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ARTICLE

# An Update on Management of Nonalcoholic Fatty Liver Disease & Nonalcoholic Steatohepapititis is the Time Ripe for Achieving Resolution of NAFLD & NASH Soon

**Kulvinder Kochar Kaur[1*] Gautam Allahbadia[2] Mandeep Singh[3]**

1. Dr Kulvinder Kaur Centre For Human Reproduction, Jalandhar, Punjab, 144001, India
2. Ex-Rotunda-A Centre for Human Reproduction, Mumbai, India
3. Swami Satyanand Hospital, Jalandhar, Punjab, India

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ABSTRACT

We earlier reviewed how obesity has assumed an endemic/pandemic proportions that has resulted in escalating incidence and prevalence of associated escalating worldwide incidence of Metabolic Syndrome (MetS) with non alcoholic fatty liver disease (NAFLD), that is correlated with enhanced morbidity. Later we tried to detail how probiotics, L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, along with Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin, Vitamin D, Allyl Isothiocyanate (AITC), might aid in treating and understand the etiopathogenesis of NAFLD. The prevalence of NAFLD all over the world is approximately 25%, with that of non alcoholic steatohepapititis (NASH), varying from 1.5%=6.45%. Particularly NASH, specifically the ones associated with fibrosis possess a greater chance of generation of side effects that include progression to cirrhosis as well as liver-associated mortality. Despite an improvement was observed with vitamin E, Pioglitazone. liraglutide in histological appearance in liver randomized controlled clinical trials (RCT), at present no drugs exists that have received FDI approval for NASH. The aim of this review was to update the newer drugs getting evaluated, undergoing phase 2-3 trials. Currently there are Obeticholic acid, elafibranor, cenicriviroc, resmetriom, in addition to aramchol, that are the five agents that are getting analysed in big, histology dependent phase 3 trials. Hopefully within another 2-4 years, newer, efficacious drugs will be available for the therapy of NASH. Besides that a lot of phase 2 trials are continuing for different drugs. Further depending on outcomes of phase 2-3 trials, combination treatments are getting evaluated. For future therapeutic approaches would be made up of variations in NASH phenotypes, besides personalized approaches based on various NASH phenotypes in addition to response of every single patient. Further recently there were reports of utilization of curcumin with nonselective beta blocker for regression from cirrhosis (reviewed by us). Hopefully once there are approved therapies for NAFLD/NASH, we can work in that direction.

**Corresponding Author:*
*Kulvinder Kochar Kaur,*
*Dr Kulvinder Kaur Centre For Human Reproduction, Jalandhar, Punjab, 144001, India;*
*Email: kulvinder.dr@gmail.com*



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## 1. Introduction

Earlier we have reviewed how obesity is assuming an endemic/pandemic proportions resulting in escalating incidence as well as Prevalence associated escalating worldwide incidence of Metabolic Syndrome (MetS) with Non alcoholic fatty liver disease (NAFLD) [1-9], that is correlated with enhanced morbidity [8]. We tried to detail how probiotics, L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, along with Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin, Vitamin D, Allyl Isothiocyanate (AITC), SGLT Inhibitors etc might aid in treating and understand the etiopathogenesis of NAFLD. By definition non alcoholic fatty liver disease(NAFLD), classificationcan be performed histologically into non alcoholic fatty liver or non alcoholic steatohepapititis (NASH). The prevalence all over the world is escalating, being approximately 25%, with that of NASH varying from 1.5%-6.45% [10]. The cases of NASH particularly the ones with fibrosis posseses greater chances of side effects like cirrhosis as well as fibrosis–associated mortality [11-13]. The maximum significant histological parameter of NAFLD correlated with long time mortality is fibrosis (stage 2-4) [12,14]. Hence of these 2 surrogate endpoints require to get validated in phase 2b or 3 trials for the conditional passing of the drug for generation: i) rectification of NASH without deterioration of fibrosis or; ii) fibrosis getting decreased by 1 or > stages without deterioration of NASH [15]. Despite no FDA approved drugs for NASH, vitamin E, Pioglitazone, along with Liraglutide escalated liver histology of patients with NASH in randomized controlled clinical trial [16-18]. In spite of Vitamin E possessing potential advantages, it has been correlated with contradictory outcomes of total mortality [19], the haemorrhagic stroke [20] as well as prostate cancer in males >than 50 years age [21]. Pioglitazone results in weight escalation [16], with its utility in NASH still getting evaluated although now Sodium–glucose cotransporter 2 (SGLT2) inhibitors are being evaluated in view of lack of above limitation, hence adversities need to get balanced with the potential advantages in NASH patients [reviewed by us], having no other option for therapy besides lifestyle changes. Currently weight reduction as well as lifestyle changes with the utilization of diet as well as exercise is advocated as the 1st line treatment [22,23]. Nevertheless, long time compliance with lifestyle changes is tough for sustenance in target population. Thus, a main requirement that has not been resolved for a new agent is to resolve NASH along with reversal of liver fibrosis are present. The current major targets for NASH treatment are these: i) bile acid pathway, insulin resistance (IR), inflammation, Thyroid hormone receptor (THR)-β stimulation, hepatic lipid metabolism, antifibrosis etc. 5 Pharmacologic drugs: i)Obeticholic acid (OCA; Farsenoid X receptor [FXR] agonist); ii) Elafibranor (a Peroxisome Proliferator Activated Receptor [PPAR] α as well as δ agonist); iii) cenicriviroc (CVC-a dual antagonist of C-C chemokine receptor (cenicriviroc CCR) types 2 as well as 5; iv) resmetriom (THR-β- agonist) as well as aramchol (stearoyl-Co A desaturase [SCD1 inhibitor-resulted in enhancement of liver histology in phase 2 studies [24-28] along with are going through evaluation of their long term effectiveness as well as safety. In addition a lot of innovative agents that target NASH-associated pathways that are undergoing phase 1 as well as 2 trials are about 200 in number. Pharmacologic drugs are being analysed for NASH therapy. Here we review the mode of action of maximum Pharmacologic drugs that are significant as well as describe the key phase 2 as well as 3 studies which got finished or are still ongoing.

