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NASH Cirrhosis: A Systematic Review of Phase 2B Trials

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease in the United States. It includes a spectrum of conditions, from simple steatosis to more severe forms such as nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Recently, NAFLD has been redefined as metabolic dysfunction-associated fatty liver disease (MAFLD) to better reflect its association with metabolic dysregulation. Moreover, people with MAFLD can have a component of alcohol use, making MAFLD and alcoholic liver disease, 2 ends of a spectrum. It also moves away from the stigma of terminology previously used. This summary reviews the findings from recent phase 2b clinical trials that assess the efficacy and safety of various drugs targeting NAFLD and NASH. A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search included databases like PubMed, Embase, Cochrane Library, and Google Scholar, focusing on studies published within the last five years. Eleven randomized controlled trials (RCTs) met the inclusion criteria. For PPAR Agonists, the EMMINENCE trial evaluated a PPAR agonist, but did not meet its primary endpoints. In contrast, the NATIVE trial assessed lanifibranor and found significant improvements. FGF-21 and FGF-19 analogs were investigated in several trials with mixed results. The Harmony trial on efruxifermin (an FGF21 analog) reported significant improvements in fibrosis, highlighting its potential in treating NASH. However, the Alpine 2/3 and Alpine 4 trials on aldafermin (an FGF19 analog) did not demonstrate significant efficacy in fibrosis reduction. These mixed outcomes suggest that while FGF-based therapies hold prom-

ise, their effectiveness needs further research. Belapectin, a galectin-3 inhibitor, did not show significant benefits. TANDEM trial assessed the combination of tropifexor (TXR) and cenicriviroc (CVC), showing safety and tolerability with notable reductions in liver enzyme levels (ALT, AST, GGT). FXR agonists like tropifexor modulate bile acid metabolism and inflammatory pathways, while CCR inhibitors like cenicriviroc target chemokine receptors involved in hepatic inflammation and fibrosis. The combination therapy approach may offer synergistic benefits in managing NASH. The reviewed trials underscore the complexity of NAFLD and NASH treatment, with multiple therapeutic targets. PPAR agonists like lanifibranor show promise, particularly in resolving NASH. The variability in the efficacy of FGF-based therapies highlights the need for further research to identify the most effective agents and patient profiles.

Keywords

PPAR, Icona, Tandem, Harmony, Falcon

1. Introduction

Non-alcoholic fatty Liver disease (NAFLD) has become the leading cause of chronic liver disease in the United States of America. It is an umbrella term incorporating a spectrum of liver disease including fat deposition or steatosis without excessive alcohol consumption or any other causes of chronic liver disease. Further, it includes progressive stages of steatohepatitis, fibrosis, and finally cirrhosis and/or hepatocellular carcinoma [1]. Recently NAFLD has been renamed to metabolic dysfunction-associated fatty liver disease (MAFLD) [2]. There has been an incidence of metabolic dysregulation in alcoholics and alcohol use in people with MAFLD, necessitating moving away from the term non-alcoholic. Moreover, people with MAFLD can have a component of alcohol use, making MAFLD and alcoholic liver disease, two ends of a spectrum. It also moves away from the stigma of terminology previously used. More recently, an even newer term, called metabolic dysfunction associated and alcohol associated liver disease, or MetALD includes people with MASLD and consume more than 210 grams of weekly alcohol (two to three beers daily).

In the initial stages, the presenting symptoms are non-specific including fatigue, or abdominal pain. This leads to a delayed diagnosis when the patients progress to hepatitis, fibrosis or even cirrhosis [3]. Etiopathogenesis includes systemic insulin resistance which leads to lipid accumulation in the liver. Lipids within hepatocytes lead to the activation of inflammatory response. Both innate and adaptive immune mechanisms involving macrophages, and lymphocytes are central drivers of the process that recognizes damage-associated molecular patterns and contributes to the inflammatory cascade. The exact triggers remain less defined. Further, the contribution of the gut biome and gut-liver axis, remain areas of interest.

There are times when fatty liver is found on incidental abdominal imaging but not followed up on. It is controversial as to the possible benefit of early diagnosis given the lack of treatment. Weight loss and lifestyle changes can be crucial in such patients.

The NAFLD activity score (NAS), a composite of steatosis, inflammation, and hepatocyte ballooning that indicates a measure of disease activity, determines the histological evidence for a NASH diagnosis [4]. Following diagnosis, the NASH Clinical Research Network (CRN) fibrosis score indicates the pace of disease progression: One is mild to moderate, two is perisinusoidal fibrosis with portal/periportal fibrosis, three is bridging fibrosis, and four is cirrhosis. The FDA have advised sponsors to concentrate their medication development efforts on the phases with the greatest need, which are identified as non-cirrhotic NASH with liver fibrosis score greater than 1 but less than 4 [4].

It is advised that researchers assess NASH and fibrosis separately and take into account the following two primary endpoints: (i) resolution of NASH defined as the absence of isolated fatty liver disease or simple steatosis with no worsening of liver fibrosis, and/or (ii) improvement of liver fibrosis greater than or equal to stage 1 (NASH CRN fibrosis score) without worsening of NASH [5].

Given the complex process of pathogenesis and cell lines involved, different targets have been utilized to halt the progression or revert the damage in many clinical trials. These include drugs targeting insulin sensitivity, PPAR agonists, SGLT-2 inhibitors, or GLP-1 inhibitors, directly involved in lipid collection within cells. Other common targets include triglyceride metabolism, Fibroblast growth factor receptors, thyroid hormone receptors, and bile acid metabolism.

TGF-beta1 plays into cell apoptosis in the liver further causing NASH, NAFLD-cirrhosis, and HCC, making it a target. PPAR activators, currently approved for the treatment of diabetes, have shown effects on hepatocellular inflammation and fibrosis. Another transcription factor KLF15 activates twist-related protein 2 (TWIST2) reducing liver steatosis and inflammation by modulating fibroblast growth factor 21 (FGF21) signaling pathways [6]. Wnt and p53 Signaling Pathway, vascular cell adhesion molecule 1 (VCAM-1) are other possible targets.

Current treatment options include weight loss, exercise and lifestyle modifications. Bariatric surgery proves useful through weight loss. SGLT-2 inhibitors, and GLP-1 agonists have shown to lower NASH progression. More recently, the Farnesoid X receptor (FXR), a nuclear receptor that can be activated by bile acids (BAs), has anti-inflammatory and antifibrotic effects improving hepatic steatosis but not liver fibrosis and stiffness in NASH patients. Vitamin E proves useful in NASH in HIV-infected patients. Even Rifaximin in the past improved transaminase levels but failed to improve steatosis.

