# SUPPORTING INFORMATION

# Figure S1 Study-selection flow – Meta-analyses of randomized controlled trials

**830** potentially eligible studies identified by database search

**110** duplicates removed

**720** studies identified for screening

**557** studies excluded due to non-relevance after a title/abstract screening

**163** full-text studies assessed for eligibility

**157** studies excluded after a full-text assessment:

* 94 Not meta-analysis
* 32 NAFLD
* 20 Not meta-analysis of RCTs
* 8 Full-text articles cannot be retrieved
* 3 Outcomes of interest were not investigated

**6** eligible studies

* 3 NASH only
* 3 NASH and/or NAFLD

# Figure S2 Study-selection flow – randomized controlled trials indexed in PubMed during 2015 to 2020

**492** potentially eligible studies identified by database search

**292** studies excluded due to non-relevance after a title/abstract screening

**200** full-text studies assessed for eligibility

**178** studies excluded after a full-text assessment:

* 154 NAFLD
* 9 Unable to extract data (pre-post changes)
* 7 Not RCTs
* 4 Cited in the included MAs of RCTs
* 4 Outcomes of interest were not investigated

**22** eligible studies

# Figure S3 Study-selection flow – randomized controlled trials registered in ClinicalTrial.gov during 2015 to 2020

**543** potentially eligible study records identified by database search

**80** study records excluded due to non-relevance after a title/abstract screening

**463** detail study records assessed for eligibility

**385** studies excluded after a full-text assessment:

* 173 Not RCTs
* 161 NAFLD
* 12 Diagnosis
* 9 Cirrhosis
* 8 Duplicate articles with conference abstracts   
   presented at AASLD or EASL
* 7 Unknown
* 5 Duplicate articles with RCTs in PubMed
* 5 Withdrawn
* 5 Terminated

**70** eligible study records

* 62 ongoing trial
* 8 completed trial with no   
   reported results yet

**8** Additional published trials

**Table S1 Characteristics of meta-analyses of randomized controlled trials of interventions for nonalcoholic steatohepatitis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **First author** | **Year** | **No. of studies** | **Population** | **Intervention (s)** | **Comparator (s)** |
| Mahady SE(1) | 2011 | 7 | NASH only | Thiazolidinediones: Pioglitazone, Rosiglitazone | Placebo OR Active comparators |
| Li Y(2) | 2013 | 9 | NASH and/or NAFLD | Metformin | Placebo |
| \*\*Sawangjit R(3) | 2016 | 44 | NASH and/or NAFLD | Pharmacological and non-pharmacological interventions | Placebo OR Active comparators |
| Said A(4) | 2017 | 9 | NASH only | Thiazolidinediones: Pioglitazone, Rosiglitazone | Placebo |
| \*\*Lombardi R(5) | 2017 | 77 | NASH and/or NAFLD | Pharmacological interventions | Placebo OR Active comparators |
| Li Y(6) | 2018 | 8 | NASH only | Angiotensin receptor blockers | Placebo |

Note: \* Network meta-analysis

Abbreviations: NASH – nonalcoholic steatohepatitis, NAFLD – nonalcoholic fatty liver disease

**Table S2 Characteristics of randomized controlled trials of interventions for nonalcoholic steatohepatitis (Trials are obtained from PubMed)**

