Table 1. Placebo-controlled or active-controlled RCTs of different PPAR agonists (pioglitazone, elafibranor, saroglitazar or lanifibranor) for the treatment of NAFLD or NASH (n=8 studies ordered by publication year).

Author, Year, Country (PMID)	RCT's characteristics	Interventions (n), RCT's length	Efficacy and/or effectiveness outcomes	Major adverse effects
Belfort et al., 2006, USA (PMID: 17135584)	Adults with T2DM or prediabetes and biopsy-confirmed NASH Mean age: 51 years; male sex: 45%; BMI: 33.2 kg/m^2; HbA1: 6.2%; ALT: 64 IU/L; AST: 44 IU/L	A. Pioglitazone 30 mg/d for 2 months, then 45 mg/day (n=29) B. Placebo (n=25) Length: 24 weeks	Pioglitazone, as compared with placebo, was associated with improvement in hepatic fat content (54% vs. 0%, p<0.001), and necro-inflammation (85% vs. 38%, p=0.001). Percent with liver fibrosis improvement was not significant: 46% vs. 33%, p=0.08 Changes from baseline (p-value), between-groups p-value: AST: -19 (p<0.001) vs. -9 IU/L (p=0.08), p=0.04 ALT: -39 (p<0.001) vs. -21 IU/L (p=0.03), p<0.001 Weight: 2.5 (p<0.001) vs. -0.5 kg (p=0.53), p=0.003 BMI: 1.1 (p<0.001) vs. -0.2 kg/m^2 (p=0.62), p = 0.005	Serious AEs: NR Withdrawal due to AEs: 1/29 (3.5%) in pioglitazone group vs. 1/25 (4%) in placebo group
Aithal, 2008, UK (PMID: 18718471)	Non-diabetic adults with biopsy-confirmed NASH Mean age: 53 years; male sex: 61%; BMI: 30.3 kg/m^2; HbA1: NR; ALT and AST: no reported	A. Pioglitazone 30 mg/day (n=37) B. Placebo (n=37) Length: 52 weeks	Number (%) with improvement (p- value), between-groups p-value: Steatosis: 15/31 (48%) (p=0.001) vs. 11/30 (37%) (p=0.03), p=0.19 Liver fibrosis: 9/31 (29%) (p=0.006) vs. 6/30 (20%) (p=0.81), p=0.05 Changes from baseline (p-value), between-groups p-value: Weight: 2.6 (p=0.005) vs. -3.5 kg (p=0.69), p=0.02	Serious AEs: NR Withdrawal due to AEs: 3/37 (8.1%) in pioglitazone group vs. 4/37 (10.8%) in placebo group
Sanyal, 2010, USA, PIVENS (PMID: 20427778)	Non-diabetic adults with biopsy-confirmed NASH Mean age: 46 years; male sex: 40%; BMI: 34 kg/m^2; ALT: 83 IU/L; AST: 56 IU/L	A. Pioglitazone 30 mg/day (n=80) B. Vitamin E 800 IU/d (n=84) C. Placebo (n=83) Length: 96 weeks	Changes from baseline (p-value vs. placebo): NASH improvement, n (%): 27/80 (34%) (p=0.04) vs. 36/84 (43%) (p=0.001) vs. 16/83 (19%) NAFLD activity score: -1.9 (p<0.001) vs. -1.9	Serious AEs: NR Withdrawal due to AEs: None

			(p<0.001) vs. -0.5 Steatosis: -0.8 (p<0.001) vs. -0.7 (p<0.001) vs. -0.1 Fibrosis: -0.4 (p=0.10) vs. -0.3 (p=0.19) vs. -0.1 AST: -20.4 (p< 0.001) vs. -21.3 (p<0.001) vs. -3.8 IU/L ALT: -40.8 (p< 0.001) vs. -37.0 (p=0.001) vs. -20.1 IU/L Weight: 4.7 (p<0.001) vs. 0.4 (p=0.65) vs. 0.7 kg	
Sharma, 2012, India (PMID: 25755455)	Adults with biopsy-confirmed NASH Mean age: 39 years; male sex: 54%; BMI: 24.9 kg/m^2; pre-existing T2DM: no reported; HbA1c: no reported; ALT: 96 IU/L; AST: 65 IU/L	A. Pentoxifylline 1200 mg/day (n=29) B. Pioglitazone 30 mg/day (n=30) Length: 24 weeks	Changes from baseline (p-value), between-groups p-value: Brunt's score: -0.34 (p=0.10) vs. -1.2 (p=0.005), p = 0.04 Steatosis: -0.83 (p=0.02) vs. -1.18 (p=0.005), p=0.60 Fibrosis: 0.08 (p=0.70) vs. -0.46 (p=0.19), p=0.26	Serious AEs: NR Withdrawal due to AEs: None
Cusi, 2016, USA (PMID: 27322798)	Patients with T2DM or prediabetes and biopsy-confirmed NASH Mean age: 51 years; male sex: 70%; BMI: 34.4 kg/m^2; pre-existing T2DM: 51%; HbA1c in T2DM patients (n=51): 6.9%, HbA1c in patients with prediabetes (n=50) 5.7%; ALT: 59 UI/L; participants with biopsy diagnosed NASH: 86%	A. Pioglitazone 45 mg/day (n=50) B. Placebo (n=51) All patients were prescribed a hypocaloric diet Both groups followed with an open-label phase with pioglitazone for 18 months Length: 72 weeks (144 weeks for open-label phase)	Greater than 2-point reduction of NAS without worsening fibrosis: 29% vs 17%, p<0.001 Fibrosis; greater than 1 point improvement: 39% vs 25%, p >0.05 (NS) Fibrosis mean change in score improved with pioglitazone: 0 vs - 0.5, p<0.05 Weight: pioglitazone group gained 2.5 kg, p<0.05	NR
Ratziu, 2016, Multinational, GOLDEN-505 (PMID: 26874076)	Patients with biopsy-confirmed NASH Mean age: 52 years; male sex: 54% male; BMI: 31.3 kg/m^2; pre-existing T2DM: 39%; HbA1c: 6.1%; ALT: 63 IU/L; AST: 43 IU/L	A. Elafibranor 80 mg/day (n=93) B. Elafibranor 120 mg/day (n=89) C. Placebo (n=92) Length: 52 weeks	No differences among elafibranor and placebo groups for percentage of patients with resolution of NASH without worsening of fibrosis, according to the protocol-defined definition: 23% in elafibranor 80 mg group, 21% in elafibranor 120 mg group and 17% in placebo	Serious AEs: 11 patients in the placebo (12%), 15 patients in elafibranor 80 mg group (16%), and 14 patients in elafibranor 120 mg group (16%) group Withdrawal due to AEs: 17 patients