## 2. Classification of the Agents Dependent on the Mode of Action

### 2.1 AObeticholic Acid (OCA; Farsenoid X receptor [FXR] agonist)

OCA is obtained from the primary human bile acid, chenodeoxycholic acid, that is a natural Farsenoid X receptor [FXR] agonist [29]. FXR is a nuclear receptor which gets significantly expressed in the liver along with small intestine, having a significant part in the generation in addition to enterohepatic circulation of bile acids (Figure 1) [30,31]. Stimulation of FXR decreases bile acids generation by hampering the transformation of cholesterol to bile acids, as well as it has anti-inflammatory along with anti-fibrogenic action [32]. Stimulation of FXR in the ileum further hampers the uptake of bile acids by resulting in downregulation of Sodium dependent bile acid transporter. Lastly, OCA influences anticholestatic as well as hepatoshielding action by controlling the metabolism of cholesterol as well as bile acids [33].

In a phase 2a Clinical trial over OCA, patients with type 2 Diabetes mellitus (DM) as well as NAFLD were randomly divided to groups receiving 25 mg OCA (n=20), or groups receiving 50 mg OCA (n=21) or groups receiving placebo (n=23) once/day for 6 weeks (NCT00501592) [34]. Enhancement of insulin sensitivity occurred by 24.5 (p=0.011) in the combined OCA groups, while a reduction by 5.5% occurred in the placebo group. Significant decrease in the amounts of γ glutamyl transferase (γGT) as well as alanine amino transferase (ALT). Further occurred in the OCA groups, besides dose-associated weight reduction. Further, a significant reduction in the amounts of liver fibrosis markers were observed in the OCA groups

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receiving 25 mg. In a phase 2b clinical trial, noncirrhotic patients with NASH had a random division into 1:1 to groups receiving placebo (n=142) as well as 25 mg OCA (n=141) once/day for 72 weeks (FLINT NCT012605498) [24]. Fifty (45%) of the 110 patients in the OCA groups displayed enhancement of liver histology in contrast to 23 (21%) of 109 patients in the placebo group (RR,1.9; 95% Confidence interval [CI], 1.3-2.8P=0.0002). Further 2.3% of the OCA groups had pruritus occurring in contrast to 6% the placebo group. Enhancement of histological parameters of NASH, nevertheless, its long time advantage as well as safety requires more elaboration.

During the interim evaluation of an ongoing, phase 3 study of OCA, patients with NASH, an NAFLD activity score (NAS) of a minimum of 4, as well as fibrosis stage F2-F3, or F1 with a minimum of one associated comorbidity got randomly divided to into 1:1:1 ratio for getting placebo, OCA 10 mg or OCA 25 mg (GENERATE, NCT02548351) [35]. The primary evaluation implicated 931 patients with stage F2-F3 fibrosis (311 in the placebo group, 312 in the OCA 10 mg group as well as 308 in the OCA 25 mg group). The fibrosis escalation endpoint was attained by 37 (12%) patients in the placebo group, 55 (18%) in the OCA 10 mg group (p=0.045), as well as 71 (23%) in the OCA 25 mg (P=0.0002). The resolution point in NASH was not reached. Nevertheless, the outcomes of this interim evaluation demonstrated that, OCA 25 mg resulted in significant ameliorated fibrosis along with crucial constituents of NASH action.

The safety population (1968 patients with fibrosis stage F2-F3) belonging to this trial, the commonest side effect was pruritus, that took place in 5% of the OCA 25 mg group, 28% of the OCA 10 mg group, as well as 19% of placebo group. Mostly pruritus was of mild moderate degree. Nevertheless, 9% of OCA 25 mg safety population omitted the drug secondary to pruritus. The lipoprotein profile was further watched in the safety population. The average low density lipoprotein (LDL) cholesterol as well as total cholesterol amount reached maximum amounts at 3 months in the OCA group. Further 17% of the OCA group as well as 7% of the placebo group required statin therapy.

A phase 2 trial (CONTROL, NCT02633956) that tried to analyse the utilization of OCA in combination of statin therapy for NASH demonstrated that utilization of OCA at 5, 10 or 25 mg/day escalated the LDL-C amounts following 4 weeks of therapy along with atorvastatin supplementation resulted in reduction of LDL-C amounts lower than baseline in each OCA group by 8$^{th}$ week [36]. OCA combination with atorvastatin was usually safe in addition to having a good tolerance.

This OCA use has further been expanded to cirrhosis, as well as a phase 3 trial of OCA in patients with compensated cirrhosis secondary to NASH is ongoing. Patients got randomly allotted to 1:1:1 to the groups receiving OCA 10 mg, 10 mg with titration to 25 mg OCA at 3 months, or placebo for 18 months (REVERSE, NCT03439254). In the REVERSE study utilization of dose enhancement strategy is done in view of hepatic decompensation resulting in patients where cholestatic liver disease is markedly advanced that gets therapy with OCA [37]. The primary end point is the percentage of cases showing benefit in fibrosis by a minimum of 1 stage without any deterioration of NASH.

### 2.2 Non Bile Acid [FXR] Agonist

#### i) Tropifexor(LIN-452)

Tropifexor (TXR; LIN-452) represents a significantly potent. Non bile acid FXR agonist, which stimulates the expression of target genes at minimal dosage without any important Takeda G-protein coupled receptor clones 5 getting stimulated [38]. A phase 2 trial on TXR in NASH patients for 48 weeks is going on (FLIGHT-FXR, NCT02855164) [39]. During an interim evaluation of an ongoing trial for 12 weeks, akin to that of OCA, TXR illustrated lipid alterations that were not favourable with a dose-associated escalation in the LDL-C amounts as well as a reduction in the high density lipoprotein cholesterol (HDL-C) amount, besides pruritus, at greater dosages in contrast to placebo. Further a relative reduction in the liver fat amounts by magnetic resonance imaging (MRI) protein density fat fraction (MRI-PDFF) of -9.8% in placebo, -16.9% with TXR 60 mg , as well as -15.6% with TXR 90 mg, in the interim evaluation. More evaluation illustrated that TXR possessed greater benefit in patients possessing a lesser body mass index (BMI), which pointed that a weight dependent strategy, might be essential [40].