| **First author** | **Year** | **Phase** | **Population** | **Intervention** | **Comparator** | **Duration  (months)** | **Title acronym** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Lalazar G(7) | 2015 | 2a | NASH | Muromonab-CD3 0.2 mg (n=9)  Muromonab-CD3 1 mg (n=9)  Muromonab-CD3 5 mg (n=9) | Placebo (n=9 | 1 |  |
| Abd El-Kader SM(8) | 2016 | - | NASH with BMI of 30 to 35 kg/m2 | Moderate aerobic exercise (n=50) | No intervention (n=50) | 3 |  |
| Armstrong MJ(9) | 2016 | 2 | NASH | Liraglutide 1.8 mg (n=7) | Placebo (n=7) | 3 | LEAN |
| Armstrong MJ(10) | 2016 | 2 | NASH | Liraglutide 1.8 mg (n=26) | Placebo (n=26) | 12 | LEAN |
| Cusi K(11) | 2016 | 4 | NASH with prediabetes or T2DM | Pioglitazone 45 mg (n=50) | Placebo (51) | 36 |  |
| Ratziu V(12) | 2016 | 2 | NASH without cirrhosis | Elafibranor 80 mg (n=93)  Elafibranor 120 mg (n=91) | Placebo (n=91) | 12 | GOLDEN-505 |
| Joy TR(13) | 2017 | - | NASH | Sitagliptin 100 mg (n=6) | Placebo (n=6) | 6 |  |
| Wah Kheong C(14) | 2017 | 2 | NASH with a NAS ≥4 | Silymarin 700 mg (n=49) | Placebo (n=50) | 12 |  |
| Abdel-Razik A(15) | 2018 | - | NASH | Rifaximin 1,100 mg (n=25) | Placebo (n=25) | 6 |  |
| Friedman SL(16) | 2018 | 2b | NASH with stage F1-F3 fibrosis and a NAS ≥4 | Cenicriviroc 150 mg (n=145) | Placebo (n=144) | 12 (interim analysis) | CENTAUR |
| Geier A(17) | 2018 | - | NASH | Vitamin D 2100 IU (n=10) | Placebo (n=10) | 12 |  |
| Harrison SA(18) | 2018 | 2 | NASH with stage F1-F3 fibrosis, a NAS ≥4, and ≥8% hepatic fat content | Aldafermin (NGM282) 3 mg (n=27)  Aldafermin (NGM282) 6 mg (n=28) | Placebo (n=27) | 3 |  |
| Harrison SA(19) | 2018 | 2b | NASH with bridging fibrosis (F3) | Simtuzumab 75 mg (n=71)  Simtuzumab 125 mg (n=74) | Placebo (n=74) | 24 | GS-US-321-0105 |
| Loomba R(20) | 2018 | 2 | NASH with stage F1-F3 fibrosis or ≥8% hepatic fat content, and ≥2.5 kPa liver stiffness | Firsocostat 5 mg (n=51)  Firsocostat 20 mg (n=49) | Placebo (n=26) | 3 |  |
| Barbakadze G(21) | 2019 | - | NASH | Ursodeoxycholic acid 15 mg (n=NR) | Vitamin E 800 mg plus Vitamin C 500 mg (n=NR) | 12 |  |
| Bomhof MR(22) | 2019 | - | NASH with a NAS ≥5 | Prebiotic: Oligofructose 8 g for 12 weeks followed by 16 g for 24 weeks (n=8) | Isocaloric placebo (n=6) | 9 |  |
| Ghetti FF(23) | 2019 | - | NASH | Dietary intervention plus Nutritional orientation (n=20) | Nutritional orientation (n=20) | 3 |  |
| Harrison SA(24) | 2019 | 2 | NASH with stage F1-F3 fibrosis | Resmetirom 80 mg (n=84) | Placebo (n=41) | 36 |  |
| Navarro VJ(25) | 2019 | 2 | NASH without cirrhosis with a NAS ≥ 4 | Silymarin 420 mg (n=27)  Silymarin 700 mg (n=26) | Placebo (n=25) | 12 | SyNCH |
| Oliveira CP(26) | 2019 | - | NASH | N-acetylcysteine 1.2 g plus Ursodeoxycholic acid 15 mg/kg plus Metformin 850-1,500 mg (n=26) | Ursodeoxycholic acid 20 mg/kg plus Metformin 850-1,500 mg (n=13)  N-acetylcysteine plus Metformin 850-1,500 mg (n=14) | 12 |  |
| Oshakbayev K(27) | 2019 | - | Severe NASH with T2DM | Fast weight loss (n=44) | Conventional drug treatment (n=36) | 12 |  |
| Sanyal A(28) | 2019 | 2a | NASH with stage F1-F3 fibrosis, ≥8% hepatic fat content, and ≥25 kg/m2 BMI | Pegbelfermin 10 mg once a day (n=25)  Pegbelfermin 20 mg once a week (n=24) | Placebo (n=26) | 4 |  |
| Younossi ZM(29) | 2019 | 3 | NASH with stage F2-F3 fibrosis | Obeticholic acid 10 mg (n=312)  Obeticholic acid 25 mg (n=308) | Placebo (n=308) | 18 (interim analysis) | REGENERATE |
| Harrison SA(30) | 2020 | 2b | NASH with stage F1-F3 fibrosis | MSDC-0602K 62.5 mg (n=99)  MSDC-0602K 125 mg (n=98)  MSDC-0602K 250 mg (n=101) | Placebo (n=94) | 12 | EMMINENCE |
| Harrison SA(31) | 2020 | 3 | NASH and bridging fibrosis (F3) | Selonsertib 6 mg (n=321)  Selonsertib 18 mg (n=322) | Placebo (n=159) | 12 | STELLAR-3 |
| Harrison SA(32) | 2020 | 2 | NASH with stage F1-F3 fibrosis | Emricasan 5 mg (n=107)  Emricasan 50 mg (n=106) | Placebo (n=105) | 18 | ENCORE-NF |
| Newsome PN(33) | 2020 | 2 | NASH with ≥5 steatosis without cirrhosis | Volixibat 5 mg (n=49)  Volixibat 10 mg (n=50)  Volixibat 20 mg (n=49) | Placebo (n=49) | 12 |  |
| Newsome PN(34) | 2020 | 2 | NASH with stage F1-F3 liver fibrosis | Semaglutide 0.1 mg (n=80)  Semaglutide 0.2 mg (n=78)  Semaglutide 0.4 mg (n=82) | Placebo (n=80) | 18 | NN9931-4296 |
| Patel K(35) | 2020 | 2 | NASH ≥8% hepatic fat content, and ≥2.5 kPa liver stiffness or historical liver biopsy | Cilofexor 30 mg (n=56)  Cilofexor 100 mg (n=56) | Placebo (n=28) | 6 |  |
| Ratziu V(36) | 2020 | 2b | NASH with stage F1-F3 fibrosis and a NAS ≥4 | Cenicriviroc 150 mg for 2 years (n=145)  Placebo for 1 year then Cenicriviroc 150 mg for 1 year (n=72) | Placebo for 2 years (n=72) | 24 | CENTAUR |
| Abdelmalek MF(37) | AASLD 2018 | 2a | NASH with a NAS ≥4 | IMM-124E 600 mg (n=43)  IMM-124E 1200 mg (n=46) | Placebo (n=44) | 6 |  |
| Diehl AM(38) | EASL 2018 | 2 | NASH with stage F1-F3 fibrosis, a NAS ≥4 (1 point in each component), ≥6% hepatic fat content, and elevated liver aminotransferases | JKB-121 5 mg (n=21)  JKB-121 10 mg (n=22) | Placebo (n=22) | 6 |  |
| Port G(39) | EASL 2019 | N/A | NASH | Probiotics; Lactobacillus acidophilus 1x109 CFU and Bifidobacterium lactis 1x109 CFU (n=NR) | Placebo (n=NR) | 6 |  |
| Francque SM(40) | AASLD 2020 | 2b | Non-cirrhotic, highly active NASH with a SAF score of 3-4 | Lanifibranor 800 mg (n=83)  Lanifibranor 1200 mg (n=83) | Placebo (n=81) | 6 | NATIVE |
| Harrison SA(41) | AASLD 2020 | 2a | NASH with stage F1-F3 fibrosis | Efruxifermin 28 mg (n=19)  Efruxifermin 50 mg (n=20)  Efruxifermin 70 mg (n=20) | Placebo (n=21) | 4 | BALANCED |
| Harrison SA(42) | AASLD 2020 | 2b | NASH with stage F2-F3 fibrosis, a NAS ≥ 4, and ≥8% hepatic fat content | Aldafermin (NGM 282) 1 mg (n=53) | Placebo (n=25) | 6 | ALPINE 2/3 |
| Loomba R(43) | AASLD 2020 | 2 | NASH with stage F1-F3 fibrosis, ≥8% hepatic fat content | TVB-2640 25 mg (n=30)  TVB-2640 50 mg (n=28) | Placebo (n=27) | 3 | FASCINATE-1 |
| Lucas KJ(44) | AASLD 2020 | 2 | NASH with stage F2-F3 fibrosis | Tropifexor 140 mcg (n=50) Tropifexor 200 mcg (n=51) | Placebo (n=51) | 11 | FLIGHT-FXR |
| Aspinall R(45) | EASL 2020 | 2 | NASH | Nidufexor 50 mg (n=44)  Nidufexor 100 mg (n=37) | Placebo (n=40) | 3 |  |
| Lawitz E(46) | EASL 2020 | 2 | NASH | MET409 50 mg (n=19)  MET409 80 mg (n=20) | Placobo (n=19) | 3 |  |
| Ratziu V(47) | EASL 2020 | 2a | Non-cirrhotic, fibrotic NASH | EDP-305 1 mg (n=55)  EDP-305 2.5 mg (n=53) | Placebo (n=24) | 3 | ARGON-1 |

Abbreviations: BMI – body mass index, CFU – colony forming unit, N/A – not applicable, NAS – nonalcoholic fatty liver disease activity score, NASH – nonalcoholic steatohepatitis, NR- not report, SAF score – steatosis, activity, and fibrosis score, T2DM – type 2 diabetes mellitus