Amongst approved drugs, saroglitazar, dual peroxisome proliferator-activator receptor (PPAR) alpha and gamma agonist, was approved in 2020 after favorable results in Evidence trials in Indian patients [7]. Outside of India, a Phase 2 EVIDENCES IV trial in the US finished in October 2020 and achieved its main goal

of lowering ALT in patients with NAFLD and NASH following 16 weeks of therapy [8].

Recently Resmetirom, a Selective Thyroid Hormone Receptor Beta Agonist has been approved for noncirrhotic NASH after a successful Maestro phase 3 trial. This landmark trial paves the way for other possible drugs currently in trials for the treatment [9].

In our study, we delve into current phase 2b trials that aim to assess the efficacy and safety of various drugs in the treatment of NAFLD.

2. Materials and Methods

This study is being reported in accordance with the Preferred Reporting Items for Systematic Reviews and Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA-2020 guidelines (**Figure 1**) [10].

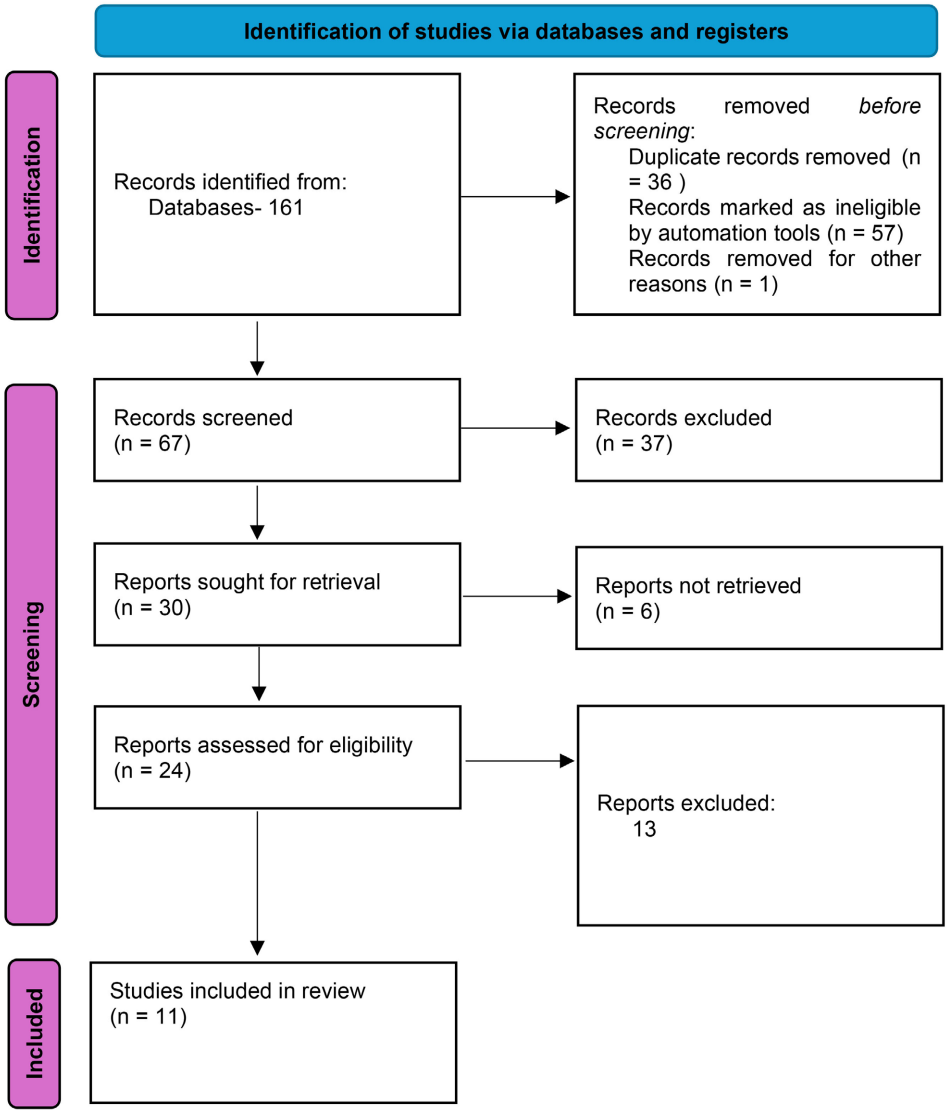

Figure 1. Prisma flow diagram.

Literature Search:

The literature search was performed by 3 independent researchers. Databases, including PubMed, Embase, Cochrane Library, and Google Scholar, were used to search for available studies. Various clinical trial registry websites were also searched for phase 2b trials completed in the last 5 years.

Inclusion criterion included Randomized controlled trials done is last 5 years, currently in phase 2B trials, published in English. Authors were flexible whether biopsies were taken and what end points were to have a more inclusive analysis. Reviews, case reports and trials in other stages were excluded.

Study Selection and Data Extraction:

Three independent reviewers went through the title and abstract of the available studies to determine if the PICO principles-based literature inclusion-exclusion criteria were suitable for this study. A full-text review of selected studies was performed to ensure that the inclusion criteria had been met. Standardized data extraction was performed based on the Cochrane Handbook for Systematic Reviews of Interventions [11].

Quality Assessment:

Cochrane Risk of Bias Tool (2.0) for RCTs was utilized to perform a critical appraisal of the selected studies. The different dimensions of quality assessment include the risk of bias arising from the randomization process, the risk of bias owing to deviations from the intended interventions, the risk of bias from missing outcome data, the risk of bias in the measurement of the outcome, and risk of bias in the selection of the reported result [12]. The risk of bias was low in all of the above domains.

Prisma chart is below as in **Figure 1**.

3. Results and Discussion

Study Characteristics:

11 randomized control trials (**Table 1**) were included in this study. An overview of the study's features is provided in **Table 1** and **Table 2**, which includes the trial name, author name, study type, inclusion, and total number of participants. All of the RCT's included in this systematic review are randomized double blinded studies; 10 of the 11 are placebo-controlled, where the TANDEM trial compares tropifexor to cenicriviroc [13]-[23]. Adults were the only trial participants in all the RCT's that were included. All the studies only included patients with histological confirmation of NASH most required a biopsy performed within 6-months from screening. The NAS score was used as a screening tool in 5 of the 11 studies, and among these 5 studies the RCT's only included patients with a NAS> 4 [2] [16] [17] [21] [23]. The Native study used the SAF activity score [15]. While most studies included patients with fibrosis stages 1, 2, and 3, only 2 studies included patients with fibrosis 4, that is, cirrhosis 1. The smallest RCT is the Falcon 2 trial, which included 100 patients, whereas the largest has 392 participants. It is shown in **Tables 1 - 3**.

