FXR activation leads to reduction in serum and hepatic triglyceride levels.[11] Obeticholic acid is a semi-synthetic FXR agonist currently in a phase 3 trial (national clinical trial number (NCT)02548351).

FGF19 and FGF21 are circulating proteins that bind to FGF receptors (primarily FGFR4 and FGFR1c, respectively) with the cofactor β-Klotho.[12,13] In animal models, FGF19 and FGF21 improve lipid profiles (decreasing triglycerides, low-density lipoprotein (LDL) and total cholesterol, and increasing high-density lipoprotein (HDL)), improve glucose control, and lead to weight loss.[14–16] In a recent study on animal models, FGF15 (the murine FGF19) fused with apolipoprotein reduced hepatic lipid and bile acid accumulation and improved survival.[17] Similar results were seen in two phase 1 studies of FGF21 analogues in human subjects.[18,19] BMS-986036, a pegylated FGF21, and NGM282, a synthetic FGF19 variant, are being studied in phase 2 trials (NCT02443116; NCT02443116).

PPAR-α, δ and γ are transcription factors involved in lipid metabolism. PPAR-α is implicated in fatty acid catabolism. PPAR-α activation increases lipolysis cellular lipid uptake.[20] Treatment with fibrates, which are PPAR-α ligands, reduces circulating triglycerides and increased HDL levels.[21] In animal models, PPAR-δ activation leads to fatty acid consumption in skeletal muscle and adipose tissue.[22] PPAR-γ may reduce hepatic steatosis by shifting fat deposition to adipose tissue.[23] Rosiglitazone, a PPAR-γ agonist, has been shown to reduce liver fat content and laboratory markers of hepatocellular injury, but was also shown to increase cardiovascular risks.[24,25] Elafibrinor is a PPAR-α/δ agonist currently in a phase 3 trial (NCT02704403).

Apoptosis signal-regulating kinase 1, also known as mitogen-activated protein kinase 5, mediates pathways leading to apoptosis, fibrosis, lipogenesis and the release of inflammatory cytokines.[26,27] It is activated by angiotensin II receptor type I. Olmesartan, an angiotensin receptor blocker, reduces hepatic steatosis and NASH in animal models.[28–30] In small trials on patients with cirrhosis, olmesartan reduced serum markers of inflammation.[31,32] Selonsertib is an apoptosis signal-regulating kinase 1 inhibitor in phase 3 trials for NASH (NCT03053050 and NCT03053063).

As hyperglycemia independently up-regulates fat synthesis via activation of the carbohydrate response element-binding protein transcription factor,[33] drugs that reduce blood glucose are also being investigated as potential therapies for NASH. Glucagon-like peptide 1 (GLP-1) receptor agonists, also known as an incretin mimetics, may reduce NASH via weight loss and reduction of blood glucose. GLP-1 agonists may influence lipid metabolisms by direct mechanisms as well.[34] Meta-analysis of patients with diabetes suggests GLP-1 agonists reduce steatosis, inflammation and fibrosis on histology as well as serum markers of inflammation.[35] Liraglutide is a long-acting GLP-1 receptor agonist approved for the treatment of diabetes and is in a phase 3 trial for the treatment of NASH (NCT02654665).

C-C motif chemokine receptor (CCR) 2 and CCR5 are chemokine receptors expressed on circulating monocytes as well as on Kupffer cells. Activation of these receptors induces migration of macrophages into the liver.[36–38] Cenicriviroc (CVC) is a CCR2/5 antagonist in phase 2 and phase 3 trials (NCT02217475 and NCT03028740).

Caspases are key mediators of inflammation and apoptosis.[39] Apoptosis is, in turn, profibrotic.[40,41] Emricasan (IDN-6556) is a pan-caspase inhibitor that is being studied in phase 2 trials (NCT02686762 and NCT02960204).

Expedited FDA approval process

The natural history of NASH is typically characterized by a time period of years to decades between the onset of fatty liver to the development of liver cirrhosis and its complications, including liver-related mortality. Regulatory endpoints focused on clinical outcomes such as progression to liver cirrhosis, liver failure, hepatocellular carcinoma, need for liver transplantation, and liver-related death are not feasible within a registration program. Based on evidence confirming the association of surrogate histologic and clinical endpoints and clinical outcomes, the FDA has established regulatory pathways which incorporate non-invasive, clinical and histologic endpoints for phase 2 and 3 clinical development, with the expectation for postmarketing clinical outcome evaluation in phase 4 studies.[42]