**Table S*3* Characteristics of randomized controlled trials of interventions for nonalcoholic steatohepatitis registered on ClinicalTrials.gov**

| **Phase** | **Therapeutic class** | **Intervention** | **NCT** | **Title acronym** | **Intervention group** | **Comparator group** | **Target sample size** | **Duration (months)** | **Key primary endpoint** | **Key secondary histological endpoint** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Completed RCTs** | | | | | | | | | | |
| 1 | FXR agonist | EYP001a | NCT03976687 |  | EYP001a Dose A,  EYP001a Dose B | EYP001a  Dose C | 16 | 1 week | Pharmacokinetics, Adverse events |  |
| 1/2 | ACC inhibitor | Gemcabene | NCT03508687 |  | Gemcabene 300 mg | Gemcebene 300-600 mg | 5 | 6 | Triglycerides | NAS |
| 2 | A3 adenosine receptor agonist | CF102 | NCT02927314 |  | CF102 | Placebo | 60 | 3 | **ALT, Hepatic fat content by MRI-PDFF** |  |
| 2 | AOC3 inhibitor | BI 1467335 | NCT03166735 |  | BI 1467335 | Placebo | 114 | 4 | Plasma AOC3 activity |  |
| 2 | Mineralocorticoid receptor antagonist | Apararenone (MT-3995) | NCT02923154 |  | MT-3995 | Placebo | 48 | 18 | ALT |  |
| 2 | FXR agonist + Unspecified mechanism | Ursodeoxycholic acid + Berberine salt (HTD1801) | NCT03656744 |  | HTD1801 | Placebo | 100 | 18 | **Hepatic fat content by MRI-PDFF** |  |
| 2 | GLP-1 receptor agonist | Semaglutide | NCT03987074 |  | Semaglutide | Firsocostat or Cilofexor | 109 | 6 | Adverse events |  |
| 2/3 | SCD inhibitor | Aramchol | NCT02279524 | Aramchol\_005 | Aramchol 400 mg, Aramchol 600 mg | Placebo | 247 | 12 | Hepatic fat content by NMRS | **≥1 improvement in fibrosis with no worsening of NASH, ≥2 improvement in NAS with no worsening of fibrosis,** ≥2 improvement in SAF with no worsening of fibrosis**, NASH resolution without worsening of fibrosis** |
| **Ongoing RCTs** | | | | | | | | | | |
| 1 | Galectin-3 antagonist | GB1211 | NCT03809052 |  | GB1211 | Placebo | 87 | 3 | Adverse events |  |
| 1 | RNAi | ALN-HSD | NCT04565717 |  | ALN-HSD | Placebo | 128 | 12 | Adverse events | Pharmacokinetics |
| 1 | RNAi | ARO-HSD | NCT04202354 |  | ARO-HSD Injection | Placebo | 74 | 1 | Adverse events |  |
| 1 | RNAi | AZD2693 | NCT04483947 |  | AZD2693 | Placebo | 52 | 9 | Adverse events | **Hepatic fat content by MRI-PDFF, ALT, AST**, Pharmacokinetics |
| 1/2 | Galectin-3 antagonist | GB1211 | NCT04607655 |  | GB1211 | Placebo | 72 | 3 | Adverse events | Pharmacokinetics |
| 1/2 | FGF21 analogue | BIO89-100 | NCT04048135 |  | BIO89-100 | Placebo | 81 | 4 | Adverse events, Pharmacokinetics, **Hepatic fat content by MRI-PDFF** |  |
| 1/2 | Mineralocorticoid  receptor antagonist | Spironolactone | NCT03576755 |  | Spironolactone 100 mg | Placebo | 30 | 12 | Liver stiffness by MRE | NAS |
| 1/2 | PDE non-selective  inhibitor | ZSP1601 | NCT04140123 |  | ZSP1601 | Placebo | 36 | 1 | Adverse events |  |
| 2 | Androgen Receptor  Agonist: Oral bioidentical testosterone prodrug | LPCN 1144 Formulation A, LPCN 1144 Formulation B | NCT04134091 |  | LPCN 1144  Formulation A,  LPCN 1144  Formulation B | Placebo | 75 | 12 | **Hepatic fat content by MRI-PDFF** | NAS, NASH resolution, **NASH resolution with no worsening of fibrosis**, Fibrosis, **≥1 improvement in fibrosis with no worsening of NAS** |
| 2 | Angiogenesis inhibitor | ALS-L1023 | NCT04342793 |  | ALS-L1023 1,200 mg,  ALS-L 1023 1,800 mg | Placebo | 60 | 6 | **Hepatic fat content by MRI-PDFF, ALT, AST** |  |
| 2 | Antioxidants | Vitamin E | NCT03669133 |  | Vitamin E | Placebo | 56 | 12 | **Hepatic fat content by MRI-PDFF** |  |
| 2 | Anti-CCR5 receptor monoclonal antibody | Leronilmab (PRO 140) | NCT04521114 |  | Leronlimab | Placebo | 90 | 3 | Adverse events, FibroScan fibrosis and steatosis score | ALT, AST |
| 2 | Beta-Klotho/FGFR1c receptor complex agonist | MK-3655 | NCT04583423 |  | MK-3655 | Placebo | 328 | 12 | **NASH resolution with no worsening of fibrosis,** Adverse events | **Hepatic fat content by MRI-PDFF, ≥1 improvement in fibrosis with no worsening of NASH**, ≥2 improvement in NAS without worsening of fibrosis |
| 2 | Cardiac glycosides | Digoxin | NCT04216693 |  | Digoxin | Placebo | 60 | 6 | ≥2 improvement in NAS, Steatosis | Fibrosis |
| 2 | CCR2/5 dual receptor antagonist + FXR agonist | Tropifexor + Cenicriviroc | NCT03517540 | TANDEM | Tropifexor, Tropifexor + Cenicriviroc | Cenicriviroc | 200 | 11 | Adverse events | Fibrosis, NASH resolution |
| 2 | CYP2E1 inhibitor | SNP-610 | NCT03468556 |  | SNP-610 | Placebo | 80 | 3 | ALT |  |
| 2 | DGAT2 inhibitors | BMS-986263 | NCT04267393 |  | BMS-986263 | Placebo | 270 | 3 | ≥1 improvement in fibrosis | **≥1 improvement in fibrosis with no worsening of NAS**, ≥2 improvement in fibrosis |
| 2 | FGF21 analogue | BFKB8488A | NCT04171765 | BANFF | BFKB8488A | Placebo | 260 | 12 | **NASH resolution with no worsening of fibrosis** | NAS, Fibrosis |
| 2 | FGF21 analogue | Pegbelgermin (BMS-986036) | NCT03486899 | FALCON 1 | Pegbelgermin | Placebo | 160 | 6 | **≥1 improvement in fibrosis with no worsening of NASH OR NASH resolution with no worsening of fibrosis**, Fibrosis, NAS | **NASH resolution with no worsening of fibrosis**, NASH resolution, NASH improvement, NASH improvement without worsening of fibrosis, **Progression to cirrhosis** |