Table 1. Study, type, and participants.

Study	Type	Number of participants
Emminence [13]	Randomized, double blind, placebo-controlled study	392
Study GT 026 52W [14]	Randomized, double-blind, placebo-controlled trial comparing 2 doses of belapectin to placebo	162
Native [15]	Phase 2b randomized, placebo-controlled, double-blind, parallel-assignment, dose-range study	247
Harmony [16]	Multicenter, randomized, double-blind, placebo-controlled, phase 2b	128
Icosubate-ICONA [17]	Randomized, Double-Blind, Placebo-controlled, Parallel Group Study	280
Tandem [18]	Phase 2b randomized, multicenter, double-blind study	193
Alpine 4 [19]	Randomised, double-blind, placebo-controlled	160
Alpine 2/3 [20]	Randomised, double-blind, placebo-controlled	171
Falcon 1 [21]	Randomized, phase 2b, multicenter, double-blind, placebo-controlled study	197/160
Falcon 2 [22]	Randomized, phase 2b, multicenter, double-blind, placebo-controlled study	100
Enliven [23]	Randomized, double-blind, placebo-controlled	222

Table 2. Inclusion criterion.

Study	Inclusion criterion
Emminence [13]	1. ≥ 18 years of age 2. Biopsy (within 9 months) confirmed NASH 3. Fibrosis F1-F3 4. ≥1 in each component [steatosis, ballooning, inflammation] 5. NAS ≥4 6. If biopsy >9 months, repeat biopsy after AST ≥ 20 U/L b. FibroScan with CAP score ≥ 270 db/m and kPa ≥ 8.5 criteria is met 7. Patient with T2DM on stable dose of medication for atleast 3 months and A1c < 9.5 8. Female. s participants should be post-menopausal or surgically
Study GT 026 52W [14]	1. HVPG ≥ 6 mm Hg 2. A liver biopsy with cirrhosis 3. ≥18 years of age and <75 years of age 4. Absence of hepatocellular carcinoma by valid imaging 5. Able to provide written informed consent 6. Was not pregnant and had a negative serum pregnancy test and agree to use effective means of contraception 7. Agreed to discontinue breastfeeding 8. Agreed to avoid sperm donation 9. On stable dose of statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or b-1 selective adrenergic receptor inhibitors for at least 2 months

Continued

Native [15]	1. Age ≥ 18 years 2. Liver biopsy performed within 6 months of screening confirming NASH 3. Presence of steatosis (any degree ≥5%) 4. Lobular inflammation of any degree 5. Liver cell ballooning of any amount)] without cirrhosis (< stage 4 fibrosis) 6. SAF Activity score of 3 or 4 (>2) 7. SAF steatosis score ≥ 1 8. Weight stability
Harmony [16]	1. Adults with biopsy-proven NASH 2. Fibrosis stage 2/3 3. NAS of ≥4 (with at least a score of 1 in each of steatosis, ballooning degeneration and lobular inflammation) 4. HFF of ≥8% by MRI–PDFF 5. Fibro Scan measurement >8.5kPa 6. History of or presence of 2 or more components of metabolic syndrome
Icosubate-ICONA [17]	1. Provides signed written 2. Male or female aged 18 to 75 years, inclusive 3. Histological diagnosis of NASH 4. Has (NAS) greater than or equal to 4, with a score of at least 1 in each component (steatosis, lobular inflammation, and ballooning) 5. Has a fibrosis score F1 to F3, inclusive (F1 capped at 30%) 6. Has a Proton Density Fat Fraction (PDFF) greater than or equal to 10% on MRI at screening
Tandem [18]	1.Male and female patients 2. Aged ≥18 years 3. Weighing between 50 and 200 kg 4. Presence of NASH, fibrosis stages F2/F3 as demonstrated by histologic evidence
Alpine 4 [19]	1. Liver biopsy consistent with NASH cirrhosis 2. Compensated cirrhosis due to NASH
Alpine 2/3 [20]	1. Histologically confirmed NASH diagnosis as defined by the NASH CRN 2. Total liver fat content of ≥ 8% as measured by MRI-PDFF
Falcon 1 [21]	1. Liver biopsy within 6 months with NASH and indicates: Score of ≥1 for each NAS (steatosis, lobular inflammation, and ballooning) and Stage 3 fibrosis according to the NASH CRN classification 2. On stable regimens for ≥3 months (≥6 weeks for statins) for diabetes, obesity, or dyslipidemia if any 3. On stable dose for ≥6 months if taking vitamin E doses ≥800 IU/day
Falcon 2 [22]	1. Liver biopsy within 6 months with NASH and cirrhosis by NASH CRN classification 2. On stable regimens for ≥3 months (≥6 weeks for statins) for diabetes, obesity, or dyslipidemia if any 3. On stable dose for ≥6 months if taking vitamin E doses ≥800 IU/day
Enliven [23]	Performed within 6 months 4. Childbearing age patients agreeable for double contraception up to 30 days after the last dose of IP. Female should not donate oocytes and males must not donate sperm. Females with a negative urine pregnancy test on Day 1and prior to dosing, condom use amongst sexually active males with pregnant wives

Peroxisome proliferator-activated receptors (PPARs) belong to a class of nuclear receptors. PPAR ligands have been researched as potential therapeutic agents for non-alcoholic fatty liver disease (NAFLD) due to their significant role in the transcriptional regulation of glucose and lipid metabolism [24]. Different RCTs included in the systematic review explore the effect of various drugs with different mechanisms of action on the hepatocytes in NAFLD. The EMMINENCE trial and the NATIVE trial include medications that act via the peroxisomal proliferator-activated receptor (PPAR), while MSDC-0662K, the experimental drug studied in the EMMINENCE trial targets the gamma subgroup of PPAR, Lanifibranor is a pan-PPAR agonist [13] [15].

Fibroblast growth factors and their receptors (FGF/FGFR) play an important role in maintaining metabolic homeostasis also in the liver and disorders in signaling have been identified to contribute to those pathophysiologic conditions leading to hepatic lipid accumulation and chronic inflammation. Treatment for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is still scarce, despite the fact that specific and well-tolerated inhibitors of fibroblast growth factor receptor activity are currently being developed for (non-liver) cancer therapy [25]. 6 among the 11 RCT's included explore the efficacy of therapeutic targets that work on the FGF at different levels. While the Harmony, Enliven and Falcon 1 and 2 trial focus on FGF21 [16] [21]-[23], the Alpine trials include drugs that work on FGF19 [19] [20].