Advances in the development of serum biomarkers, imaging and elastography have permitted their use as viable trial endpoints in early human studies, which inform the design of phase 2 trials using a primary endpoint of improvement of ≥2 points in the NAFLD activity score (NAS) including improvement in lobular inflammation or hepatocellular ballooning with no worsening in fibrosis. Phase 3 trials are focused on a primary endpoint of either NASH resolution without worsening of liver fibrosis, or liver fibrosis regression of at minimum one stage without worsening of NASH activity. Phase 4 studies are focused on long-term assessment of clinical outcomes (e.g., all-cause mortality, liver transplant, hepatic decompensation events), progression to cirrhosis, or an increase in model for end-stage liver disease score from <12 to ≥15.[43] The development of surrogate biomarkers that are "reasonably likely to predict a drug's intended clinical benefit" and are independent of liver histology remains of great interest to clinicians, researchers, and the FDA.[44]

Summary of drugs in phase 2 and 3 trials

We identified eight active phase 3 studies (Table 1) and 23 active phase 2 studies (Table 2). Trials of nutritional supplements, such as "Synbiotics Supplement" (NCT02530138), curcumin (NCT02908152), resveratrol (NCT02216552), caffeine and chlorogenic acid (NCT02929901), and CPAP (NCT01849081), were not included.

Drugs in phase 3 trials

Herein, we report key agents currently under evaluation within the eight ongoing or proposed phase 3 trials registered on ClinicalTrials.gov for the treatment of NASH (Table 1). One study of hydroxytyrosol and vitamin E for the treatment of children with NASH (NCT02842567) is not reviewed due to its focus on pediatric patients.

Obeticholic acid (OCA): OCA (Intercept Pharmaceuticals, New York, NY, USA) is a farnesoid X nuclear receptor (FXR) ligand that is currently being evaluated in the phase 3 study REGENERATE (NCT02548351) for the treatment of NASH. OCA was granted accelerated approval by the FDA in May 2016 for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid in adults with an inadequate response or intolerance to ursodeoxycholic acid and marketed under the brand name Ocaliva.[45]

In a small phase 2 trial, treatment with OCA was shown to increase insulin sensitivity and reduce alanine aminotransferase levels and serum markers of fibrosis in patients with diabetes and NAFLD.[46] Subsequently, OCA was studied in the phase 2b FLINT trial (NCT01265498), where 283 patients with non-cirrhotic NASH were randomized 1:1 to receive OCA 25 mg or placebo for 72 weeks (Table 3).[47] The primary outcome was improvement in NAS by ≥2 points without worsening of fibrosis. In both the planned interim analysis and the end of treatment cohorts, OCA demonstrated superiority over placebo in meeting the primary endpoint at 72 weeks on an intention-to-treat basis (45% vs. 21%, $p = 0.0002$), and in addition demonstrated improvement in liver fibrosis (35% vs. 19%, $p = 0.004$). Although well-tolerated, a trend for a small increase in LDL and decrease in HDL was identified, but was reversible with HMG-CoA reductase inhibitor therapy, resolved spontaneously upon withdrawal of OCA, and was not associated with any difference in cardiovascular events.[48] Of note, however, are safety concerns, including liver injury, liver decompensation, liver failure and death, that have been reported for a small number of patients with moderate or severe hepatic impairment (Child-Pugh B/C) taking OCA for the treatment of PBC.[49] Although these adverse events were specifically seen in patients with advanced cirrhosis, careful attention to the safety profile of OCA is warranted in phase 3 NASH trials in participants with both normal and impaired hepatic function.

Recruiting for the phase 3 REGNERATE trial began in 2015 with a target *n* of 2000 participants with biopsy-proven, non-cirrhotic NASH to be randomized 1:1:1 to OCA 10 mg, OCA 25 mg or placebo groups. The two specified coprimary endpoints are liver fibrosis improving one stage without worsening of NASH, and NASH resolution with no worsening of fibrosis at 18 months. Other primary outcomes include death or liver-related adverse events at approximately 6 years. The target primary completion date is October 2021.

Elafibranor: Elafibranor (also known as GFT505) is a dual PPAR-α/δ agonist produced by GENFIT (Loos, France) that is currently undergoing evaluation in the phase 3 RESOLVE-IT trial (NCT02704403). The drug was granted 'Fast Track' designation by the FDA in February 2014 for the treatment of NASH and received clearance by the FDA in November 2016 for evaluation in PBC.[50,51]

Elafibranor was tested in the phase 2b GOLDEN-505 trial (NCT01694849) which randomized 276 patients with NASH without cirrhosis to elafibranor 80 mg, elafibranor 120 mg or placebo groups in a 1:1:1 fashion (Table 3).[52] The protocol-defined primary outcome was reversal of NASH on histologic NAS scoring with resolution of steatosis, ballooning, or inflammation without progression to bridging fibrosis or cirrhosis (if bridging fibrosis was evident at baseline) at 52 weeks. Although this primary endpoint was not met in the intention-to-treat analysis, a post-hoc analysis based on a modified definition of response (resolution of NASH defined by disappearance of ballooning with disappearance or mild persistence of lobular inflammation and a pathological diagnosis of steatosis with or without mild inflammation and no worsening of fibrosis) did confirm superiority of the 120 mg dose compared to placebo (19% vs. 12%, $p = 0.045$), with stronger response among participants with baseline moderate or severe NASH (20% vs. 11%, $p = 0.018$). Significant reduction in fibrosis was noted in patients who responded to the 120 mg dose based on the modified definition compared to those who did not. Furthermore, elafibranor was well tolerated, without causing weight gain or cardiac events, and both lipid/glucose profiles and markers of systemic inflammation were reduced. However, a mild, reversible increase in serum creatinine was observed.