| 2 | FGF21 analogue | Pegbelgermin (BMS-986036) | NCT03486912 | FALCON 2 | Pegbelgermin | Placebo | 152 | 12 | **≥1 improvement in fibrosis with no worsening of NASH** | NASH resolution, NASH improvement |
| 2 | FXR agonist | EDP-305 | NCT04378010 |  | EDP-305 1.5,  EDP-305 2 mg | Placebo | 336 | 18 | **≥1 improvement in fibrosis with no worsening of NASH AND/OR NASH resolution with no worsening of fibrosis** |  |
| 2 | FXR agonist | EYP001a | NCT03812029 |  | EYP001a | Placebo | 160 | 3 | **Hepatic fat content by MRI-PDFF,** Adverse events |  |
| 2 | FXR agonist | TERN-101 | NCT04328077 |  | TERN-101 | Placebo | 96 | 4 | Adverse events |  |
| 2 | FXR agonist | Tropifexor (LJN452) | NCT04065841 | ELIVATE | Tropifexor | Licogliflozin | 210 | 6 | **NASH resolution with no worsening of fibrosis OR ≥1 improvement in fibrosis with no worsening of NASH** | **≥1 improvement in fibrosis with no worsening of NAS, NASH resolution with no worsening of fibrosis,** Fibrosis, ≥2 improvement in fibrosis with no worsening of NASH |
| 2 | GIP/GLP-1  dual receptor agonist | Tirzepatide | NCT04166773 | SYNERGY-NASH | Tirzepatide | Placebo | 196 | 12 | **NASH resolution with no worsening of fibrosis** | **≥1 improvement in fibrosis with no worsening of NAS**, Fibrosis, ≥2 improvement in NAS with ≥1 improvement in ≥2 NAS components |
| 2 | GLP-1 receptor agonist | Semaglutide | NCT03987451 |  | Semaglutide | Placebo | 65 | 12 | **≥1 improvement in fibrosis with no worsening of NASH** | NASH resolution, Fibrosis, NAS |
| 2 | GLP-1/ GIP/Glucagon Triple Agonist | HM15211 | NCT04505436 |  | HM15211 | Placebo | 112 | 12 | **Hepatic fat content by MRI-PDFF** |  |
| 2 | Insulin | ORMD-0801  (insulin oral formulation) | NCT04618744 |  | ORMD-0801  (insulin oral formulation) | Placebo | 36 | 4 | Adverse events | **Hepatic fat content by MRI-PDFF** |
| 2 | JNK inhibitor | CC-90001 | NCT04048876 |  | CC-90001 | Placebo | 300 | 12 | Fibrosis | **≥1 improvement in fibrosis with no worsening of NAS,** ≥2 improvement in NAS, **NASH resolution with no worsening of fibrosis, Histological progression to cirrhosis** |
| 2 | Ketohexokinase inhibitor | PF-06835919 | NCT03969719 |  | PF-06835919 | Placebo | 150 | 4 | **Hepatic fat content by MRI-PDFF**, HbA1c |  |
| 2 | Mineralocorticoid/glucocorticoid  dual receptor antagonist | Miricorilant (CORT 118335) | NCT03823703 |  | CORT118335 600 mg | Placebo | 120 | 3 | **Hepatic fat content by MRI-PDFF**, Adverse events |  |
| 2 | Mitochondrial pyruvate carrier inhibitor | PXL065 (Deuterium-stabilized R-pioglitazone) | NCT04321343 |  | PXL065 | Placebo | 120 | 9 | **Hepatic fat content by MRI-PDFF** | Liver biopsy |
| 2 | Nutritional intervention | ATI reduced diet | NCT04066400 | NASH-ATI | ATI reduced diet (reduced dietary gluten uptake) | Wheat-based diet | 45 | 4 | **ALT** |  |
| 2 | Pan-Cyclophilin inhibitor | CRV431 | NCT04480710 | AMBITION | CRV431 | Placebo | 18 | 1 | Adverse events, Pharmacokinetics |  |
| 2 | PPARα/γ dual agonist | Saroglitazar | NCT03863574 | EVIDENCES VI | Saroglitazar Mg 2,  Saroglitazar Mg 4 mg | Placebo | 15 | 6 | ≥1 improvement in NAS with no worsening of fibrosis | ≥2 improvement in NAS with improvement in ≥2 NAS components and no worsening of fibrosis, NASH resolution, Steatosis, Inflammation, Ballooning, Fibrosis |
| 2 | PPARσ agonist | Seladelpar | NCT03551522 |  | Seladelpar | Placebo | 181 | 12 | **Hepatic fat content by MRI-PDFF, Adverse events** | **NASH resolution with no worsening of fibrosis, ≥1 improvement in fibrosis with no worsening of NAS**, ≥2 improvement in NAS |
| 2 | Structurally engineered fatty acid | Icosabutate | NCT04052516 | ICONA | Icosabutate | Placebo | 264 | 12 | **NASH resolution with no worsening of fibrosis** | NAS, Steatosis, Ballooning, Inflammation, Fibrosis |
| 2 | Thiazolidinedione | Pioglitazone | NCT04501406 |  | Pioglitazone 15 mg | Placebo | 138 | 18 | ≥2 improvement in NAS without worsening of fibrosis | **NASH resolution with no worsening of fibrosis**, NAS, Steatosis, Ballooning, Lobular inflammation, Fibrosis, ≥2 improvement in fibrosis |
| 2 | THR-β  agonist | VK2809 | NCT04173065 | VOYAGE | VK2809 | Placebo | 337 | 12 | **Hepatic fat content by MRI-PDFF** | **NASH resolution with no worsening of fibrosis** |
| 2 | TLR-4 antagonists | JKB-121 | NCT04255069 |  | JKB-122 | Placebo | 300 | 12 | **NASH resolution with no worsening of fibrosis, ≥1 improvement in fibrosis with no worsening of NAS** | **Hepatic fat content by MRI-PDFF** |
| 3 | Antioxidants | Metadoxine | NCT02541045 |  | Metadoxine | Placebo | 108 | 6 | **NASH resolution with ≥2 improvement in NAS and no worsening of fibrosis, ≥1 improvement in fibrosis with no worsening of NASH** |  |
| 3 | CCR2/5 dual receptor antagonist | Cenicriviroc | NCT03028740 | AURORA | Cenicriviroc | Placebo | 2000 | 12 | **≥1 improvement in fibrosis with no worsening of NASH, Composite endpoint of Histological progression to cirrhosis, liver-related clinical outcome, and all-cause mortality** | **≥1 improvement in fibrosis with no worsening of NASH** |