#### ii) Cilofexor (GS-9674)

With OCA possessing troublesome adverse actions like pruritus, hyper cholesterolemia, in addition to hepatic decompensation, selective, non bile acid synthetic FXR agonists have got generated. Cilofexor (GS-9674), represents a potent, nonsteroidal FXR agonist which basically works by stimulation of FXR in the intestine as well as don't go through enterohepatic circulation [41]. FXR agonism in the intestine by Cilofexor amplifies the physiologic liberation of fibroblast growth factor (FGF) 19, as well as might ameliorate the harmful actions of the systemic FXR stimulation, that are dyslipidemia. Pruritus hepatotoxicity [41]. 10 subjects of NASH as well as fibrosis stage F2-F3 in a



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proof of concept study received 30 mg/day of Cilofexor for 12 weeks documented reduction of hepatic fat amounts as well as stiffness, along with enhancement of liver biochemistry [42].

In a phase 2 trial 140 non cirrhotic as well as NASH patients got randomly allotted to Cilofexor 100 mg (n=56), Cilofexor 30 mg (n=56), or placebo (n=28) for 24 weeks (NCT02854605) [43]. The outcomes pointed that Cilofexor 100 mg resulted in reduction in the hepatic fat amounts, along with had reasonable enough tolerance. Commonly Pruritus was not encountered, but had a greater frequency in 100 mg (14%) vis a vis 30 mg (4%) Cilofexor as well as placebo groups (4%). No variation in Pruritus was encountered at the Cilofexor 30 mg in contrast to placebo, however, like a lot of other FXR agonists, Cilofexor resulted in Pruritus in a dose based method, with greater moderate –severe Pruritus in the ones getting 100 mg dose in contrast to placebo. Cilofexor for 24 weeks led to a significant decrease in hepatic steatosis, liver biochemistry, as well as serum bile acids in NASH patients. Other FXR agonists (nidufexor) [44], as well as EDP-305 [45] have got generated, being in phase 2 trials.

### 2.3 Fibroblast Growth Factor 19 (FGF19Analogue), NGM 282

The FGF family of hormones modulates metabolic functions in addition to tissue repair as well as regeneration [46]. FGF19 represents a downstream target of FXR getting activated, as well as FXR results in FGF19 liberation via the intestine. FGF19 is a hormone that is controlling bile acids generation along with glucose homeostasis [47], whereas NGM 282 is an artificially generated FGF19Analogue (Figure 1).

During a phase 2 study having 82 patients that had bi-

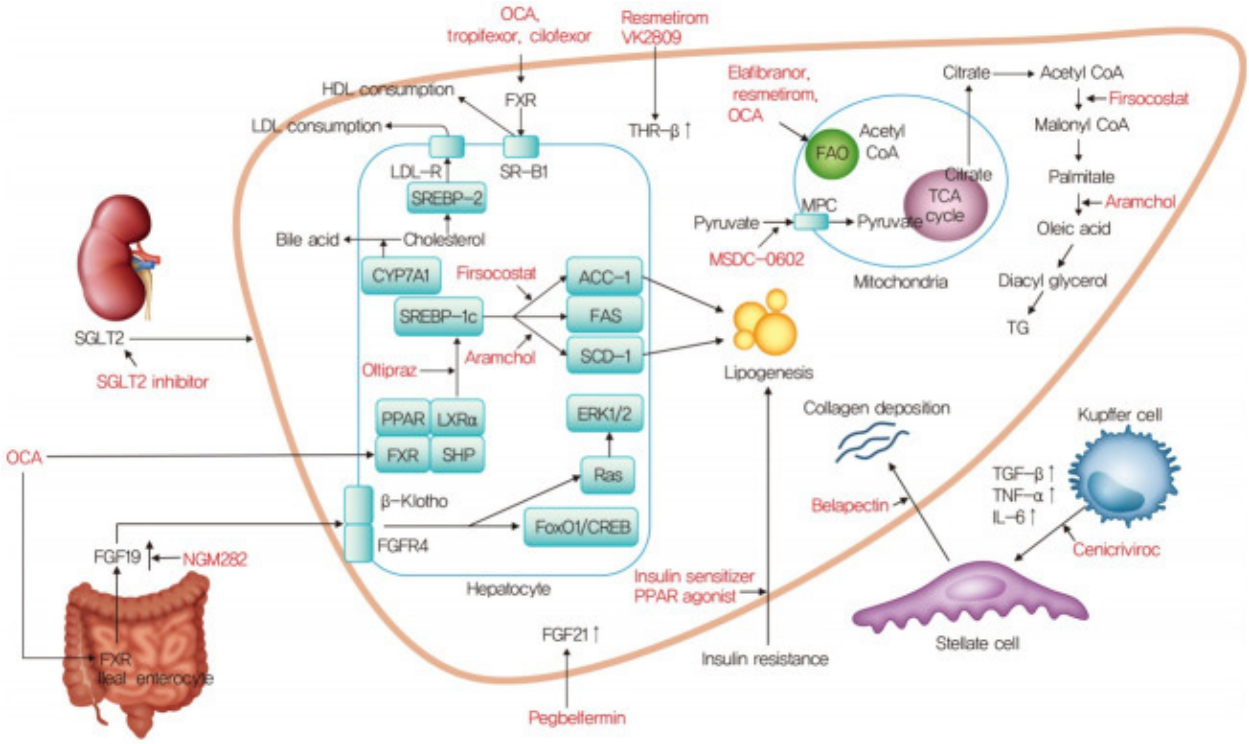


**Figure 1.** Fibroblast Growth Factor 19 (FGF19Analogue), NGM 282

Courtesy ref no 31-Mechanism of action for nonalcoholic steatohepatitis treatment. OCA, obeticholic acid; HDL, high density lipoprotein; LDL, low density lipoprotein; SGLT2, sodium glucose cotransporter 2; FXR, farnesoid X receptor; THR-β, thyroid hormone receptor-β; LDL-R, low density lipoprotein receptor; SR-B1, scavenger receptor class B type 1; SREBP-2, sterol regulatory element-binding proteins-2; CYP7A1, cholesterol 7α-hydroxylase; SREBP-1c, sterol regulatory element binding protein-1c; ACC-1, acetyl-coenzyme A carboxylase-1; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; PPAR, peroxisome proliferator-activated receptor; LXRα, liver X receptor α; SHP, small heterodimer partner; ERK1/2, extracellular signal-regulated kinase 1/2; FGFR4, fibroblast growth factor receptor 4; FoxO1, forkhead box protein O1; CREB, cAMP response element-binding protein; FGF, fibroblast growth factor; FAO, fatty acid β-oxidation; CoA, coenzyme A; TCA, tricarboxylic acid; MPC, mitochondrial pyruvate carrier; TG, triglyceride; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