The phase 3 RESOLVE-IT trial began in March 2016 with the goal of recruiting 2000 patients with biopsy-proven moderate or severe (F2-F3) NASH. Patients will receive either 120 mg of elafibranor or placebo. The primary endpoints include the proportion of patients with resolution of NASH without worsening of fibrosis and a composite long-term outcome (all-cause mortality, cirrhosis and liver-related clinical outcomes) at 72 weeks with estimated follow-up of 4 years. The study is actively recruiting with an estimated primary completion date in December 2021.

Selonsertib: Selonsertib (also known as GS-4997) is an apoptosis signal-regulating kinase 1 inhibitor produced by Gilead (Foster City, CA, USA) that is currently under evaluation in two phase 3 clinical trials (STELLAR-3 [NCT03053050] and STELLAR-4 [NCT03053063]) for the treatment of NASH. It is intended to reduce JNK- and p38 MAPK-mediated hepatic stellate cell activation and cytokine production.[27]

Early human studies revealed that selonsertib reduces inflammation and hepatocyte apoptosis.[53] Selonsertib was studied in a phase 2, open label, randomized controlled trial (NCT02466516) conducted throughout the USA and Canada.[54] It enrolled 72 adults with biopsy-proven NASH and randomized them to receive selonsertib 6 mg or 18 mg with or without simtuzumab for 24 weeks (Table 3). The study recruited participants with stage F2-F3 fibrosis and NAS ≥5. Selonsertib was determined to be superior to placebo in achieving the primary efficacy endpoint of fibrosis improvement of one stage or greater (43% of 18 mg-, 30% of 6 mg- and 20% of placebo-treated), as well as fibrosis improvement without worsening NASH (37% of 18 mg-, 30% of 6 mg- and 20% of placebo-treated) and progression to cirrhosis (3% of 18 mg-, 7% of 6 mg- and 20% of placebo-treated). However, there was no difference in achieving a decrease in NAS of at minimum two points (23% of 18 mg-, 19% of 6 mg- and 20% of placebo-treated) or NASH resolution (0% of 18 mg-, 4% of 6 mg- and 0% of placebo-treated).

Table 1. Active phase 3 clinical trials for the pharmacologic treatment of NASH registered on ClinicalTrials.gov

Drug (Alias)	Mechanism	Study Name (ClinicalTrials.gov ID; Sponsor)	Target Completion Date*	Target Enrollment	Inclusion Criteria			Primary Outcome Measures
					NAS	Fibrosis Stage	Diagnosis	
Obeticholic acid (OCA)	FXR ligand	REGENERATE (NCT02548351; Intercept Pharmaceuticals, New York, NY, USA)	Oct 2021	2000	≥4, with ≥1 of each component of the score	F1–3†	Biopsy	• Histologic improvement - improvement in liver fibrosis and resolution of NASH at 18 months • Composite outcome - death, MELD ≥15, cirrhosis, transplant, HCC, hospitalization, others at 6 years (est.)
Elafibranor (GFT505)	PPAR-α/δ agonist	RESOLVE-IT (NCT02704403; Genfit, Loos, France)	Dec 2021	2000	≥4, with ≥1 of each component of the score	F1–3‡	Biopsy	• Histologic improvement - resolution of NASH without worsening of fibrosis at 72 weeks • Composite outcome - all-cause mortality, cirrhosis, "liver-related clinical outcomes" at 4 years (est.)
Selonsertib (GS-4997)	ASK-1 inhibitor	STELLAR-3 and STELLAR-4 (NCT03053050 and NCT03053063; Gilead Sciences, Foster City, CA, USA)	Jan 2020	800 (each)	–	F3 (STELLAR-3) F4 (STELLAR-4)	Biopsy	• Histologic improvement - ≥1 stage improvement in fibrosis without worsening of NASH at 48 weeks • Event-free survival at 240 weeks
Cenicriviroc (CVC)	Dual CCR2/ CCR5 antagonist	AURORA (NCT03028740; Tobira Therapeutics, South San Francisco, CA, USA)	Jul 2019	2000	–	F2–3	Biopsy	• Histologic improvement - ≥1 stage improvement in fibrosis without worsening of NASH at 12 months • Composite outcome - cirrhosis on histology, liver-related clinical outcomes, and all-cause mortality at 5 years (est.)
Liraglutide$^{\Delta}$	GLP-1 analogue	CGH-LiNASH (NCT02654665; Changi General Hospital, Singapore)	Sep 2017	36	–	–	Liver chemistries, ultrasound, ± biopsy	• Improvement in NASH at 12 months • Reduction/normalization in aminotransferases, liver fat at 12 months
Metadoxine	Antioxidant (glutathione source)	(NCT02541045; Hospital General de Mexico, Mexico City, Mexico)	Aug 2018	108	≥3, with ≥1 of each component of the score	F0–2	Biopsy	• Improvement in NAS at 6 months
Hydroxytyrosol and vitamin E$^{\Psi}$	Antioxidant	(NCT02842567; Bambino Gesù Hospital and Research Institute, Rome, Italy)	Apr 2017	80	–	–	Biopsy	• Laboratory markers of inflammation and oxidative stress at 4 months • Laboratory markers of metabolic syndrome at 4 months