| 3 | FXR agonist | Obeticholic acid | NCT02548351 | REGENERATE | Obeticholic Acid | Placebo | 2480 | 84 | **≥1 improvement in fibrosis with no worsening of NASH OR NASH resolution with no worsening of fibrosis, Composite endpoint of Histological progression to cirrhosis, all-cause mortality, MELD score ≥15, ascites requiring medical intervention, hospitalization for onset of variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis** | **≥1 improvement in fibrosis with no worsening of NASH, NASH resolution with no worsening of fibrosis**, No worsening of fibrosis AND no worsening of NASH, Fibrosis, Inflammation, Ballooning, Steatosis, ≥2 improvement in fibrosis, ≥2 improvement in NAS with no worsening of fibrosis, ≥1 improvement in fibrosis and NASH resolution, Fibrosis resolution, **Histological progression to cirrhosis** |
| 3 | Mitochondrial pyruvate carrier inhibitor | MSDC-0602K | NCT03970031 | MMONARCh | MSDC-0602K | Placebo | 3600 | 12 | HbA1c, **NASH resolution with no worsening of fibrosis** |  |
| 3 | SGLT2 inhibitor | Dapagliflozin | NCT03723252 | DEAN | Dapagliflozin | Placebo | 100 | 12 |  | NASH resolution, Fibrosis, NAS |
| 3 | THR-β  agonist | Resmetirom (MGL-3196) | NCT03900429 | MAESTRO-NASH | MGL-3196 | Placebo | 2000 | 12 | **NASH resolution with ≥2 improvement in NAS and no worsening of fibrosis, Composite endpoint of cirrhosis, all-cause mortality, and liver-related clinical outcomes** | **≥1 improvement in fibrosis with no worsening of NAS** |
| 3/4 | SCD inhibitor | Aramchol | NCT04104321 | ARMOR | Aramchol | Placebo | 2000 | 12 | **NASH resolution with no worsening of fibrosis OR ≥1 improvement in fibrosis with no worsening of NASH, Composite endpoint of all-cause mortality, liver transplant, histological progression to cirrhosis, MELD score ≥15, hospitalization due to hepatic decompensated events** |  |
| 4 | GLP-1 RA plus SGLT-2 inhibitors | Semaglutide plus empagliflozin | NCT04639414 | COMBAT\_T2\_NASH | Semaglutide plus empagliflozin | Empagliflozin  Placebo | 192 | 11 | **NASH resolution with no worsening of fibrosis** | NAS, Fibrosis, Steatosis, Inflammation, Ballooning |
| 4 | GLP-1 RA | Dulaglutide | NCT03648554 | REALIST | Dulaglutide (TRULICITY®) 1.5 mg + Reinforced dietary monitoring | Reinforced dietary monitoring | 93 | 12 | NAS | NASH resolution, Fibrosis, Steatosis, Inflammation, Ballooning |
| 4 | Unspecified mechanism | Berberine | NCT03198572 | EASYBEinNASH | Berberine + Lifestyle intervention | Placebo + Lifestyle intervention | 120 | 48 | ≥1 improvement in the hepatocellular ballooning with no increase in the fibrosis score; and either a decrease in NAS to ≤3; with ≥1 improvement in either the lobular inflammation or steatosis score. | NAS, Steatosis, Ballooning, Inflammation, Fibrosis, NASH resolution |
| N/A | Antioxidants | Vitamin E | NCT02962297 | VENS | Vitamin E | Placebo | 120 | 24 | Either ≥2 improvement in NAS OR post-treatment NAS of ≤3 points with ≥1 improvement ballooning and no worsening of fibrosis |  |
| N/A | Device | Insulin pump therapy | NCT04270656 | STEATO-POMPE | Insulin pump therapy | Multi-injection treatment | 52 | 6 | **Hepatic fat content by MRI-PDFF** |  |
| N/A | Gut microbiota modulation | Oatmeal flakes with prebiotic | NCT03897218 | ADLH | Oatmeal flakes with prebiotic | Millet flakes | 84 | 5 | Steatosis by CAP, **ALT** |  |
| N/A | Gut microbiota modulation | Probiotics | NCT03467282 | PROBILIVER | Probiotic | Placebo | 46 | 6 | Fibrosis by hepatic elastography |  |
| N/A | Gut microbiota modulation | Probiotics | NCT04555434 |  | Probiotic | Placebo | 120 | 2 | **ALT, AST** |  |
| N/A | Gut microbiota modulation | Yaq-001 (non-absorbable carbons of controlled porosity selectively modulating stool microbiome) | NCT03962608 | NASH-Safety | Yaq-001 | Placebo | 70 | 12 | Adverse events |  |
| N/A | Surgical procedure | Bariatric surgery | NCT04298736 | BeLEANeR | Bariatric Surgery | Lifestyle modification | 50 | 12 | NASH resolution |  |
| N/A | Surgical procedure | Bariatric surgery | NCT03472157 | NASHSURG | Bariatric surgery | Lifestyle therapy | 100 | 15 | **NASH resolution with no worsening of fibrosis** | NAS, ≥2 improvement in NAS with no worsening of fibrosis |
| N/A | Surgical procedure | Endomina®, an endoscopic sutured gastroplasty | NCT04653311 | ENDONASH | Endomina®, an endoscopic sutured gastroplasty + Lifestyle intervention | Lifestyle intervention | 100 | 12 | **NASH resolution with no worsening of fibrosis** | NAS, Steatosis, Ballooning, Lobular inflammation, Fibrosis, ALT, AST |
| N/A | Surgical procedure | ESG with OverStitch® system | NCT04060368 | TESLA-NASH | ESG with OverStitch® system + Lifestyle modifications | LSG + Lifestyle modifications | 30 | 24 | **NASH resolution with no worsening of fibrosis,** Fibrosis |  |
| N/A | Surgical procedure | RYGB | NCT03524365 | BRAVES | RYGB + Lifestyle modification or SG + Lifestyle modification | Intensive Lifestyle Modification | 288 | 12 | **NASH resolution with no worsening of fibrosis** | Fibrosis, NASH resolution |
| N/A | Surgical procedure | VSG | NCT03587831 |  | VSG | Lifestyle Modification Counseling | 60 | 12 | NAS |  |