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opsy validated NASH got randomly allotted to get 3 mg (n=27) or 6 mg subcutaneous NGM 282 (n=28) or placebo (n=27) (NCT02443116) [48]. The primary end point was the sheer alteration in liver fat amounts from baseline till week 12. Definition of responders were patients attaining a 5% or higher decrease in sheer liver fat amounts as estimated by MRI-PDFF. Subsequent to 12 weeks, 20 (74%) patients in the 3 mg groups as well as 22 (79%) in the 6 mg groups attained a minimum of 5% decrease in sheer liver fat amounts from baseline vs 2 (7%) in the placebo groups. NGM 282 generated fast as well as significant decrease in sheer liver fat amounts with the safety parameters that could be accepted in NASH patients. The histological efficiency of NGM 282 in a recent open label evaluation, in biopsy validated NASH was evaluated [49].

Paired liver biopsies from 43 patients delivered subcutaneous NGM 282 (1 mg; n=24; 3 mg, n=19) once/day for 12 weeks got assessed, that were blinded to time point, subject as well as clinical knowledge. At 12$^{th}$ week, NGM 282 enhanced the histological parameters of NASH, with important decreases in the NAS along with fibrosis scores, that was correlated with enhancement in noninvasive imaging in addition to serum markers. A larger phase 2 study possessing a target of 250 enrolled biopsy validated NASH is presently enrolling in an active manner (NCT02443116).

## 2.4 Pegylated Fibroblast Growth Factor 21, Pegbelfermin (MBS-986036)

Fibroblast growth factor 21 (FGF21) has further been believed to be a part of bile acid pathway. Stimulation of FXR in addition to PPARα, results in hepatic expression as well as liberation of FGF21 [50]. FGF21, that represents a nonmitogenic hormone, that is a crucial controller of energy metabolism [52]. Endogenous FGF21 possesses a small half life of 1-2 h, but utilization of different manipulation approaches have aided in generation of FGF21 analogues that possess a longer half life. Pegbelfermin (MBS-986036), represent a polyethylene glycol that has been a conjugated recombinant analogue of Fibroblast growth factor 21 that possess a longer half life which aids in weekly dosing.

In a randomized, double blinded, placebo-controlled phase 2a trial, 75 patients having a minimum BMI of 25 kg/m$^2$, biopsy validated NASH (fibrosis stage 1-3) as well as liver fat amounts of a minimum of 10% by MRI-PDFF got randomized into 3 groups (25 patients to get 10 mg Pegbelfermin/day as well as in the groups getting 20 mg Pegbelfermin weekly in contrast to the placebo groups. Maximum side effects were mild, of which the commonest one was diarrhea in 8 (16%) of 49 patients who received Pegbelfermin. Pegbelfermin treatment for 16 weeks was usually well accepted as well as significantly led to a reduction in hepatic fat fraction in patients with NASH. At present 2 large trials in phase 2 (FALCON 1, n=160, FALCON 2, n=152) are ongoing for evaluation of the effectiveness in addition to safety of Pegbelfermin.

## 2.5 Insulin Resistance

### i) Peroxisome Proliferator Activated Receptor (PPAR )-agonist

### a) Elafibranor

PPARs represent nuclear Receptors that possess critical part in cellular events controlling metabolic homeostasis. Three kinds of nuclear Receptors isoform, PPARα PPARβ/δ as well as PPARγ, that get encoded by separate genes [54]. Elafibranor (GFT505) is a double PPARα as well as δ agonist, which controls the lipid along with insulin metabolism. Maximum PPARα expression occurs in the liver, whose activation is performed by hypolipidemic fibrates. PPARα has the role of regulation of the lipid flux in the liver via modulation of fatty acids (FA) as well as β oxidation along with results in enhancement of plasma lipids by reduction in the triglycerides amounts as well as causing escalation of HDL-C [55]. In reference to advanced NASH, the PPARα amounts are decreased, that return to normal subsequent to treatment as well as enhancement [56]. PPARδ (alias PPARβ) controls the metabolism in the liver as well as peripheral tissues. PPARδ agonists cause enhancement of FAtransfer in addition to oxidation, escalated the HDL-C amounts, as well as enhance glucose homeostasis as well as escalation of insulin sensitivity as well as hampering hepatic glucose output [57]. In a pilot trial, a selective PPARδ agonist, decreased hepatic fat amounts, as well as led to enhancement of insulin sensitivity along with plasma lipid amounts in addition to reduction in the γGT amounts [58].

From the phase 2b study, performed on Elafibranor patients presenting with NASH who were non cirrhotic got randomized into getting Elafibranor 80 mg (n=83), elafibranor 120 mg (n=91) or placebo groups (n=92)/day for 52 weeks (GOLDEN 505, (NCT01694849) [25]. The primary end point was NASH getting resolved without deterioration of fibrosis, with the utilization of protocol definition as well as modification of definitions. During an intention to treat evaluation, no important variations among the Elafibranor as well as placebo groups in the primary end point was observed. Nevertheless, in a posthoc evaluation of patients with NAS (≥4) (n=234), elafibranor 120 mg demonstrated resolution of NASH in a larger percentage of patients in contrast to placebo,



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dependent on the definition of protocol (20% vs 11%; odds ratio 3.16, 3.52; p=0.013). Further patients where elafibranor resulted in resolution of NASH. Subsequentl to receipt of Elafibranor 120 mg demonstrated reduction in liver fibrosis in contrast to those where no resolution of NASH resulted. The amounts of liver enzymes, lipids as well as systemic inflammation in addition to glucose profile illustrated significant reduction in the elafibranor 120 mg vis a vis placebo groups. Tolerance of Elafibranor was good without resulting in weight accretion or cardiac processes, although did lead to mild reversible enhancement of the serum creatinine amounts.