*Estimated primary completion date. All studies except NCT02842567 (hydroxytyrosol and vitamin E) were recruiting as of the date of data acquisition.

†Patients with stage 1 fibrosis were enrolled only if they have body mass index ≥30, diabetes mellitus type 2, or alanine aminotransferase elevation.

‡F2 or F3 fibrosis and "[a] group of patients with F1 fibrosis and concomitant cardiometabolic comorbidities, which are associated with rapid progression of the disease" (http://www.genfit.com/pipeline/elafibranor/).

$^{\Delta}$Compares liraglutide 0.6 mg subcutaneous injection daily increasing at 0.6 mg/week to a maximum of 3 mg to bariatric surgery and to lifestyle modification.

$^{\Psi}$Study of pediatric patients ages 4–16

Abbreviations: ASK, apoptosis signal-regulating kinase; CCR, C-C motif chemokine receptor; FXR, farnesoid X nuclear receptor; GLP, glucagon-like peptide; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease score; NAS, NAFLD activity score [scored steatosis 0–3, ballooning 0–2, and lobular inflammation 0–3]; PPAR, peroxisome proliferator-activated receptor.

Table 2. Active phase 2 clinical trials for the pharmacologic treatment of NASH registered on ClinicalTrials.gov

Drug (Alias)	Mechanism	Study Name (ClinicalTrials.gov ID; Sponsor)	Target Completion Date	Target Enrollment	Inclusion/Exclusion Criteria			Primary Outcome Measures
					BMI as kg/m^2	Fibrosis Stage	Diagnosis	
NGM282 (M70)	Variant of FGF-19	(NCT02443116; NGM Biopharmaceuticals, San Francisco, CA, USA)	Apr 2018	82; planned for 140	–	F1–3	Biopsy	• Imaging - ≥5% reduction in absolute liver fat content as measured by MRI at 12 weeks
BMS-986036	Pegylated FGF-21	(NCT02413372; Bristol-Myers Squibb, New York, NY. USA)	Jan 2017	74	≥25	F1–3	Biopsy	• Imaging - hepatic fat fraction on MRI at 16 weeks
Emricasan (IDN-6556)	Caspase Inhibitor	ENCORE-NF (NCT02686762; Conatus Pharmaceuticals, San Diego, CA, USA)	Sep 2018	330	–	F1–3	Biopsy	• Histologic improvement - improvement of fibrosis by at least one stage without worsening of steatohepatitis at 72 weeks
Emricasan (IDN-6556)	Caspase Inhibitor	ENCORE-PH (NCT02960204; Conatus Pharmaceuticals, San Diego, CA, USA)	Oct 2018	240	–	F4	Biopsy	• Mean change in HVPG at 24 weeks
Aramchol	Synthetic lipid SCD1 inhibitor	(NCT02279524; Galmed Pharmaceuticals, Tel Aviv, Israel)	Mar 2018	240	25–40	F0–3	Biopsy	• Change in triglyceride concentration on NMRS at 52 weeks
Atorvastatin and/or L carnitine	HMG-CoA reductase inhibitor/involved in lipid transport	(NCT01617772; Tehran University of Medical Sciences, Tehran, Iran)	Oct 2018	440	–	Fibroscan <8 (~F2 and below)	Steatosis on imaging; ALT >1.5x ULN 3 months apart	• Improvement in liver stiffness by Fibroscan at 2 years
MGL-3196	Selective THR-β agonist	(NCT02912260; Madrigal Pharmaceuticals, West Conshohocken, PA, USA)	Sep 2017	117	<45	F1–3	Biopsy	• Imaging - Change in hepatic fat fraction on MRI-PDFF at 12 weeks
Volixibat (SHP626)	ASBT inhibitor	(NCT02787304; Shire Pharmaceuticals, Dublin, Ireland)	Jul 2020	266	–	F0–3	Biopsy and MRI for steatosis	• Histologic improvement - ≥2 point improvement in NAS without worsening of fibrosis at 48 weeks
GS-9674	FXR agonist	(NCT02854605; Gilead Sciences, Foster City, CA, USA)	Jan 2018	125	≥18	F1–3	Biopsy or MRE	• Safety - emergent adverse events and laboratory abnormalities at "up to 24 weeks plus 30 days"
Semaglutide	GLP-1 analogue	(NCT02970942; Novo Nordisk, Bagsværd, Denmark)	Jul 2019	372	25–45	F2–3	Biopsy	• Histologic improvement - NASH resolution without worsening of fibrosis at 72 weeks
Saroglitazar	PPAR-α/γ agonist	EVIDENCES II (NCT03061721; Zydus Discovery, Ahmedabad, India)	Jun 2018	104	25–40	F0–3	Biopsy, ultrasound, CT, or MRI	• Change in aminotransferases at 16 weeks