**Abbreviations:** ACC1/2 – acyl-CoA carboxylase isoform 1 and 2, ALT – alanine aminotransferase, AOC3 – amine oxidase copper-containing 3, ASK1 – apoptosis signal-regulating kinase 1, AST – aspartate aminotransferase, ATI – amylase trypsin inhibitor, CAP – controlled attenuate parameter, CCR2/5 – chemokine receptor 2/5, CYP2E1 – cytochrome P450 family 2 subfamily E member 1, DGAT2 – diacylglycerol-acyl transferase-2, ESG – endoscopic sleeve gastroplasty, FASN – fatty acid synthase, FGF – fibroblast growth factor, FGFR1c – fibroblast growth factor receptor 1c, FXR – farnesoid X receptor, GIP/GLP-1 – glucagon-dependent insulinotropic polypeptide and glucagon-like peptide-1, GLP-1 RA – glucagon-like peptide-1 receptor agonist, JNK – Jun N-terminal kinase, LOXL2 – lysyl oxidase-like 2, LSG - laparoscopic sleeve gastrectomy, MRE – magnetic resonance elastography, MRI-PDFF – magnetic resonance imaging proton density fat fraction, N/A – not applicable, NAS – nonalcoholic fatty liver disease activity score, NASH – nonalcoholic steatohepatitis, NMRS – nuclear magnetic resonance spectroscopy, PDE – phosphodiesterase, PPAR – peroxisome proliferator-activated receptor, RCTs – Randomized controlled trials, RNAi – RNA interference, RYGB – Roux-en-Y gastric bypass, SAF – steatosis-activity-fibrosis, SCD – stearoyl Coenzyme A desaturase, SG – sleeve gastrectomy, SGLT2 – sodium-glucose transport protein 2, THR – thyroid hormone receptor, TLR-4 – toll-like receptor 4, VSG – vertical sleeve gastrectomy