A phase 3 trial one Elafibranor comprising of 2000 NASH patients (NAS(≥4) with stage 2-3 fibrosis is ongoing (RESOLVE-IT, NCT02704403). The primary end points is the percentage of patients where resolution of NASH without deterioration of fibrosis resulted at 72 weeks. Further the trial did an analysis of a composite long term results, comprising all cause mortality, cirrhosis as well as liver associated results at 4 years. The trial got initiated in March 16 as well as the outcomes are expected in December 21.

### b) Lanfibranor

Lanfibranor (IVA337) represents an agonist of all the 3 isoforms of, having a well balanced stimulation of PPARα as well as δ, along with part stimulation of PPARγ [59]. Whereas other PPAR agonists target 1 or 2 of the PPAR isoforms. Lanfibranor represents the lone pan PPAR agonists that is undergoing clinical generation.

In a phase 2b clinical trial conducted on lanfibranor (IVA337) in case of patients with NASH in addition to liver steatosis as well as moderate to robust necroinflammation without cirrhosis, 247 patients got randomized into getting Lanfibranor 800 mg, 1200 mg or placebo/day for 24 weeks (NATIVE, NCT03008070). The primary end point was a reduction from baseline in the SAF (steatosis, activity as well as fibrosis) activity score. The study got initiated in January 2017 as well as was over by March 2020. The early outcomes were anticipated in December 2020 first half.

### ii) a.Glucagon like peptide 1(GLP-1) Receptor agonist-Semaglutide

No Pharmacological treatments have got proven for NASH in addition to T2DM. The major thing is to find the most appropriate anti diabetic agents for the therapy of NASH, for avoidance of the propagation of hepatic fibrosis as well as cardiovascular or renal processes. Glucagon like peptide 1 (GLP-1) Receptor agonist along with Sodium–glucose cotransporter 2 (SGLT2) inhibitors are anticipated to mitigate NASH in addition to NAFLD. GLP-1 represents a gut generated incretin hormone which stimulates reduction of weight of patients along with insulin sensitivity. GLP-1 analogues got approval for utilization in T2DM along with obesity. The advantages of these analogues are weight reduction, escalated glycaemic regulation, lesser hypoglycemia processes along with a decreased incidence of cardiovascular processes [60,61]. The part of GLP-1 in the management of NASH along with NAFLD appear lucrative [17,62,63].

In a recent randomized, placebo-controlled trial implicating 52 patients with biopsy corroborated NASH 1.8 mg of subcutaneous Liraglutide delivered/day for 48 weeks had a correlation with greater NASH resolution as well as lower propagation of fibrosis [17]. Nevertheless, the American Association for the study of liver disease practice guidance 2018 advocated that it was preterm to think of GLP-1 agonists for the treatment of liver disease in cases of NASH along with NAFLD [23].

Semaglutide represents a novel GLP-1 analogue that posseses a prolonged half life of about a week. During phase 2 study of the actions of Semaglutide on NASH, 320 patients with NASH got randomly allocated to placebo groups or 3 dosage amounts of Semaglutide by subcutaneous injection for 72 weeks (NCT02970942). The primary end point comprised resolution of NASH without deterioration of fibrosis. Early outcomes from the study were anticipated in May 2020. In a separate phase 2 study implicating weekly Semaglutide 2.4 mg x 48 weeks. The primary results are enhancement of amelioration of liver fibrosis by a minimum of a stage without deterioration of NASH following 48 weeks (NCT0387451). Semaglutide seems to be the one that is most attractive for the treatment of NASH correlated with DM. Nevertheless, if GLP-1 analogues escalated hepatic inflammation resolution or fibrosis in NASH is not clear as yet.

### b) Dapagliflozin, a Sodium –glucose cotransporter 2 inhibitor

Sodium–glucose cotransporter 2 (SGLT2) inhibitors hamper glucose reabsorprtion in the proximal tubule, resulting in glucosuria, resulting in decrease of plasma glucose amounts. Hence, (SGLT2) inhibitors possess a treatment potential for both NASH along with NAFLD. Certain studies (small) have demonstrated the action of Dapagliflozin in case of patients with NAFLD as well as type2 Diabetes mellitus (T2DM) [64]. Despite the probability can't be ruled out that a fall in body

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weight or visceral adipose tissue (VAT) secondary to Dapagliflozin might be correlated with a reduction in hepatic steatosis or fibrosis, Dapagliflozin demonstrated an advantage in patients with NAFLD. A multicenter, randomized, placebo-controlled phase 3 Clinical trial is ongoing for evaluation of the effectiveness as well as safety of Dapagliflozin for the therapy of NASH (DEAN, NCT03723252). The primary end point is enhancement of the liver histological score at 12 month. 100 subjects with NASH got randomly allocated to placebo groups or10 mg of Dapagliflozin. This study got initiated in March 19, as well as outcomes awaited in November 21.

## 2.6 Mitochondrial Target of Thiazolidenedione-MSDC-0602K

1st generation insulin sensitizers thiazolidenediones have the ability to directly bind to as well as stimulate the PPARγ nuclear hormone Receptors as well as have got utilized for the treatment of T2DM [65]. Nevertheless, they are correlated with important adverse actions like edema, bone fractures that get modulated by PPARγ, along with hypoglycemia. The 2nd generation insulin sensitizer MSDC-0602K got fashioned for decreasing these adverse actions, whereas continuing to generate insulin sensitizing Pharmacology in case of animal models of DM [66], as well as NASH [67]. It manipulates the action of extra nutrition at mitochondrial pyruvate carrier (MPC) with least PPARγ binding (Figure 1) [68]. Earlier studies demonstrated, that MSDC-0602K had the capacity of enhancement of lipid oxidation, as well as diminish denovo lipid generation as well as gluconeogenesis in the liver, both in vivo, as well as in vitro, without adverse actions of the 1st generation insulin sensitizers [69].