Study GT 026 52W analyses the effect of Belapectin a novel Galectin-3 inhibitor that plays a role in portal hypertension, ICONA trial is one of its kind that assesses the efficacy of Icosabutate which is an omega 3 fatty acid. The Tandem trial includes 2 different drug both alone and in combination with each other, these drug act via the Farsinoid X receptor (FXR) and C-chemokine receptor (CCR).

The drug mechanism of action is compiled in **Table 3**.

Table 3. Drug mechanism of action.

Study	Drug studied	Mechanism of action
Emminence [13]	MSDC-0602K	Insulin desensitizer that binds mitochondrial pyruvate kinase and minimizes direct binding to the transcriptional factor PPARγ
Study GT 026 52W [14]	GR-MD-02 (Belapectin)	Inhibitor of Galectin-3 that reduces liver fibrosis and portal hypertension
Native [15]	Lanifibranor (IVA337)	A pan-PPAR agonist improves insulin sensitivity and macrophage activation and reduces liver fibrosis and inflammatory gene expression
Harmony [16]	Efruxifermin	Long-acting Fc-FGF21 fusion protein. fibroblast growth factor 21 (FGF21) is anti-fibrotic, improves metabolic status and has potential to treat non-alcoholic steatohepatitis (NASH)
Icosubate-ICONA [17]	Icosabutate	Structurally enhanced omega-3 fatty acid molecule developed with the aim of achieving improved triglyceride (TG)-lowering efficacy

Continued

Tandem [18]	Tropifexor (TXR) Cenicriviroc (CVC)	Tropifexor (TXR) nonbile acid FXR agonist Cenicriviroc (CVC) a potent inhibitor of C-C chemokine receptor types 2/5 (CCR2/5), has demonstrated antifibrotic and anti-inflammatory properties
Alpine 4 [19]	Aldafermin	Engineered analogue of the gut hormone fibroblast growth factor 19 (FGF19)
Alpine 2/3 [20]	Aldafermin	Engineered analogue of the gut hormone fibroblast growth factor 19 (FGF19)
Falcon 1 [21]	Pegbelfermin (PGBF)	Long-acting glycopegylated (pegylated with the use of site-specific glycosyltransferases) fibroblast growth factor 21 (FGF21) analogue
Falcon 2 [22]	Pegbelfermin (PGBF)	Long-acting glycopegylated (pegylated with the use of site-specific glycosyltransferases) fibroblast growth factor 21 (FGF21) analogue
Enliven [23]	Pegozafermin	Long-acting glycopegylated (pegylated with the use of site-specific glycosyltransferases) fibroblast growth factor 21 (FGF21) analogue

For ten of the eleven studies, participant demographic information is available. Based on this data, the average age of participants is 54.3. This is very close to the mean age of participants in the HARMONY trial conducted by Akero Therapeutics. In all the RCT there were more Caucasian participants in both the placebo and treatment groups. 0.3 mg subgroup of the Alpine 4 trial consisted exclusively of the Caucasian population, whereas Study GT 026's 8mg/kg subgroup had the lowest percentage of Caucasians at 74%.

In a Japanese study conducted over 12 years, the average prevalence of fatty liver in men was 26%, wich was double than that seen in women (13%). Men, on the other hand, had a similar prevalence across all age groups, but women's prevalence increased gradually with age. In the 70-79 age range, the prevalence was higher in females than in males. A different study conducted in South China found that the prevalence of NAFLD was significantly higher in men than in women under 50 (22.4% vs. 7.1%, $p < 0.001$). When comparing this prevalence between men and women over the age of fifty, the results were reversed. (20.6% vs 27.6%, $p < 0.05$) [26] [27]. The RCT's included in this systematic review showed a female preponderance with as high as 80% in the 8mg/kg subgroup of Study GT 026. Conversely, only 43% of participants in the 15 mg/week subgroup of the Enliven trial were female.

BMI ranges between 32.5 - 38.7, which is unsurprising given that Obesity is a major driver of NAFLD and NASH, around 50% of NAFLD patients and 80% of NASH patients present with obesity [28]. **Table 4** summarizes the demographics.

Table 4. Demographics.

Study	Mean age (Age in years, (SD))	Race	Gender	BMI	Comorbidities
EMMINENCE [13]	Placebo: 54.6 (11.21), 62.5 mg: 56.9 (10.28), 125 mg: 56.0 (10.89), 250 mg: 56.8 (10.42), Total: 56.1 (10.70)	White Placebo-85%, 62.5 mg-93%, 125 mg-91%, 250 mg-91%	M: F Placebo-51%, 62.5 mg-56%, 125 mg-63%, 250 mg-58%	Placebo-35.03 (5.574), 62.5 mg-34.68 (5.177), 125 mg-35.93 (6.121), 250 mg-35.03 (6.118), Total-35.16 (5.761)	T2DM-52.3% Subgroup analysis unavailable
Study GT 026 52W [14]	Placebo: 58.4 (8.5) 2mg/kg: 59.2 (7.5) 8mg/kg: 57.1 (9.3)	White Placebo: 85% 2mg/kg: 85% 8mg/kg: 74%	Females (%) Placebo: 67% 2mg/kg: 63% 8mg/kg: 80%	Placebo-34.6 (7.1) 2mg/kg-35.7 (6.5) 8mg/kg-34.4 (5.7)	T2DM: Placebo-59% 2mg/kg-59% 8mg/kg-67%
NATIVE [15]	Placebo 53.4 (13.1) 800 mg 55.0 (10.4) 1200 mg 52.2 (13.8)	White: Placebo: 91% 800 mg: 96% 1200 mg 94%	Females Placebo-51% 800mg-65%, 1200 mg-59%	Placebo-32.8(5.1) 800 mg-32.5(5.5) 1200 mg-33.3(5.5)	T2DM: Placebo-43% 800 mg-40% 1200 mg-42%
Harmony [16]	Placebo 55.0 (10.1) 28 mg 56.5 (9.3) 50 mg 52.4 (11.4) Total 54.7 (10.4)	Placebo-91% 28 mg-91% 50 mg-95%	Placebo-63% 28 mg-69% 50 mg-53% Total-62%	Placebo-38.7 (7.7) 28 mg-38.3 (6.9) 50 mg-37.2 (6.6) Total-38 (7.0)	A1c (%(SD)) Placebo-6.8 (1.1) 28 mg-6.8(1.0) 50 mg-6.7 (1.2) Total-6.8 (1.1) A1c average available rather than % with diabetes
Icosubate-ICONA [17]	NA	NA	NA	NA	NA
Tandem [18]	TXR 140 µg-54.8 (13.4) CVC 150 mg-53.7 (11.8) TXR 140 µg + CVC 150 mg-54.7 (12.7) TXR 90 µg +CVC150mg-54.9 (12.3)	Caucasian TXR 140 µg-82.0% CVC 150 mg-91.7% TXR 140 µg + CVC 150 mg-85.1% TXR 90 µg + CVC150mg-89.6%	Female(%) TXR 140 µg-60% CVC 150 mg-64.6% TXR 140 µg + CVC 150 mg-61.7% TXR 90 µg + CVC150mg-47.9%	TXR 140 µg-33.7 (6.6) CVC 150 mg-35.7 (8.4) TXR 140 µg + CVC 150 mg-34.7 (6.9) TXR 90 µg +CVC150mg-34.3 (7.3)	TXR 140 µg-78.0% CVC 150 mg-85.4% TXR 140 µg + CVC 150 mg-83.0% TXR 90 µg + CVC 150 mg-83.3%