**Table S4 Summary of treatment effects of interventions for nonalcoholic steatohepatitis**

**Note:** Non-significant effect (YELLOW), Significant positive effect (GREEN)

| **Intervention** | **Histological outcomes (RR)** | | | | | | | | | | | | | | | **Laboratory outcomes (MD)** | | **Imaging outcomes (MD)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Progression to cirrhosis** | **≥2-point reduction in NAS with ≥1-point reduction in either inflammation or ballooning and no worsening of fibrosis** | **≥2-point reduction in NAS with no worsening of fibrosis** | **≥1-point improvement in fibrosis with no worsening of NASH** | | **NASH resolution with no worsening of fibrosis** | **NASH resolution** | **Fibrosis resolution** | **≥ 2-point improvement in Fibrosis** | **≥ 1-point improvement in Fibrosis** | **≥ 2-point improvement in NAS** | **≥ 1-point improvement in NAS** | **≥ 1-point improvement in Steatosis** | **≥ 1-point improvement in Ballooning** | **≥ 1-point improvement in Inflammation** | **ALT** | **AST** | **Hepatic fat content** |
| **Vs. Placebo** | | | | | | | | | | | | | | | | | | |
| **De novo lipogenesis inhibitors** | | | | | | | | | | | | | | | | | | |
| ACC1/2 inhibitors: Firsocostat 5 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR | NR |
| ACC1/2 inhibitors: Firsocostat 20 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR | **NR** |
| THR-β selective agonist: Resmetirom |  |  |  |  | | **OR 4.57**  **[1.03, 21.9]** |  |  |  |  | **OR 2.7**  **[1.1, 6.3]** |  |  |  |  | **-26.4**  **[-42.8, -9.9]** | **-11.1**  **[-17.8, -4.3]** |  |
| FASN inhibitor: TVB-2640 25 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | NR |
| FASN inhibitor: TVB-2640 50 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| **FXR agonists** | | | | | | | | | | | | | | | | | | |
| FXR agonist: Cilofexor 30 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR | **NR** |
| FXR agonist: Cilofexor 100 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR | **NR** |
| FXR agonist: EDP-305 1 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR |  | NR |
| FXR agonist EDP-305 2.5 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| FXR agonist: MET409 50 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| FXR agonist: MET409 80 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| FXR agonist: Nidufexor 50 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| FXR agonist: Nidufexor 100 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| FXR agonist: Obeticholic acid 10 mg (REGENERATE) |  |  | **1.2**  **[1.0, 1.6]** | **1.5**  **[1.0, 2.2]** | | 1.4  [0.9, 2.3] |  | 2.0  [0.6, 6.4] |  |  | 1.3  [0.7, 2.4] |  | 1.1  [0.9, 1.3] | 1.2  [0.9, 1.5] | 1.1  [0.9, 1.4] |  |  |  |
| FXR agonist: Obeticholic acid 25 mg (REGENERATE) |  |  | **1.5**  **[1.2, 1.9]** | **1.9**  **[1.4, 2.8]** | | 1.5  [0.9, 2.4] |  | 2.5  [0.8, 7.9] |  |  | **2.0**  **[1.1, 3.7]** |  | 1.1  [0.9, 1.3] | **1.5**  **[1.2, 2.0]** | **1.2**  **[1.0, 1.5]** |  |  |  |
| FXR agonist: Obeticholic acid 25 mg (FLINT) |  |  | **2.2**  **[1.4, 3.3]** |  | |  | 1.70  [0.89, 3.25] |  |  | **1.91**  **[1.15, 3.16]** |  | **2.19**  **[1.42, 3.28]** | **1.69**  **[1.21, 2.36]** | **1.58**  **[1.06, 2.34]** | **1.60**  **[1.12, 2.29]** | **-20**  **[-28, -11]** | **-12**  **[-18. -6]** |  |
| FXR agonist: Tropifexor 140 mcg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** | NR | **NR** |
| FXR agonist: Tropifexor 200 mcg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** | NR | **NR** |
| FXR agonist: Ursodeoxycholic acid |  |  |  |  | |  | OR 1.85  [0.88, 3.89] |  |  |  |  |  |  |  |  |  |  |  |
| **FGF analogues** | | | | | | | | | | | | | | | | | | |
| FGF-19 analogue: Aldafermin (NGM282) 3 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **-35.1**  **[-47.1, -23.1]** | **-20.4**  **[-29.8, -11.0]** | **RR 10.0**  **[2.6, 38.7]**  ***(≥5% reduction)*** |
| FGF-19 analogue: Aldafermin (NGM282) 6 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **-36.5**  **[-48.7, -24.2]** | **-22.5**  **[-32.4, -12.7]** | **RR 11.4**  **[3.0, 43.8]**  ***(≥5% reduction)*** |
| FGF-19 analogue: Aldafermin (NGM282) 1 mg  (ALPINE 2/3) |  |  |  | NR | | NR |  |  |  |  |  |  |  |  |  | **NR** | **NR** | **NR** |
| FGF-21 analogue: Pegbelfermin 10 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR | **-5.5**  **[-8.0, -2.8]** |
| FGF-21 analogue: Pegbelfermin 20 mg |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR | **-3.9**  **[-6.5, -1.2]** |
| FGF-21 analogue: Efruxifermin |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  | **NR** |
| **Antimetabolic agents** | | | | | | | | | | | | | | | | | | |
| Anti-CD3 mAb: Muromonab-CD3 |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | **NR** |  |
| ASBT inhibitor: Volixibat 5 mg |  |  | 0.95  [0.33, 2.68] |  | | 0.47  [0.11, 1.98] |  |  |  | 1.18  [0.46, 3.04] |  |  |  |  |  | 11.8  [-1.2, 24.5] |  | -0,6  [-2.3, 1.2] |
| ASBT inhibitor: Volixibat 10 mg |  |  | 0.47  [0.11, 1.98] |  | | 0.71  [0.22, 2.32] |  |  |  | 0.47  [0.11, 1.98] |  |  |  |  |  | 11.4  [-1.5, 23.8] |  | -0.6  [-2.3, 1.3] |
| ASBT inhibitor: Volixibat 20 mg |  |  | 0.98  [0.32, 3.01] |  | | 0.65  [0.16, 2.59] |  |  |  | 0.33  [0.05, 2.30] |  |  |  |  |  | 10.1  [-3.8, 22.4] |  | -0.7  [-2.6, 1.1] |
| Cholesterol-lowering agents: Ezetimibe |  |  |  |  | |  | OR 1.08  [0.25, 4.70] |  |  |  |  |  |  |  |  |  |  |  |
| DPP-4 inhibitor: Sitagliptin |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | -5  [-51, 41] | -5  [-51, 41] | 2.0  [-7.3, 11.2] |
| GLP-1 RA: Liraglutide |  |  |  |  | | **4.3**  **[1.0, 17.7]** | **OR 6.23**  **[1.20, 34.41]** |  |  | 1.9  [0.5, 6.7] |  | 1.2  [0.8, 1.7] | **1.8**  **[1.1, 3.0]** | 1.9  [1.0, 3.8] | 0.9  [0.5, 1.6] | -10.7  [-25.9, 4.5] | -6.7  [-19.3, 5.9] |  |
| GLP-1 RA: Semaglutide 0.1 mg |  |  |  | OR 1.96  [0.86, 4.51] | | **OR 3.36 [1.29, 8.86]** |  |  |  |  |  |  |  |  |  |  |  |  |
| GLP-1 RA: Semaglutide 0.2 mg |  |  |  | OR 1.00 [0.43, 2.32] | | **OR 2.71 [1.06, 7.56]** |  |  |  |  |  |  |  |  |  |  |  |  |
| GLP-1 RA: Semaglutide 0.4 mg |  |  |  | OR 1.42 [0.62, 3.28] | | **OR 6.87 [2.60, 17.63]** |  |  |  |  |  |  |  |  |  |  |  |  |
| Metformin |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | -5.18  [-25.72, 15.35] | -6.69  [-20.24, 6.86] |  |
| Metformin + TZDs |  |  |  |  | |  |  |  |  | 4.68  [0.26, 83.63] |  |  |  |  |  |  |  |  |
| PPAR-α/δ dual agonist: Elafibranor (GOLDEN-505) |  |  |  |  | | **OR 2.31**  **[1.02, 5.24]** |  |  |  |  |  |  |  |  |  |  |  |  |
| PPAR-α/δ dual agonist: Elafibranor (RESOLVE-IT) |  |  |  |  | | OR 1.38 [0.97, 1.95] |  |  |  | OR 1.13 [0.83, 1.53] |  |  |  |  |  |  |  |  |
| PPAR-γ sparing modulator: MSDC-0602 K 62.5 mg |  | OR 0.89  [0.44, 1.81] |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR |  |
| PPAR-γ sparing modulator: MSDC-0602 K 125 mg |  | OR 1.22  [0.60, 2.48] |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** | **NR** |  |
| PPAR-γ sparing modulator: MSDC-0602 K 250 mg |  | OR 1.64  [0.83, 3.27] |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** | **NR** |  |