During a randomized, double blinded, placebo-controlled phase 2b trial for 52 weeks patients with biopsy corroborated NASH as well as fibrosis (F1-F3) got a random allocation to placebo groups (n=94) or 62.5 mg (n=99), 125 mg, (n=98) or 250 mg (n=101) of MSDC-0602K (EMMINENCE, NCT02784444) [70]. The primary end point for effectiveness was the hepatic histological enhancement of ≥2 points in NAS with a ≥1point decrease in ballooning or lobular inflammation as well as no escalation in fibrosis stage at 12 months time duration. No significant influence on liver histology was observed in that particular study secondary to MSDC-0602K. Nevertheless, significant reduction in amounts of fasting blood glucose, insulin, glycated haemoglobin, as well as markers of liver damage without any dose restricting adverse actions. A phase 3 study was supposed to get started in 2020 (MMONARCh, NCT03970031).

## 2.7 Inflammation

### i) C-C chemokine receptor CCR Dual types 2 as well as 5(CCR2/CCR5) antagonist (cenicriviroc)

CVC or cenicriviroc represents an oral double antagonist of CCR2 as well as CCR5. Once CCR2 gets blocked that represents a chemokine receptor that mainly gets expressed in monocyte, along with, macrophages, causes a reduction in monocyte, along with macrophages, their migration in addition to infiltration of these cells towards the damaged areas of the liver [71]. Simultaneous inhibition of CCR5 interferes with the migration, activation along with proliferation of the activated hepatic stellate cells [71].

During a phase 2b trial for CVC in case of patients with NASH (NAS≥4) with fibrosis (F1-F3), 289 patients got a random allocation to either CVC 150 mg or placebo groups. The primary end point decided was a ≥2 point enhancement in NAS in addition to no deterioration of fibrosis at 1 year (CENTAUR, NCT02217475) [26,72]. The primary end point of enhancement in NAS in the intention for treatment population as well as NASH resolution was attained in an akin percentage of cases on CVC (n=145) as well as placebo. Nevertheless, the fibrosis end point was achieved in greater amounts of cases on CVC in contrast to placebo (20% vs 10%, p=0.02). Therapeutic advantages were higher in those displaying greater disease activity in addition to fibrosis stage at baseline. Subsequent to 1 year of CVC therapy double the number of patients attained in fibrosis without deterioration of NASH in contrast to placebo.

AURORA (NCT03028740), a randomized, double blinded, placebo-controlled, multicenter, phase 3 trial is ongoing for evaluation of efficacy as well as safety of CVC therapy for liver fibrosis in 2000 subjects of NASH presenting with stage 2-3 fibrosis. This study is planned in 2 parts. Part 1 is meant for evaluation of the surrogate end point of enhancement in fibrosis with a minimum of one stage as well as without deterioration of NASH at 12 months. Those cases from part 1 would resume in part 2 in addition to further extra patients added would get re – randomized in part 2 for estimating the long duration clinical results - histopathological – propagation to cirrhosis, Liver-associated Clinical features, in addition to all cause Mortality. This trial got initiated in April 2017, with the outcomes anticipated in December 2024.

## 2.8 Thyroid Hormone Receptor β-agonist (THR-β-agonist)

### Resmetriom (MGL-3196)

The Thyroid hormone Receptor (THR-β) gets signifi-



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cantly expressed in the hepatocyte. NASH may represent partially, a problem secondary to reduction of liver thyroid hormone amounts or hepatic hypothyroidism, along with the incidence of clinical as well as sub clinical hypothyroidism is greater in subjects with NAFLD or NASH in contrast to those age matched controls [73,74]. Activation of THR-β causes the advantageous metabolic actions on triglycerides as well as cholesterol amounts in addition to enhancement of hepatic steatosis [73]. Possessing the actions of beneficial cardiometabolic profile along with ameliorated hepatic steatosis, THR-β- agonist are getting evaluated for NASH therapy.

Resmetriom (MGL-3196) acts as a liver pointed, orally working selective THR-β- agonist fashioned to provide relief in NASH by escalation of hepatic fat metabolism as well as reduction in lipotoxicity. During a phase 2 study, patients having biopsy verified NASH (fibrosis stage 1-3) as well as hepatic fat percentage ≥10% by MRI-PDDF got a random allocation to 2:1 for getting Resmetriom 80 mg or matching placebo, orally once/day (NCT02912260) [27].

The primary results were the proportional alterations from baseline in hepatic fat percentage as evaluation done by MRI-PDDF at 12 weeks.A significant decrease in hepatic fat percentage following 12 as well as 36 weeks of Resmetriom was observed. Tolerance was good, nevertheless, it resulted in Gastrointestinal tract (GIT), side effects, that were self restricted as well as were not responsible for the study getting withdrawn.

A Phase 3 trial implicating 2000 patients with NASH along with stage 2.3 fibrosis is ongoing (MAESTRO-NASH, NCT03900429). The primary result is the action of Resmetriom 80 or 100 mg in contrast to placebo on liver histology along with a composite long duration results of the amount of patients with the initiation of any of the considered processes like cirrhosis, all cause mortality, as well as liver associated Clinical features. This trial got initiated in March 2019, with the outcomes anticipated in March 2024.

### VK2809

VK2809 represents a small molecule product of a robust THR-β-agonist. VK2809 gets selectively cleaved in the Liver tissue by the enzyme cytochrome P450 isozyme 3A4, to liberate a pharmacologically active metabolite. During a Phase 2a trial, patients possessing a hepatic fat amounts of ≥8% as evaluation done by MRI-PDDF, a LDL-C amount of ≥110 mg/dl, along with a triglycerides amount of ≥120 mg/dl got a random allocation to get oral VK2809 5 mg/day, 10 mg alternate day, 10 mg/day or placebo for 12 weeks [75].

Significant drop in hepatic fat amounts by MRI-PDFF in contrast to placebo was documented in the patients getting VK2809. The median relative alteration from baseline in hepatic fat amounts was 53.8% for VK2809 5 mg/day (p=0.0001). 56.1% for 10 mg alternate day (p=0.0018) as well as 59.7 for 10 mg/day (p=0.0004) vs 9.4% for placebo.

Dependent on these outcomes, a Phase 2b study is ongoing in 337 subjects with biopsy validated NASH, for evaluation of the effectiveness along with safety of VK2809 (1.0,2.5,5.0,10 mg) vis a vis placebo for 52 weeks. The primary result is the relative alteration in hepatic fat amounts (evaluation by MRI-PDFF) from baseline to12 weeks (VOYAGE, NCT04173065). The study was initiated in November 2019.