(*continued*)

Table 2. (*continued*)

Drug (Alias)	Mechanism	Study Name (ClinicalTrials.gov ID; Sponsor)	Target Completion Date	Target Enrollment	Inclusion/Exclusion Criteria			Primary Outcome Measures
					BMI as kg/m^2	Fibrosis Stage	Diagnosis	
AZ compound	Not specified	(NCT02605616; Mayo Clinic, Rochester, MN, USA)	Dec 2017	100	19–40	F2 or greater fibrosis	Biopsy/MRE proven	• Imaging - change in liver fat fraction at 12 weeks
LMB763	FXR agonist	(NCT02913105; Novartis, Geneva, Switzerland)	Oct 2018	100	–	–	Biopsy + ALT elevation, or elevated ALT + BMI + DM2	• Adverse event profile and safety endpoints at 12 weeks • Change in aminotransferases
IVA337	Pan-PPAR agonist	NATIVE (NCT03008070; Inventiva, Daix, France)	Jun 2018	225	<45	<F4	Biopsy	• Histologic improvement - >2 point improvement in SAF score without worsening of fibrosis
LJN452	FXR agonist	FLIGHT-FXR (NCT02855164; Novartis, Geneva, Switzerland)	Nov 2017	250	–	–	Biopsy + ALT elevation, or elevated ALT + BMI + DM2	• Adverse event profile at 12 weeks • Change in aminotransferase levels at 12 weeks
CF102	A3AR agonist	(NCT02927314; Can-Fite BioPharma, Petah-Tikva, Israel)	Feb 2018	60	≤40	Absence of cirrhosis (Fibroscan score ≤F4 + LSM of 7.13 kPa)	NMRS	• Percent change in the liver triglyceride concentration on NMRS at 12 weeks • Adverse events at 12 weeks
MT-3995	Mineralocorticoid receptor antagonist	(NCT02923154; Mitsubishi Tanabe Pharma, Osaka, Japan)	Oct 2017	40	–	–	–	• Percent change in ALT at 24 weeks
Pioglitazone	PPAR-γ agonist	(NCT01068444; Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung City, Taiwan)	Mar 2018	90	–	Up to (compensated) cirrhosis	Biopsy	• Steatosis and liver function tests at 9 months • "Clinical safety"
MN-001 (tipelukast)	Small molecule	(NCT02681055; MediciNova, La Jolla, CA, USA)	Jun 2017	40	≤45	Excludes cirrhosis	Biopsy-proven NASH or ultrasound confirmed NAFLD	• Cholesterol efflux capacity and triglyceride levels at 12 weeks
MSDC-0602K	PPAR-γ-sparing mTOT modulator	EMMINENCE (NCT02784444; Cirius Therapeutics, Kalamazoo, MI, USA)	Oct 2018	200	–	F1–3	Biopsy	• Histological improvement - decrease in NAS without worsening of fibrosis at 12 months • Histological improvement - ≥2 point decrease in the NAS without worsening of fibrosis at 12 months

(*continued*)

Table 2. (*continued*)

Drug (Alias)	Mechanism	Study Name (ClinicalTrials.gov ID; Sponsor)	Target Completion Date	Target Enrollment	Inclusion/Exclusion Criteria			Primary Outcome Measures
					BMI as kg/m^2	Fibrosis Stage	Diagnosis	
JKB-121	TLR-4 antagonist/ non-selective opioid antagonist	(NCT02442687; Manal Abdelmalek, Duke University Medical Center, Durham, NC, USA)	Jul 2017	66	≥25	F0–3	Biopsy	• Adverse events at 24 weeks • Percent change in fat content on MRI/NMRS at 24 weeks • Change in ALT at 24 weeks • Time to remission (two consecutive ALT within normal limits) at 24 weeks
IMM-124E	Gut microbiome modulator	(NCT02316717; Immuron, Armadale, Australia)	Oct 2017	130	≥25	F0–3	Biopsy	• Percent change in fat content on MRI at 24 weeks • ALT, other laboratory measures, and vitals at 24 weeks
ARI-3037MO	Synthetic analog of nicotinic acid	(NCT02574325; Arisaph, Boston, MA, USA)	Oct 2016	11	28–45	Exclusion criteria: liver biopsy within 90 days with negative results for cirrhosis and steatosis	MRI and lab elevation	• Percent change in fat content on MRI at 24 weeks • ALT and triglycerides at 24 weeks