			group NB: Using a modified definition of treatment response, the response rate was significantly higher for elafibranor 120-mg group than for placebo group (19% vs. 12%; p=0.045). Conversely, the response rate in elafibranor 80 mg group (13%) was not higher than placebo	
Gawrieh, 2021, USA, EVIDENCE IV (PMID: 33811367)	Patients with NASH or NAFLD and elevated serum ALT levels. Liver fat content was assessed by MRI-PDFF Mean age: 49 years; male sex: 53%; BMI: 34.3 kg/m^2; pre-existing T2DM: 52.8%; HbA1c: 6.3%; ALT: 89 IU/L; AST: 55 IU/L	A. Saroglitazar 1 mg/day (n=26) B. Saroglitazar 2 mg/day (n=25) C. Saroglitazar 4 mg/day (n=27) D. Placebo (n=28) Length: 16 weeks	Relative changes from baseline of liver fat content at week 16 (p-value) for each group: A. LS (least squares) Mean=+3.8%, SE (standard error)=5.7, p=0.97 B. LS Mean=+0.5%, SE=6.3, p=0.68 C. LS Mean=-19.7%, SE=5.6, p=0.004 D. LS Mean=+4.1%, SE = 5.9 The LS mean difference between saroglitazar and placebo (95% CI) in liver fat content at week 16 was -0.3 % (95% CI -16.8 to 16.2) (p=0.97), - 3.6% (95% CI -20.8 to 13.5) (p=0.67), and -23.8% (95% CI -39.9 to -7.7) (p=0.004) for saroglitazar 1-mg, 2-mg and 4-mg groups, respectively	AEs: 112 treatment-adverse events were reported in 59 patients. In particular, 13 (50%) patients in the saroglitazar 1 mg group, 13 (52%) patients in the saroglitazar 2 mg group, 14 (52%) patients in the saroglitazar 4 mg group, and 19 (68%) patients in the placebo group. No serious AEs occurred
Francque, 2021, Multinational, NATIVE (PMID: 33038502 + abstract presentation*)	Patients with biopsy-confirmed NASH and fibrosis Mean age: 54 years; male sex: 42%; BMI: 32.9 kg/m^2; pre-existing T2DM: 41.7%; HbA1c: 6.6%; ALT: 62 IU/L; AST: 47 IU/L	A. Lanifibranor 800 mg/day (n=83) B. Lanifibranor 1200 mg/day (n=83) C. Placebo (n=81) Length: 24 weeks	Resolution of NASH with no worsening of fibrosis: 33% (p=0.04 vs. placebo) in lanifibranor 800 mg group, 45% (p<0.001 vs. placebo) in lanifibranor 1200 mg group, and 19% in placebo group Improvement in fibrosis by at least 1 stage and no worsening of NASH: 28% (p=0.53 vs. placebo) in lanifibranor 800 mg group, 42% (p=0.011 vs. placebo) in lanifibranor 1200 mg group, and 24%	Serious AEs: 3 patients in the lanifibranor 800 mg group, 7 patients in the lanifibranor 1200 mg group and 3 patients in the placebo group Withdrawal due to AE: 2 in placebo group, 1 in lanifibranor 800 mg group, 2 in lanifibranor 1200 mg group

			in placebo group Resolution of NASH and improvement of fibrosis: 21% (p=0.02 vs. placebo) in lanifibranor 800 mg group, 31% (p<0.001 vs. placebo) in lanifibranor 1200 mg group, and 7% in placebo group Significant reductions of serum liver enzymes in both lanifibranor dose groups	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

Note: *Data are currently available only in an abstract presentation. However, for the data extraction of results of the NATIVE phase 2 trial, we contacted directly the authors, who have kindly provided to us the full set of slides presented to the AASLD meeting (November, 2020).