Continued

Alpine 4 [19]	Placebo QD-58.3 (8.1) 0.3 mg QD-59.7 (6.8) 1.0 mg QD-61.3 (7.6) 3.0 mg QD-59.6 (8.7)	Placebo QD-82.1% 0.3 mg QD-100.0% 1.0 mg QD-90.5% 3.0 mg QD-85.5%	Female Placebo QD-69.6% 0.3 mg QD-71.4% 1.0 mg QD-54.8% 3.0 mg QD-65.5%	Placebo QD-34.8 (7.1) 0.3 mg QD-32.8 (3.2) 1.0 mg QD-36.0 (6.3) 3.0 mg QD-34.3 (6.7)	Placebo QD-75.0% 0.3 mg QD-71.4% 1.0 mg QD-76.2% 3.0 mg QD-76.4%
Alpine 2/3 [20]	Placebo QD-53.0 (10.8) 0.3 mg QD-54.3 (11.2) 1.0 mg QD-49.8 (13.2) 3.0 mg QD-52.7 (11.1)	Placebo QD-95% 0.3 mg QD-93% 1.0 mg QD-90% 3.0 mg QD-91%	Placebo QD-60% 0.3 mg QD-65% 1.0 mg QD-69% 3.0 mg QD-67%	Placebo QD 0.3 mg QD 1.0 mg QD 3.0 mg QD No data	Placebo QD-42% 0.3 mg QD-47% 1.0 mg QD-52% 3.0 mg QD-56%
Falcon 1 [21]	Placebo-57.5 (8.0) 10-mg PGBF-56.4 (9.6) 20-mg PGBF-56.3 (10.1) 40-mg PGBF-57.4 (10.5)	White Placebo –83.7% 10-mg PGBF-87.8% 20-mg PGBF 84.0% 40-mg PGBF 85.7%	Female Placebo-59.2% 10-mg PGBF-59.2% 20-mg PGBF-54.0% 40-mg PGBF-63.3%	Placebo-35.2 (8.1) 10-mg PGBF-36.3 (6.7) 20-mg PGBF-35.1 (6.4) 40-mg PGBF-35.7 (6.6 SD)	Placebo-73.9% 10-mg PGBF 72.3% 20-mg PGBF-74.5% 40-mg PGBF-73.9%
Falcon 2 [22]	Placebo-61.4 (7.5) 10-mg PGBF-60.2 (8.0) 20-mg PGBF-58.9 (9.3) 40-mg PGBF-57.0 (10.0)	White Placebo-84.6 % 10-mg PGBF-76.9% 20-mg PGBF-81.1% 40-mg PGBF 87.2%	Female Placebo-61.5% 10-mg PGBF-71.8% 20-mg PGBF-67.6% 40-mg PGBF-53.8%	lacebo-35.4 (6.4) 10-mg PGBF-34.5 (5.9) 20-mg PGBF-35.5 (6.2) 40-mg PGBF-36.9 (5.8)	lacebo-77.8% 10-mg PGBF-77.1% 20-mg PGBF 79.4% 40-mg PGBF-80.0%
ENLIVEN [23]	Placebo-56.3 (9) 15 mg/w-55 (10.5) 30mg/w-55.3 (11.2) 44mg/2w-55.2 (11.2)	White-Placebo-94% 15 mg/w-86% 30mg/w-95% 44mg/2w-95%	Placebo-55% 15 mg/w-43% 30mg/w-68% 44mg/2w-65%	Placebo-38.1(5.6) 15 mg/w-37.8(4.8) 30mg/w-35.1(6.4) 44mg/2w-36.1(5.5)	T2DM-Placebo-69% 15 mg/w-86% 30mg/w-62% 44mg/2w-61%

The majority of the RCT's compared the efficacy of placebo to varying concentrations of experimental drug. The exception to this is the TANDEM trial which

compares Tropifexor (TXR) and Cenicriviroc either alone or in combination with each other. Additionally, this trial not only studies efficacy but the safety of the drug.

NAFLD activity score (NAS) a composite of steatosis, inflammation, and hepatocyte ballooning that indicates a measure of disease activity is one of the predictors of change in fibrosis [29], hence it is unsurprising that many of the RCT's included in this systematic review used NAS as a measure in either its primary or secondary outcomes. Endpoints of the trials are summarized in **Table 5**.

Table 5. Endpoints.