Abbreviations: A3AR, A3 adenosine receptor; ALT, alanine aminotransferase; ASBT, apical sodium-dependent bile acid transporter; BMI, body mass index; DM2, diabetes mellitus type 2; FGF, fibroblast growth factor; FXR, farnesoid X nuclear receptor; GLP, glucagon-like peptide; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; mTOT, mitochondrial target of thiazolidinediones; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; NMRS, nuclear magnetic resonance spectroscopy; PPAR, peroxisome proliferator-activated receptor; SAF, steatosis, activity, fibrosis score; SCD, stearoyl coenzyme A desaturase; THR, thyroid hormone receptor; TLR, toll-like receptor; ULN, upper limit of normal.

Table 3. Notable results from published studies that preceded active phase 3 trials for NASH pharmacotherapy

Drug (Alias)	Mechanism	Study Name[Ref]	Study Design	Population	Results
Obeticholic acid (OCA)	FXR ligand	FLINT[47]	Phase 2b U.S. multicenter, double-blind, RCT comparing obeticholic acid 25 mg daily to placebo for 72 weeks (n = 283)	Adults with biopsy-proven, non-cirrhotic NASH with NAS ≥4, with ≥1 of each component of the score*	• Primary endpoint (improvement in NAS ≥2 points without worsening of fibrosis) met in 50/110 (45%) patients in the intervention arm vs. 23/109 (23%) patients in the placebo arm ($p < 0.001$) • Fibrosis improved in 36/102 (35%) patients in the intervention arm vs. 19/98 (19%) patients in the placebo arm ($p = 0.004$)
Elafibranor (GFT505)	PPAR-α/δ agonist	GOLDEN-505[52]	Phase 2b USA and Europe multicenter, double-blind, RCT comparing elafibranor 80 mg and 120 mg daily to placebo for 52 weeks (n = 276)	Adults with biopsy-proven, non-cirrhotic NASH with NAS ≥3, with ≥1 of each component of the score*	• Protocol-defined primary outcome (reversal of NASH defined by the absence of at least 1 of steatosis, ballooning, and inflammation without progression to bridging fibrosis or cirrhosis) not significantly different between arms • Modified definition of response (resolution of NASH as defined by disappearance of ballooning with disappearance or mild persistence of lobular inflammation and a pathologic diagnosis of steatosis ± mild inflammation and no worsening of fibrosis) met in 17/89 (19%) patients in the 120 mg arm vs. 11/92 (12%) in the placebo arm ($p = 0.045$) • Fibrosis stage was significantly reduced in responders (based on the modified definition) to 120 mg vs. non-responders
Selonsertib (GS-4997)	ASK-1 inhibitor	[54]	Phase 2 U.S. and Canada multicenter, open-label, RCT comparing selonsertib 6 mg and 18 mg daily ± simtuzumab to simtuzumab monotherapy for 24 weeks (n = 72)	Adults with biopsy-proven F2–3 NASH with NAS ≥5	• Fibrosis improved in 13/30 (43%) patients in the 18 mg ± simtuzumab arm vs. 8/27 (30%) patients in the 6 mg ± simtuzumab arm vs. 2/10 (20%) patients receiving simtuzumab monotherapy • Mostly dose-dependent trends observed in ≥15% reduction in MRE stiffness, ≥30% reduction in MRI-PDFF, ≥2 point improvement in NAS, and less likely progression to cirrhosis
Cenicriviroc (CVC)	Dual CCR2/CCR5 antagonist	CENTAUR[58]	Phase 2b multinational multicenter, double-blind, RCT comparing cenicriviroc 150 mg daily to placebo for 2 years (n = 289)	Adults with biopsy-proven F1–3 NASH with NAS ≥4 and diabetes or metabolic syndrome	• Pre-specified primary endpoint (≥2 point improvement in NAS [with ≥1-point reduction in lobular inflammation or ballooning] and no worsening of fibrosis) not met at 1 year interim analysis • Fibrosis improved (without worsening of steatohepatitis) in 29/145 (20%) patients in the intervention arm vs. 15/144 (10%) patients in the placebo arm ($p = 0.023$), most pronounced in subjects with higher disease activity and stage, at 1 year interim analysis

*NAS (NAFLD activity score) scored as steatosis 0–3, ballooning 0–2, and lobular inflammation 0–3.