### 2.9 Hepatic Lipid Metabolism

### i) Stearoyl-Co A Desaturase (SCD1) Inhibitor-Aramchol

Aramchol represents arachidylamido cholanoic acid, that is an innovative synthetic lipid molecule, a conjugate of the bile acid, cholic acid as well as arachidic acid, a fatty acid. It results in transformation of saturated FAsinto monounsaturated FAs (Figure 1) [76]. Aramchol has been evaluated in a Phase 2a trial, over 3 months at doses of 100 mg as well as 300 mg/day. This study illustrated a decrease in hepatic fat by magnetic resonance spectroscopy (MRS) following 3 months of treatment in the 300 mg/day Aramchol group in contrast to placebo, but not in the 100 mg/day Aramchol group. Further a decrease in the ALT amounts, with the compounds being well tolerated [77]. Greater doses of Aramchol (400 mg/day-600 mg/day) were delivered to patients with biopsy validatedNASH (n=247) without cirrhosis in a Phase 2b trial which analysed their actions on liver triglycerides amounts with the utilization of (MRS) as well as liver biopsy (ARREST-NCT02279524) [28]. A significant ≥5% decrease in hepatic fat amounts was seen with 600 mg/day Aramchol, 47% in contrast to placebo, 24%. As per liver histology, NASH resolution without deterioration of fibrosis was observed in greater instances with 600 mg Aramchol in contrast to placebo (16.7% vs 5% OR, 4.74; 95% CI, 0.99-22.66). Despite the study being underpowered for histological evaluation a dose response pattern in favour of NASH resolution as well as fibrosis amelioration was observed. A Phase 3/4 multi nation-

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al, multicenter, double blinded, placebo-controlled study for analyzing the effectiveness along with safety of Aramchol in cases with NASH (fibrosis 2 or 3) who present as overweight or with obesity along with prediabetes or T2DM (ARMOR, NCT04104321) has been continuing since September 2019.

### ii) LiverX Receptor-α inhibitor- Oltipraz

Oltipraz represents a synthetic dithiolethione which works as anti steatotic drug by hampering LiverX Receptor-α (LXR –α) activity (Figure 1) [78]. Dithiolethiones are an innovative class of adenine monophosphate activated protein kinase (AMPK) stimulators, that avoid insulin resistance (IR) by hampering AMPK-based p70ribosomal S6 kinase1 (S6K1). AMPK represents a serine/threonine kinase possessing a key part in the controlling of carbohydrates as well as fat metabolism, besides which it might result in modulation of LXR–α action along with causing a reduction in expression of sterol regulatory element binding protein 1c (SREBP1c), a crucial Controller of lipid generation [79]. Oltipraz has a treatment potential for steatosis by stimulation of AMPK in addition to hampering S6K1. Further it encourages lipid oxidation by hampering LXR–α action along with resulting in reduction in expression of SREBP1c in the liver [78]. A Phase 2 study is presently continuing in patients with hepatic fat amounts>20% as well as hypertransaminasaemia got random allocation to get placebo (n=22), 30 mg Oltipraz (n=22), 60 mg Oltipraz (n=24), bdx 24 weeks (PMK-N01GH, NCT01373554) [80]. The primary result was the alteration in the hepatic fat amounts as evaluated by MRS from baseline x 24 weeks.

In contrast to placebo groups, a significant reduction in the hepatic fat amounts was caused by Oltipraz in a dose–based manner. Nevertheless, the sheer alterations in IR along with the amounts of liver enzymes, lipids as well as cytokines were not significantly altered in any of the groups. Moreover the side effects were similar among the groups.

A multicenter, randomized, double blinded, placebo-controlled parallel, phase 3 Clinical trial is going on for analyzing the effectiveness along with safety of Oltipraz in 144 subjects with NAFLD (NCT04142749). The primary results is the difference in the amounts of liver fat as evaluated by MRS at 24 weeks in contrast to baseline. The study was initiated in December 2019, with early outcomes anticipated in October 21.

iii) Acetyl-CoA Carboxylase inhibitor, firsocostat (GS0976)

The Controlling of denovo lipogenesis (DNL) possesses a main part in the fatty acids (FA) generation along with their catabolism. The rate restricting step in DNL is transformation of Acetyl-Coenzyme A (Acetyl-CoA) to malonyl CoA by the enzyme Acetyl-CoA Carboxylase (ACC). ACC possesses 2 isoforms. The ACC 1isoform catalyzes the generation of malonyl CoA, that is the main substrate for the (FA) generation within the cytosol. ACC2 resides in the mitochondria, where malonyl CoA works as a robust allosteric inhibitor of carnitine palmitoyl transferase (CPT)1, that is the carrier protein of FA into mitochondria for the β oxidation [77,81]. Hampering of ACC 1 as well as ACC 2 would get anticipated to decrease DNL as well as a escalate mitochondria β oxidation, respectively, pointed that hampering of ACC would be a treatment target in NASH [82]. Firsocostat (GS0976) represents a liver targeted, small molecule allosteric *i*nhibitor of both ACC 1 as well as ACC 2 in the generation of NASH (Figure 1).

During a recent phase 2 trial, 126 cases with hepatic steatosis of ≥8% dependent on MRI-PDFF, as well as liver stiffness of ≥2.5 kPa, dependent on MRE, or biopsy that corroborated with NASH as well as F1-F3 fibrosis got a random allocation to (2:2:1) for getting GS0976 (20 mg), GS0976 (5 mg), or placebo groups day for 12 weeks. During that study, 20 mg delivery of GS0976 was safe along with resulted in significant decrease in liver fat amounts by MRI-PDFF as well as a reduction in TIMP1. That is a marker of fibrogenesis (NCT02856555) [83].