Study	Subgroups	Primary outcome	Secondary outcome	Other outcomes
EMMINENCE [13]	1. placebo (n = 94) 2. 62.5 mg (n = 99) 3. 125 mg (n = 98) 4. 250 mg (n = 101)	1. ≥2-point NAS decrease with a ≥1-point reduction in either ballooning or lobular inflammation and no increase in fibrosis stage	1. NAS improvement without worsening fibrosis 2. NASH resolution 3. fibrosis reduction	1. changes in insulin sensitivity 2. liver injury 3. liver fibrosis markers
Study GT 026 52W [14]	1. Placebo (n = 54) 2. (Belapectin) 2mg/kg (n = 54) 3. Belapectin 8 mg/kg (n = 54)	1. Efficacy of belapectin in reducing HVPG as a measure of portal pressure compared with placebo after 12 months of treatment	1. Baseline adjusted mean change in the collagen proportion area 2. proportion of participants with ≥ 1 point change in fibrosis stage, 3. baseline adjusted mean change in liver stiffness, and 4. complications of cirrhosis, esophageal varicealhemorrhage or portal hypertensive gastropathy hemorrhage (confirmed by endoscopy), clinically apparent ascites or spontaneous bacterial peritonitis, -overt hepatic encephalopathy, an increase in Child Turcotte-Pugh score ≥2 points, -newly diagnosed varices in a participant without prior varices or progression from small to medium or large varices, -reaching a model for end-stage liver disease score ≥15 as measured on 2 consecutive occasions, -listing for a liver transplant or the performance of a liver transplant, or liver-related mortality	1. incidence of treatment-emergent adverse events (TEAEs), 2. serious adverse events (SAEs), and 3. study discontinuation

Continued

NATIVE [15]	Placebo (n=81) Lanifibranor 800mg (n=83) Lanifibranor 1200 mg (n=83)	1. decrease of at least 2 points of the SAF Activity score without fibrosis progression (any stage increases of fibrosis) from baseline to week 24.	1. 2-point decrease of NAS with no fibrosis worsening, 2. NASH resolution (defined as normal liver or steatosis with or without mild inflammation, no ballooning and no fibrosis worsening at week 24), 3. improvement in each histological parameter (steatosis, ballooning, inflammation, activity, CRN-fibrosis, Ishak-fibrosis, EPoS staging system) 4. inflammatory markers (fibrinogen, high sensitivity C-reactive protein, alpha2 macroglobulin and haptoglobin levels), 5. glucose metabolism (fasting glucose and insulin, HOMA-IR and HbA1c in patients with T2DM) and 6. main plasma lipid levels (total cholesterol, HDLeC, calculated LDL-C, triglycerides and Apolipoprotein A1)	1. fibrosis markers including TIMP-1, TIMP-2, cytokeratin K, 18 (CK18), hyaluronic acid, procollagen-3 N-terminal petide (P3NP), matrix metalloproteinase (MMP) 2, MMP9, N-terminal propeptide of type 3 procollagen (proeC3) 2. markers of lipids and glucid metabolism 3. inflammation markers including interleukins (IL)-6, IL-13, tumor necrosis factor alpha (TNFα) 4. markers of bone remodelling 5. TE and controlled attenuation parameter (CAP) 6. genotype signatures such as patatin-like phospholipase domain containing protein 3 (PNPLA3) and TM6SF2
Harmony [16]	efruxifermin, a long-acting Fc-FGF21 fusion protein	Placebo (n = 42) 28 mg (n = 42) 50 mg (n = 43)	1. Improvement in liver fibrosis score >1 without worsening of NASH	1. Resolution of NASH and no worsening of liver fibrosis 2. Improvement in liver fibrosis > 1and resolution of NASH 3. Improvement in liver fibrosis >2, no worsening of NASH 4. Changes in HFF
Icosubate-ICONA [17]	Placebo (n = 35) 300 mg (n = 40) 600 mg (n = 39)	1. percentage of patients with resolution of NASH, (disappearance of ballooning (score = 0) with lobular inflammation score 0 or 1) with no worsening of fibrosis.	1.Change in Nonalcoholic fatty liver disease (NAFLD) activity score (NAS) in 52 w 2. Changes in individual histological scores for steatosis, ballooning, inflammation, and fibrosis in 52 w 3. Changes in the liver enzymes Aspartate Aminotransferase (AST) U/L, Alanine Aminotransferase (ALT)U/L and Gamma Glutamyl Transferase (GGT) U/L in 52 weeks 4. Change in bilirubin mg/dL	

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Tandem [18]	TXR140 (n = 50) CVC (n = 48) TXR140 + CVC (n = 47) TXR90 + CVC (n = 48)	1. Safety and efficacy of the combination versus monotherapy	1. 1-point improvement in fibrosis stage 2. Steatohepatitis resolution without worsening of fibrosis
Alpine 4 [19]	Placebo (n = 56) 0.3 mg (n = 7) 1 mg (n = 42) 3 mg (n = 55) 0.3 mg group was discontinued to limit exposure	1. Change in Enhanced Liver Fibrosis from baseline to week 48.	1. Fibrosis improvement without NASH worsening
Alpine 2/3 [20]	Aldafermin Placebo QD (n = 43) 0.3 mg QD (n = 43) 1.0 mg QD (n = 42) 3.0 mg QD (n = 43)	1. Improvement in liver fibrosis of at least one stage with no worsening of NASH at week 24	
Falcon 1 [21]	Placebo (n = 490 10 mg PGBF (n = 49) 20 mg PGBF (n = 50 40 mg PGBF (n = 49)	1. Measured at week 24, ≥ 1 stage fibrosis improvement (NASH CRN fibrosis score) without worsening of NASH (*i.e.*, increase in NAS by ≥1 point) 2. NASH improvement (*i.e.*, decrease in NAS by ≥2 points with contribution from at least 2 NAS components) without worsening of fibrosis (*i.e.*, increase in NASH CRN fibrosis score by ≥1 stage)	1. NASH CRN fibrosis score improvement at Week 24 2. modified Ishak Score improvement at Week 24 3. Decrease in CPA at Week 24 Proportion of patients with NASH resolution without worsening of fibrosis at Week 24 4. NASH resolution at Week 24 5. NASH improvement without worsening of fibrosis at Week 24 6. ≥1 stage improvement in NASH CRN fibrosis score without NASH worsening at Week 24 7. NASH improvement at h. h. Progression to cirrhosis at Week 24

Continued

Falcon 2 [22]	Placebo (n = 39) 10-mg PGBF (n = 39) 20-mg PGBF (n = 37) 40-mg PGBF (n = 37)	1. Improvement by 1 or more fibrosis stages without NASH worsening at week 48	1.Modified Ishak Score improvement at Week 48 2. NASH resolution at Week 48 NASH improvement at Week 48 3. ≥1 stage improvement in NASH CRN fibrosis score without NASH worsening OR NASH improvement at Week 48 4. ≥1 stage improvement in NASH CRN fibrosis score at Week 48 5. Decrease in CPA at Week 48	
ENLIVEN [23]	Placebo (n = 71) 15 mg/w (n = 21) 30 mg/w (n = 73) 44 mg/2w (n = 57)	At 24W, 1. Reduction in fibrosis of at least one stage, without worsening of NASH (defined as an increase in ballooning, inflammation, or steatosis) 2. NASH resolution (defined as the total absence of ballooning and absent or mild inflammation) without worsening of fibrosis (increase of ≥1 stage)	1. An improvement of at least 2 points in the NAS and no worsening of fibrosis. 2. MRI-PDFF 3. Liver chemistry tests 4. N-terminal type III collagen propeptide 5. Metabolic variables (adiponectin, serum triglycerides, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, low-density lipoprotein [LDL] cholesterol, and glycated hemoglobin)	1. Iron-corrected T1 (which assesses fibro inflammation) 2. the Enhanced Liver Fibrosis test score, liver stiffness 3. Fibro Scan–aspartate aminotransferase (FAST) score 4. Fibrosis-4 index score 5. liver and spleen volumes