Abbreviations: ASK, apoptosis signal-regulating kinase; CCR, C-C motif chemokine receptor; FXR, farnesoid X nuclear receptor; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; RCT, randomized controlled trial.

Selonsertib was well-tolerated overall, although key adverse effects included fatigue, headache and nausea.

STELLAR-3 is a multinational phase 3 randomized, placebo-controlled, double-blind clinical trial designed to assess the safety and efficacy of selonsertib 6 mg and 18 mg in patients with stage F3 fibrosis. STELLAR-4 is a phase 3 randomized, placebo-controlled, double-blind clinical trial which evaluates the safety and efficacy of selonsertib in patients with compensated cirrhosis. The primary outcomes for both protocols are liver fibrosis regression ≥1 stage at 48 weeks, and event-free survival at 240 weeks. They are currently recruiting with a target enrollment of 800 participants, each with an estimated completion date of January 2020.

CVC: CVC is an oral, dual CCR2/CCR5 inhibitor owned by Tobira Therapeutics (San Francisco, CA, USA). In animal fibrosis models it is demonstrated to have anti-inflammatory and antifibrotic properties.[55–57] CVC is being evaluated in phase 2 and phase 3 trials.

CENTAUR (NCT02217475), a phase 2b study of CVC in 289 patients with F1-F3 fibrosis and one or more of diabetes, body mass index above 25 kg/m^2 with features of metabolic syndrome, and bridging fibrosis (or definite NASH), is fully enrolled and ongoing (Table 3). The 1 year primary analysis showed that in the intention-to-treat population, the primary endpoint, a ≥2-point improvement in NAS (with ≥1-point reduction in lobular inflammation or hepatocyte ballooning) and no worsening of fibrosis, was not met.[58] However, twice as many CVC-treated subjects (29/145 [20%]) compared to placebo (15/144 [10%]) attained ≥1 stage improvement in fibrosis without worsening of steatohepatitis (p = 0.023). A subgroup analysis of this secondary endpoint identified predictors of response, including NAS ≥5, hepatocellular ballooning grade ≥2, and fibrosis stages F2-F3 (p = 0.049).

AURORA (NCT03028740) is a phase 3 trial of CVC, targeting patients with F2-F3 fibrosis and having an anticipated enrollment of 2000. Primary outcome measures include: 1) histologic improvement of at least one stage in fibrosis without worsening of NASH at 12 months; and 2) a composite endpoint of histologic progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality. The estimated primary completion date is July 2019.

Liraglutide: Liraglutide is a glucagon-like peptide (GLP)-1 analogue approved by the FDA for the treatment of type II diabetes and is marketed under the brand name Victoza. Liraglutide recently demonstrated encouraging results for patients with NASH in several small, randomized trials,[59,60] including the phase 2 LEAN study sponsored by its manufacturer, Novo Nordisk (Bagsværd, Denmark). In this double-blind, multicenter trial, 52 participants with biopsy-proven NASH (stage F0-F4 fibrosis) were randomized to receive liraglutide or placebo for 48 weeks. The primary outcome was resolution of definitive NASH without worsening of fibrosis from baseline to end of treatment. In the modified intention-to-treat analysis, nine of 23 (39%) patients treated with liraglutide with pre- and posttreatment biopsies had resolution of NASH versus two of 22 (9%) such patients in the placebo group. Patients receiving liraglutide experienced an improvement in weight and hemoglobin A1c, although no significant change in total NAS or fibrosis stage was observed.

Although liraglutide will not be further evaluated in phase 3 development, Novo Nordisk has initiated a phase 2b trial (NCT02970942) evaluating another GLP-1 analogue, semaglutide (Table 2) versus placebo in 372 participants with stage F2-F3 fibrosis and NAS ≥4 with a score of at least 1 for each of the components (steatosis, ballooning, and lobular inflammation). The primary outcome is NASH resolution without worsening of fibrosis, and the estimated primary completion date for this protocol is 2019.

Metadoxine: Metadoxine (pyridoxine-L-2-pyrrolidone-5-carboxylate) is an antioxidant that is proposed to be a source of glutathione, capable of inhibiting adipocyte differentiation, limiting hepatic lipid accumulation, and exerting antifibrotic properties.[61–63] It has largely been studied in patients with alcoholic steatosis[64] and alcoholic hepatitis,[65,66] and may have a role in managing acute alcohol intoxication,[67] alcohol dependence,[68] and attention-deficit/hyperactivity disorder.[69]

In the only significant randomized controlled trial in patients with NASH, metadoxine was compared to placebo for 16 weeks in 134 participants with stage F0-F3 fibrosis.[70] Although it did not improve liver histology or serum aminotransferases compared to placebo, it did improve steatosis assessed by ultrasound. This improvement in steatosis is consistent with prior results in patients with alcoholic liver disease.[64] A proposed phase 3 trial in Mexico (NCT02541045) of metadoxine in overweight and obese patients with stage F0-F2 fibrosis is currently seeking to enroll 108 patients. The primary outcome is improvement in NAS score at six months and the trial has an estimated completion date of August 2018.