## 2.10 Anti Fibrotic Drugs

### i) Galectin-3 inhibitor, Belamectin (GRMD-02)

Galectins represent carbohydrate-binding proteins that belong to the family of non-integrinβ-galactoside–binding lectins [84]. Galectin-3 (Gal-3) is the commonest Galectin liberated in disease, basically by macrophages. Gal-3 through its intracellular (antiapoptotic, macrophages differentiation) along with extracellular (chemokinetic as well as chemotactic factor) actions is significant to the pathophysiology of hepatic fibrosis that result secondary to a lot of chronic Liver diseases [85,86]. Galectin inhibitors represent a new class of drugs which target both liberated as well as membrane – correlated Galectins in view of their high molecular weight [87]. Belamectin (GRMD-02), represents galactoarabino-rhamnogalacturonate) is a complicated carbohydrate molecule obtained from anatural plant source, that possesses oligosaccharide chains having



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galactose residues as well as binds to the Galectin3 with a lesser amount to Galectin1. A phase 1 study has illustrated that Belamectin possesses good effectiveness along with safety at single along with multiple doses of 2, 4 as well as 8 mg/kgin patients possessing NASH having all properties of proved NASH in addition to advanced fibrosis but no cirrhosis [88].

During a multicenter, randomized double blinded, placebo-controlled phase 2b trial, 162 patients with NASH, cirrhosis as well as portal hypertension (with hepatic venous pressure gradient [HVPG]≥6 mmHg) got a random allocation to get biweekly infusion of Belamectin 2 mg/kg (n=54), 8 mg/kg (n=54), or placebo (n=54) for 52 week [89]. The primary end point was the alteration in HVPG (-28) by the finishing of 52 weeks duration in contrast to baseline. Despite belpectin being safe, it was not correlated with a significant decrease in HVPG or fibrosis, in contrast to placebo. Nevertheless in a subgroup evaluation of patients without esophageal varices, 2 mg/kg belapectin actually led to a reduction in the generation of varices. A phase 3 study for analyzing the safety along with effectiveness of belapectin for the avoidance of esophageal varices in case of as well as patients with NASH cirrhosis without esophageal varices is getting started (NCT 04365868).

## 3. Combination Treatment

NASH represents a multifactorial disease implicating various modes for its genesis with no definite approved treatments. In future combination of drugs are attractive in view of targeting a lot of pathways. Maximum drug combinations are constituted by metabolic, inflammatory as well as fibrotic drugs or as an other way an anti diabetic might be utilized. At present 3 Combination treatments options for NASH are there.

### 3.1 TXR as well as CVC

A randomized, double blinded, multicenter, placebo-controlled phase 2b study for patients evaluation of safety along with effectiveness of TXR as well as CVC IN 200 cases with NASH fibrosis (stage2/3) (TANDEM, NCT03517540) [90]. Randomization of patients in a 1:1:1:1 ratio for getting TXR 140 μg+CVC 150 mg once a day. The study is designed as a 48 week treatments time as well as 4 week follow up. The primary aim is analysis of safety along with tolerance of this combination treatments as compared to monotherapies over 48 weeks. The secondary aim is effectiveness that by definition is ≥1 point enhancement in liver fibrosis vis a vis baseline or resolving of steatohepatitis following 48 weeks. Thus this combination treatments targets steatotic, inflammatory as well as /or fibrotic pathways that are accountable for NASH.

### 3.2 Selonosertib, Firsocostat, as well as Cilofexor

A recent phase 2 study analysed safety along with effectiveness of a combination of Selonosertib, firsocostat, as well as cilofexor in patients with bridging fibrosis of compensated cirrhosis without deterioration of NASH. Results were anticipated in 2020.

### 3.3 Semaglutide, Firsocostat as well as Cilofexor

During a phase 2 study where utilization of combination of Semaglutide, firsocostat as well as cilofexor wasdone, 109 cases presenting with NASH fibrosis (stage 2/3) got a random allocation to Semaglutide groups, Semaglutide+ firsocostatgroup, Semaglutide+ cilofexor 30 mg group, Semaglutide+ cilofexor 100 mg, or Semaglutide + firsocostat + cilofexor group (NCT039U7074). The primary aim is analysis of safety along with tolerance of the study drug/drugs in adult cases with NASH.

### 3.4 TXR as well as Licogliflozin

Licogliflozin is a once/day, oral SGLT1/2 double inhibitor. A phase 2b randomized, double blinded, multicenter, study is doing evaluation of the safety along with effectiveness of as well as tolerance of oral TXR as well as licogliflozin in combination treatments in contrast to monotherapies, in case of subjects with NASH as well as liver fibrosis. The primary end point is the population of patients with NASH resolution by a minimum of one stage without deterioration of fibrosis at 48 weeks in contrast to baseline (ELIVATE, NCT 04065841).

## 4. Conclusions

Despite Vitamin E, pioglitazone, Liraglutide cause enhancement of liver histology, no FDA approved agent exist for NASH currently. Hence weight reduction by utilization of lifestyle modifications, that are diet along with exercise remains the major way of treatment of NAFLD. Here we have given an overview of the key phase 2-3 trials dependent on the mode of working in NASH (Figure 2).

5 Pharmacological drugs like Obeticholic acid, elafibranor, cenicriviroc, resmetriom, in addition to aramchol are getting analysed in big, histology dependent phase 3

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trials. Depending on the outcome of these trials, newer agents possessing greater efficacy are anticipated in 2 to 4 years. Various phase 2 trials are ongoing with different drugs like non bile acid Farsenoid X receptor antagonists, FGF19 along with 21 analogues, GLP-1RA, SGLT2 inhibitors, pan-PPAR agonists, MPC inhibitors. ACC inhibitors as well as Gal-3 antagonists. Combination treatments are further getting analyzed. In view of NASH occurring secondary to a lot of factors combination treatments appear to be promising. Lastly, finally further approaches of treatments would be composed of combination treatments along with precision medicine depending on the various phenotypes of NASH along with personalised patients treatment response.


**Figure 2.** key phase 2-3 trials dependent on the mode of working in NASH

Courtesy ref no 31-The classification of phase 2,3 trials based on mechanism of action in nonalcoholic steatohepatitis (NASH) treatment. FXR, farnesoid X receptor; FGF, fibroblast growth factor; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium glucose cotransporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MPC, mitochondrial pyruvate carrier; SCD1, stearoylCoA desaturase 1; ACC, acetyl-coenzyme A carboxylase; THR-β, thyroid hormone receptor-β.



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