Both the Emminence trial, which is evaluating the effectiveness of the experimental drug MSDC-0602K, and the Native trial, which is evaluating various doses of Lanifibranor, involve drugs that influence liver fibrosis by acting on the PPAR pathway. The insulin desensitizer MSDC-0602K minimizes direct binding to the transcriptional factor PPARγ, whereas Lanafibranor pan-PPAR agonist reduces liver fibrosis and inflammatory gene expression. The emminence trial compares the efficacy of 3 different concentrations of drug (62.5 mg, 125 mg, 250 mg) to placebo with a primary interest in more than 2-point decrease in NAS with a more than 1-point reduction in either ballooning or lobular inflammation and no increase in fibrosis. The Native trial differs from the other trials in this study by using the SAF activity score in place of NAS. While NAS was originally established for monitoring therapeutic effects, SAF score was initially designed to differentiate between NAFLD and NASH [30].

Although the PPAR agonist in emminence trial failed to acheive its primary end point, patients treated with lanifibranor who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher among those who received the 1200-mg dose, but not among those who received the 800-mg dose of lanifibranor than among those who received placebo (1200-mg dose vs. placebo, 55% vs. 33%, P=0.007; 800-mg dose vs. placebo, 48% vs. 33%, P = 0.07)

In addition, in cases where the Emminence trial failed to meet its secondary objectives, the Native trial demonstrated that 49% of patients receiving the 1200-mg dose of lanifibranor, 39% of patients receiving the 800-mg dose, and 22% of patients receiving a placebo experienced resolution of NASH at week 24 from baseline (risk ratio for a response in the 1200-mg lanifibranor group vs. the placebo group, 2.2; 95% CI, 1.5 to 3.3; and risk ratio in the 800-mg lanifibranor group vs. the placebo group, 1.7; 95% CI, 1.1 to 2.7). Lanifibranor is currently involved in phase 3 studies.

Study GT 026 was assessing the efficacy of belapectin an inhibitor of galectin-3 which was found to reduce liver fibrosis and portal hypertension in rats. The study analysed 2 different concentrations of Belapectin (2mg/kg and 8mg/kg) compared to placebo. Sadly, there was no statistically significant difference between either concentration of belapectin and placebo when it came to reducing the hepatic vein pressure gradient (HVPG), a measure of portal pressure. This was the study's main objective. It is noteworthy, nevertheless, that the LS mean change with belapectin 2 mg/kg was significantly different (-1.61 mm Hg, P 0.02) in the subgroup of patients without varices at baseline compared with placebo (0.40 mm Hg), but not with belapectin 8 mg/kg (-0.28 mm Hg, P 0.4). This gives rise to the argument that either the benefits of belapectin 2 mg/kg on the development of new varices and HVPG are caused by mechanisms other than directly improving liver fibrosis, or the sample size in this subgroup was too small to detect the histologic changes associated with belapectin 2 mg/kg treatment. Additionally, this supports the idea that small animal model systems do not consistently translate well into human clinical trials. It has been approximated, for instance, that less than 10% of animal models successfully translate into human cancer clinical trials [31].

The 52-week ICONA trial, which had NASH resolution without fibrosis worsening as the primary endpoint and NAS changes as a secondary end point, was designed to assess the effectiveness of icosabutate in NAFLD. However, the trial was unable to demonstrate any statistically significant changes with respect to the primary endpoint. The greatest treatment effect was seen in T2D patients, who responded to Icosabutate 600 mg with a NASH resolution rate of 35.5% (p = 0.007 vs. placebo) and a NAS decrease of at least two points, compared to 4% in patients receiving a placebo. For fibrosis improvement without worsening in NASH, 28.6% (p = 0.005) and 19.4% (p = 0.02) of T2D patients achieved a ≥ 1-stage improvement in the 300mg and 600mg arms respectively, versus none in placebo. Given these findings, Icosabutate could be a potential treatment modality for patients

with NASH and T2DM.

The only non-placebo-controlled trial in this series, the Tandem trial, included four treatment arms: TXR 140 μg once daily, CVC 150 mg daily, TXR 140 μg + CVC 150 mg qd, and TXR 90 μg + CVC 150 mg qd. By tracking adverse events (AEs), vital signs, and laboratory values over the course of 48 weeks of treatment, as opposed to TXR and CVC monotherapy, this trial sought to assess the safety and tolerability of TXR plus CVC in patients with NASH and fibrosis (stages F2/F3). Regarding safety, pruritus, nausea, and fatigue were the most commonly reported adverse events (AEs). The incidence of pruritus was highest in the TXR monotherapy group and significantly lower in the TXR140 + CVC combination treatment group. This could be explained by the noted decrease in postdose TXR levels (~10%) when CVC is present. Over the course of the 48-week trial, ALT, AST, and GGT decreased in the TXR monotherapy and combination groups relative to the base line; no such decrease was seen in the CVC monotherapy group. The TXR140 + CVC group had the highest MRI-PDFF measurement (52.4%) at week 24, but at week 48, the TXR140 monotherapy group had the greatest proportion of patients with a ≥30% reduction in HFF (37.5%).

Members of the FGF superfamily, FGF19 and FGF21, have been extensively researched since the time they were cloned in 1999 and 2000 respectively [32] [33]. While FGF21 is produced by the liver, FGF 19 is a gut derived hormone [6] [34]. Both hormones exert their effects by binding to the FGFR's that are widely expressed in the body. FGF19 in the presence of βKlotho (KLB) is able to bind multiple isoforms of FGFR's, FGF21 requires the presence of an unknown co factor in addition to βKlotho (KLB). While the N-termini of both factors control their FGF receptor specificity, the C-terminal tails of FGF19 and FGF21 are responsible for these hormones' capacity to bind KLB. While FGF21 is thought to be a major regulator of glucose and lipid homeostasis, it is also thought to play a role in modulating BA/cholesterol synthesis. If anything, FGF21 may have some less potency in modulating BA/cholesterol synthesis in mice than FGF19 [35] [36].