Drugs in phase 2 trials

Approximately two-dozen phase 2 clinical trials are currently actively looking at novel pharmacotherapies for adults with NASH (Table 2). Of these, only the following three have publicly published results: CVC, as mentioned above in the CENTAUR trial; NGM282 (NGM Biopharmaceuticals, Inc, South San Francisco, CA, USA); and BMS-986036 (Bristol-Myers Squibb, Princeton, NJ, USA).

NGM282: NGM282 (formerly known as M70) is a non-tumorigenic, engineered variant of fibroblast growth factor (FGF)-19 that acts through FGF receptors 1c and 4 to reduce steatosis and lipotoxicity. It was studied in a randomized, double-blind, placebo controlled phase 2 trial (NCT02443116) in 82 patients with biopsy-proven non-cirrhotic NASH with ≥8% absolute liver fat content by MRI proton density fat fraction (MRI-PDFF). The primary outcome was a ≥5% reduction in absolute liver fat content as measured by MRI-PDFF after 12 weeks of treatment. The results were presented at The International Liver Congress 2017 and demonstrated that 79% of NMG282-treated subjects met the primary outcome compared with 7% in the placebo group.[71] Other findings included lower alanine aminotransferase values and lower enhanced liver fibrosis scores[72] for the treatment groups, but higher LDL levels were also observed.[73] Similar results were seen in a phase 2 trial in patients with PBC.[74] No information is available regarding design of potential phase 2b or 3 trials.

BMS-986036: BMS-986036 is a pegylated analogue of FGF-21 that has been shown to decrease hepatic steatosis, NAS and fibrosis in a mouse model of NASH,[75] and to have beneficial effects on insulin sensitivity, lipids and fibrotic markers in obese diabetic patients with a high prevalence of NAFLD.[76,77] The results of a phase 2 randomized, double-blind, placebo controlled trial (NCT02413372) involving 74 participants with a body mass index ≥25 kg/m^2, biopsy-proven non-cirrhotic NASH, and ≥10% absolute liver fat content by MRI-PDFF were presented at The International Liver Congress 2017.[78] The primary outcome, a change in percent hepatic fat fraction by MRI-PDFF after 16 weeks of

treatment, was shown to be statistically significant compared to placebo. Other pertinent outcomes were improvements in adiponectin levels, triglycerides, LDL, HDL, aminotransferases, serum Pro-C3, and liver stiffness measured by magnetic resonance elastography. Bristol-Myers Squibb has suggested further investment in BMS-986036 for the treatment of NASH though no phase 2b or 3 trials have yet been proposed.[79]

Looking ahead

With the recent advent of highly effective oral direct-acting antiviral agents for the treatment of hepatitis C virus, the prevalence of hepatitis C and its associated burden of liver cirrhosis and its complications is expected to decline. Concurrently, NASH is rapidly emerging as the most common cause of liver cirrhosis and liver failure requiring liver transplantation. In context of a limited treatment paradigm focused on medical weight loss without a single FDA-approved pharmacotherapy for NASH, there exists significant interest in novel agents that may meaningfully alter the natural history of the disease. Several agents are currently in phase 3 clinical trials, and are expected to reach completion within the next 2–4 years. The regulatory framework for drug development remains focused on two pathways to approval, including: 1) NASH resolution without worsening of liver fibrosis; and 2) histologic regression of liver fibrosis of at least one stage without worsening NASH.

Although key clinical development programs have largely evaluated single agents for NASH therapy, future treatment paradigms may involve combination regimens which incorporate two or more complementary mechanisms of action that target metabolic, inflammation, and/or fibrosis factors and/or pathways to optimize efficacy in NASH resolution and liver fibrosis regression. Due to the established association between NASH and both cardiovascular disease and malignancy, careful attention to off-target adverse effects will be essential. Ongoing scientific advances in the pathogenesis of NASH and identification of novel agents addressing key targets of disease activity will be necessary to further expand our capacity to both treat NASH and reduce long-term clinical outcomes, including cirrhosis, liver failure and liver cancer.

Conflict of interest

JKL reports research contracts from Allergan, Conatus, Genfit, Gilead, Intercept, and Prometheus. The others have no conflict of interests related to this publication.

Author contributions

Drafting of the manuscript (JJC, KO, JKL), contributing to the conception and design of the study (JJC, KO, JKL), contributing to critical revisions of the manuscript (JKL).

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