| PPAR-α/δ/γ pan agonist: Lanifibranor 800 mg |  |  |  | 1.18  [0.70, 2.00] | | **1.76 [1.01, 3.05]** |  |  |  |  |  |  |  |  |  |  |  |  |
| PPAR-α/δ/γ pan agonist: Lanifibranor 1200 mg |  |  |  | **1.80**  **[1.13, 2.87]** | | **2.40 [1.43, 4.03]** |  |  |  |  |  |  |  |  |  |  |  |  |
| TZDs: Pioglitazone, Rosiglitazone | OR 5.99  [0.71, 50.28] |  |  |  | |  | OR 1.68  [0.44, 6.44] |  |  | OR 1.58  [0.98, 2.54] |  |  | **OR 3.51**  **[2.14, 5.78]** | OR 1.84  [0.94, 3.58] | **OR 2.65**  **[1.69, 4.15]** |  |  |  |
| TZDs: Pioglitazone phase 4, Cusi |  |  | **3.29**  **[1.74, 6.22]** |  | |  | **2.65**  **[1.43, 4.91]** |  |  | 1.57  [0.88, 2.80] |  |  | **2.75**  **[1.66, 4.54]** | **2.13**  **[1.21, 3.75]** | **2.32**  **[1.28, 4.19]** | **-24**  **[-35, -12]** | **-14**  **[-22, -6]** | **-7**  **[-10, -4]** |
| **Antioxidants** | | | | | | | | | | | | | | | | | | |
| Anti-TNF-α agent: Pentoxifylline |  |  |  |  | |  |  |  |  | 2.27  [0.81, 6.36] |  | **2.70**  **[1.21, 6.03]** | **2.40**  **[1.15, 5.03]** | 1.73  [0.48, 6.24] | 1.73  [0.48, 6.24] |  |  |  |
| Betain |  |  |  |  | |  |  |  |  |  |  | 0.38  [0.14, 1.04] |  |  |  |  |  |  |
| Metadoxine |  |  |  |  | |  |  |  |  | 1.35  [0.57, 3.21] |  |  | **2.97**  **[1.52, 2.67]** |  |  |  |  |  |
| Silymarin - Navarro |  |  |  |  | |  |  |  |  | 0.93  [0.38, 2.27] | 1.23  [0.31, 4.98] | 1.08  [0.42, 2.78] | 1.16  [0.35, 3.83] | 0.93  [0.30, 2.82] | 0.79  [0.31, 2.04] |  |  |  |
| Silymarin – Wah Kheong | 0.34  [0.04, 3.16] |  |  |  | | 1.30  [0.66, 2.57] |  | 1.70  [0.43, 6.73] |  | **3.74**  **[1.11, 12.60]** |  | 0.98  [0.68, 1.42] | 0.71  [0.33, 1.50] | 1.20  [0.72, 2.00] | 1.09  [0.61, 1.95] |  |  |  |
| Silymarin - Lombardi | OR 0.11  [0.01, 2.15] |  |  |  | |  | OR 11.72  [0.60, 227.31] |  |  |  |  |  |  |  |  |  |  |  |
| Vitamin D |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR |  |
| Vitamin E plus Vitamin C |  |  |  |  | |  | **OR 2.14**  **[1.10, 4.19]** |  |  |  |  |  |  |  |  |  |  |  |
| **Anti-inflammatory agents** |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Anti-LPS immunoglobulins: IMM-124E |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** | **NR** |  |
| ARBs |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | -5.18  [-25.72, 15.35] | -6.69  [-20.24, 6.86] |  |
| Omega-3 PUFAs |  |  |  |  | |  |  |  |  | 0.58  [0.22, 1.57] |  | 0.89  [0.61, 1.29] | 0.84  [0.43, 1.65] | 0.63  [0.29, 1.38] | 0.74  [0.36, 1.52] |  |  |  |
| TLR4 antagonists: JKB-121 |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR |  | NR |
| **Anti-apoptotic agents** | | | | | | | | | | | | | | | | | | |
| Pan-caspase inhibitor: Emricasan 5 mg |  |  |  | OR 0.54  [0.25, 1.16] | | OR 0.33  [0.10, 1.08] |  | OR 0.78  [0.20, 2.98] |  |  | OR 0.52  [0.23, 1.15] |  |  |  |  |  |  |  |
| Pan-caspase inhibitor: Emricasan 50 mg |  |  |  | OR 0.59  [0.28, 1.27] | | OR 0.60  [0.22, 1.62] |  | OR 0.19  [0.02, 1.66] |  |  | OR 0.47  [0.21, 1.07] |  |  |  |  |  |  |  |
| **Anti-fibrotic agents** | | | | | | | | | | | | | | | | | | |
| Anti-LOXL2 mAb: Simtuzumab 75 mg | 0.89  [0.45, 1.75] |  |  |  | |  | 1.88  [0.33, 10.77] |  |  | 0.83  [0.43, 1.62] | 1.85  [0.87, 3.93] |  |  |  |  |  |  |  |
| Anti-LOXL2 mAb: Simtuzumab 125 mg | 0.96  [0.50, 1.83] |  |  |  | |  | 2.18  [0.42, 11.45] |  |  | 0.77  [0.40, 1.51] | 1.49  [0.68, 3.25] |  |  |  |  |  |  |  |
| ASK1 inhibitor: Selonsertib 6 mg | 0.99  [0.64, 1.54] |  |  | 0.92  [0.56, 1.51] | | 0.50  [0.24, 1.01] |  |  |  | 0.84  [0.54, 1.31] |  |  |  |  |  | NR | NR |  |
| ASK1 inhibitor: Selonsertib 18 mg | 0.83  [0.53, 1.31] |  |  | 0.73  [0.43, 1.23] | | 0.56  [0.28, 1.13] |  |  |  | 0.78  [0.49, 1.23] |  |  |  |  |  | NR | NR |  |
| CCR2/5 dual antagonist: Cenicriviroc |  | OR 0.82  [0.44, 1.52] |  | **OR 2.20 [1.11, 4.35]  (1 yr)** | OR  1.15 [0.48, 2.75]  (2 yr) | OR 1.40  [0.54-3.63] |  |  |  |  |  |  |  |  |  |  |  |  |
| **Others** | | | | | | | | | | | | | | | | | | |
| Antibiotics: Rifaximin |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **-0.76**  **[-1.32, -0.19]** | **-0.58**  **[-1.14, -0.03]** |  |
| Moderate aerobic exercise |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** | **NR** |  |
| Prebiotics |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR |  |  |
| Probiotics |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR |  |  |
| **Vs. Active comparators** | | | | | | | | | | | | | | | | | | |
| Dietary intervention + Nutritional orientation (vs. Nutritional orientation) |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | **NR** |  |
| Fast weight loss method (vs. conventional drug treatment) |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **-4.50**  **[-5.41, -3.60]** | **-7.18**  **[-8.50, -5.87]** |  |
| Metformin + N-acetylcysteine (vs. Metformin + Ursodeoxycholic acid) |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR |  |
| Metformin + N-acetylcysteine + Ursodeoxycholic acid (vs. Metformin + Ursodeoxycholic acid) |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR |  |
| Metformin + N-acetylcysteine + Ursodeoxycholic acid (vs. Metformin + Ursodeoxycholic acid) |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | NR | NR |  |
| TZDs (vs. Placebo OR Metformin OR Metformin + TZD OR Vitamin E) |  |  |  |  | |  |  |  |  | **1.38**  **[1.01, 1.89]** |  |  | **2.03**  **[1.57, 2.62]** | **1.62**  **[1.15, 2.28]** | **1.71**  **[1.32, 2.21]** | **-14.00**  **[-24.00, -11.00]** |  |  |
| TZDs (vs. Vitamin E) |  |  |  |  | |  | OR 1.63  [0.87, 3.05] |  |  |  |  |  |  |  |  |  |  |  |
| TZDs + ARBs (vs. TZDs) |  |  |  |  | |  | 0.76  [0.37, 1.57] |  |  | 0.91  [0.48, 1.73] |  | 1.14  [0.76, 1.71] | 1.42  [0.90, 2.26] | 0.99  [0.49, 2.00] | 0.91  [0.46, 1.80] |  |  |  |
| TZDs + Metformin (vs. TZDs + ARBs) |  |  |  |  | |  | 0.92  [0.42, 2.00] |  |  | 1.20  [0.66, 1.98] |  | 0.73  [0.48, 1.13] | 0.84  [0.57, 1.26] | 0.84  [0.41, 1.71] | 0.84  [0.41, 1.71] |  |  |  |
| Vitamin E (vs. TZD) |  |  |  |  | |  | 0.84  [0.56, 1.23] |  |  | 1.01  [0.69, 1.49] |  | 1.27  [0.86, 2.34] | 0.85  [0.65, 1.12] | 1.23  [0.86, 1.75] | 0.97  [0.72, 1.32] |  |  |  |
| Vitamin E + Vitamin C (vs. Ursodeoxycholic acid) |  |  |  |  | |  |  |  |  |  |  |  |  |  |  | **NR** |  |  |

**Abbreviations:** ACC1/2 – acyl-CoA carboxylase isoform 1 and 2, ALT – alanine aminotransferase, ARBs – angiotensin receptor blockers, ASBT – apical sodium-dependent bile acid transporter, ASK1 – apoptosis signal-regulating kinase 1, AST – aspartate aminotransferase, CCR2/5 – chemokine receptor 2/5, DPP-4 – dipeptidyl peptidase-4, FASN – fatty acid synthase, FGF – fibroblast growth factor, FXR – farnesoid X receptor, GLP-1 RA – glucagon-like peptide-1 receptor agonist, LOXL2 – lysyl oxidase-like 2, LPS – lipopolysaccharide, mAb – monoclonal antibody, NAS – nonalcoholic fatty liver disease activity score, NASH – nonalcoholic steatohepatitis, NR – not report, OR – odd ratio, PPAR – peroxisome proliferator-activated receptor, PUFAs – poly unsaturated fatty acids, THR – thyroid hormone receptor, TLR4 – toll-like receptor 4, TNF – tumor necrosis factor, TZDs – thiazolidinediones

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