Harmony, Enliven, and Falcon 1 and 2 trials focus on FGF21 [16] [21]-[23], while the Alpine trials include drugs that work on FGF19 [19] [20]. The Harmony trial compared efficay of efruxifermin, along-acting FGF21 analogue, to placebo. Trial used 2 different doses of efruxifermin: 8 mg and 50 mg. The primary end point of the trial was to look for improvement in liver fibrosis score without worsening of NASH. eight (19%) of 43 patients in the placebo group met this endpoint versus 15 (36%) of 42 in the efruxifermin 28 mg group (RR 2.2 [95% CI 1.0 - 4.8]; p = 0.033) and 14 (33%) of 43 in the efruxifermin 50 mg group (1.9 [0.8 – 4.3]; p = 0.123). Additionally, 2 of the secondary endpoints including Resolution of NASH and no worsening of fibrosis at 24 weeks, improvement in liver fibrosis ≥1 and resolution of NASH were satisfied [16].

Pegozafermin at a dose of 15 mg once weekly, 30 mg once weekly, or 44 mg every 2 weeks was compared to placebo once weekly or once every two weeks in the Enliven trial. The study's two main outcomes were assessed at week 24 in com-

parison to the baseline: a minimum of one stage improvement in fibrosis without worsening of non-alcoholic steatosis, or NASH (defined as an increase in ballooning, inflammation, or steatosis), and a complete lack of ballooning and mild to no inflammation without worsening of fibrosis (increase of ≥ 1 stage). At 24 weeks, pegozafermin was significantly more effective than placebo in terms of the percentage of patients who had improved their fibrosis by at least one stage without their NASH getting worse. This was true for both the weekly 30-mg dose (26% vs. 7%; difference, 19 percentage points, 95% confidence interval [CI], 5 to 32; P = 0.009) and the every-two-week 44-mg dose (27% vs. 7%; difference, 20 percentage points, 95% CI, 5 to 35; P = 0.008). As determined by MRI-PDFF, the groups receiving 15 mg, 30 mg, and 44 mg of pegozafermin had the least-squares mean percentage changes from baseline in liver fat content (−27.1%, 48.2%, and 41.9%, respectively) at week 24, while the placebo group was (−5.0%) [23].

Falcon 1 and 2 are the other 2 trials that act via the FGF21 pathway. They study the effect of Pegbelfermin v/s placebo. While Falcon 1 concludes at 24 weeks, Falcon 2 reports the effects at 48 weeks. Additionally, three distinct pegbelfermin dosages-10, 20, and 40 mg-were used in this investigation. The main goals are to improve fibrosis by at least one stage (NASH CRN fibrosis score) without making NASH worse (*i.e.*, increase in NAS by at least one point) and to improve NASH (*i.e.*, decrease in NAS by at least two points with contribution from at least two NAS components) without making fibrosis worse (*i.e.*, increase in NASH CRN fibrosis score by at least one stage) at 24 weeks for falcon 1. The Falcon 2 focuses on improvement by 1 or more fibrosis stages without NASH worsening at week 48. Unfortunately, both falcons 1 and 2 were unable to achieve statistically significant results in comparison to placebo with respect to the primary outcomes.

The alpine 2/3 trial included 171 patients who were randomized into placebo group v/s one of the 3 different dosages of aldafermin (0.3, 1 mf, 3 mg). The study took place over a period of 24 weeks. At week 24, of the patients who had biopsies at baseline and week 24, seven (19%) of the 36 patients in the placebo group, eleven (31%) of the 36 patients in the 0.3 mg aldafermin group (difference 90% CI 12% [−9 to 33]; p=0.11), five (15%) of the 34 patients in the 1.0 mg group (difference −5% [−24 to 13]; p = 0.80), and eleven (30%) of 37 patients in the 3.0 mg group (difference 10% [−9 to 30]; p = 0.12) had improved liver fibrosis of at least one stage without worsening of NASH, without meeting the prespecified significance for dose response (p = 0.55). The trial failed to show any significant improvement in fibrosis.

The alpine 4 trial the only trial that involved patients with established cirrhosis randomized patients to similar groups as Alpine 2/3 however the effects were measured at the end of 48 weeks. The 3 mg group and the placebo group had a least-squares mean difference in the change in Enhanced Liver Fibrosis of −0.5 (95% CI, −0.7 to -0.2; p = 0.0003). In patients receiving placebo, 1 mg, and 3 mg, respectively, 15%, 21%, and 23% achieved fibrosis improvement of at least one stage; in patients receiving 16%, 17%, and 20%, fibrosis improvement of at least

one stage was achieved without a worsening of NASH.

4. Conclusions

The systematic review of randomized controlled trials (RCTs) investigating the efficacy and safety of various pharmacological treatments for non-alcoholic steatohepatitis (NASH) reveals mixed outcomes. Trials like Emminence and Native, which focused on drugs influencing the PPAR pathway, yielded varying results. While MSDC-0602K did not achieve its primary endpoint, lanifibranor showed significant improvements in fibrosis and NASH resolution at higher doses, suggesting a dose-dependent efficacy. Similarly, the study of belapectin in the GT 026 trial indicated potential benefits in specific subgroups, though overall results were not statistically significant.

The ICONA trial with icosabutate demonstrated promising results in patients with type 2 diabetes (T2D), with notable improvements in NASH resolution and fibrosis. This suggests that icosabutate could be particularly effective for patients with concurrent T2D and NASH.

FGF21 analogues, such as efruxifermin (Harmony trial) and pegozafermin (Enliven trial), showed efficacy in improving liver fibrosis and NASH without worsening the condition, highlighting the potential of targeting the FGF21 pathway. However, the Falcon trials with pegbelfermin did not achieve significant primary outcomes, y*et al*gain indicating variability in response amongst similar targeted therapies.

With FGF19-focused Alpine trials, 2/3 trial did not demonstrate significant improvements in fibrosis but the Alpine 4 trial in patients with established cirrhosis showed some promise in the higher dose group over a longer treatment period.
Overall, these findings underscore the complexity of pathophysiology further translating to heterogeneity in response to different therapeutic approaches despite targeting similar pathways. Subgroup and dosedependent variations are critical for further explanations into actual efficacy versus a possible confounding factor. The ongoing phase 3 studies of promising agents like lanifibranor and icosabutate will be crucial in determining their long-term efficacy and safety. The success of Maestro trials has garnered attraction yet algain for a possible treatment for NASH patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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