

Supplementary Table 10. Leave-one-out sensitivity analyses for liver histology improvement across therapeutic targets

Note: ACC, acetyl-coenzyme A carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulintropic polypeptide; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist.

Supplementary Table 10.1 SUCRA and rankings for fibrosis improvement by ≥ 1 stage without steatohepatitis worsening

Excluding trials	Omitting durations	GLP-1 RA	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)- Pioglitazone	FGF19 analogue	PPAR agonist
NCT03976401	16 weeks	30.1 (9)	55.1 (6)	31.2 (8)	60.6 (4)	71.0 (3)	71.5 (2)	78.5 (1)	41.4 (7)	59.9 (5)
AASLD-5017	24 weeks	30.1 (8)	55.1 (6)	30.1 (8)	62.4 (4)	72.2 (2)	69.3 (3)	79.6 (1)	39.2 (7)	61.3 (5)
NCT03008070	24 weeks	28.5 (9)	52.1 (6)	29.8 (8)	55.9 (5)	66.2 (3)	65.1 (4)	74.6 (2)	38.1 (7)	89.2 (1)
NCT02443116	24 weeks	31.5 (9)	56.8 (6)	32.7 (7)	62.3 (4)	73.2 (2)	69.8 (3)	78.4 (1)	31.7 (8)	61.8 (5)
NCT01068444	24 weeks	31.6 (9)	57.9 (5)	33.1 (8)	63.1 (4)	74.2 (2)	70 (3)	80.8 (1)	41.5 (7)	47.2 (6)
NCT03912532	24 weeks	28.0 (9)	53.0 (7)	29.8 (8)	60.4 (4)	70.8 (2)	67.5 (3)	77.3 (1)	53.6 (6)	58.7 (5)
NCT04929483	24 weeks	30.5 (9)	57.7 (6)	32.5 (8)	63.8 (3)	61.3 (5)	71.4 (2)	79.7 (1)	39.5 (7)	62.8 (4)
NCT02912260	36 weeks	28.6 (9)	54.2 (6)	35.1 (8)	60.3 (4)	72.7 (2)	69.9 (3)	79.8 (1)	39.6 (7)	59.3 (5)
NCT04321343	36 weeks	32.4 (8)	59.4 (5)	33.4 (7)	64.5 (4)	78.1 (1)	73.6 (2)	--	42.7 (6)	65.5 (3)
NCT04771273	48 weeks	32.4 (8)	58.0 (5)	33.0 (7)	64.4 (3)	76.5 (2)	--	79.5 (1)	41.5 (6)	63.8 (4)
NCT03486899	48 weeks	28.5 (9)	53.3 (6)	30.7 (8)	61.6 (4)	79.6 (1)	67.5 (3)	77.2 (2)	39.7 (7)	61.4 (5)
AASLD-5016	52 weeks	30.4 (8)	56.0 (6)	29.8 (9)	62 (4)	72.9 (2)	69.9 (3)	79.3 (1)	39.4 (7)	59.9 (5)

Excluding trials	Omitting durations	GLP-1 RA	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)-Pioglitazone	FGF19 analogue	PPAR agonist
NCT04166773	52 weeks	31.2 (8)	56.5 (5)	33.3 (7)	--	73.7 (2)	71.6 (3)	80.9 (1)	39.7 (6)	62.6 (4)
NCT03900429	52 weeks	31.7 (8)	55.4 (6)	29.0 (9)	62.0 (4)	71.4 (2)	69.8 (3)	78.5 (1)	39.4 (7)	61.8 (5)
AASLD-5018	72 weeks	32.5 (8)	53.4 (6)	31.8 (9)	61.8 (4)	73.2 (2)	68.6 (3)	78.3 (1)	38.7 (7)	60.7 (5)
NCT02548351	72 weeks	31.6 (8)	--	33.1 (7)	60.1 (5)	72.3 (2)	71.1 (3)	78.7 (1)	41.1 (6)	61.4 (4)
NCT02970942	72 weeks	30.4 (9)	54.7 (6)	30.9 (8)	60.2 (4)	73.0 (2)	71.2 (3)	78.4 (1)	41.1 (7)	59.6 (5)

Note: Values are SUCRA (%). Numbers in parentheses indicate the corresponding rank.

Supplementary Table 10.2 The comparisons between different therapeutic targets and placebo for fibrosis improvement by ≥ 1 stage without steatohepatitis worsening

Excluding trials	Omitting durations	GLP-1 RA	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GC G dual RA	d-(R)- Pioglitazone	FGF19 analogue	PPAR agonist
NCT03976401	16 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.40 (1.72, 6.71)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
AASLD-5017	24 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.74 (1.62, 8.65)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT03008070	24 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	7.00 (1.98,24.75)
NCT02443116	24 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	1.82 (0.61, 5.41)	2.94 (1.66, 5.24)
NCT01068444	24 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.35 (1.23, 4.48)
NCT03912532	24 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.76 (0.81, 9.39)	2.94 (1.66, 5.24)
NCT04929483	24 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	2.90 (1.30, 6.47)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT02912260	36 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.18 (1.51, 3.15)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT04321343	36 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	--	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT04771273	48 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	--	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)

Excluding trials	Omitting durations	GLP-1 RA	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GC G dual RA	d-(R)-Pioglitazone	FGF19 analogue	PPAR agonist
NCT03486899	48 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	4.21 (1.93, 9.17)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
AASLD-5016	52 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	1.97 (1.36, 2.84)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT04166773	52 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	--	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT03900429	52 weeks	2.02 (1.48, 2.74)	2.70 (1.70, 4.29)	1.87 (0.98, 3.55)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
AASLD-5018	72 weeks	1.98 (0.93, 4.22)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT02548351	72 weeks	2.02 (1.48, 2.74)	--	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)
NCT02970942	72 weeks	2.02 (1.44, 2.83)	2.70 (1.70, 4.29)	2.04 (1.45, 2.87)	3.01 (1.29, 7.02)	3.52 (1.81, 6.85)	3.40 (1.53, 7.56)	4.75 (1.21, 18.58)	2.19 (0.97, 4.94)	2.94 (1.66, 5.24)

Note: Values are odds ratios (95% confidence interval).

Supplementary Table 10.3 SUCRA and rankings for steatohepatitis improvement without fibrosis worsening

Excluding trials	Omitting durations	GLP-1 RA	PPAR agonist	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)- Pioglitazone	FGF19 analogue
NCT03976401	16 weeks	61.2 (4)	41.9 (7)	33 (8)	48.8 (6)	91.3 (1)	61.3 (3)	86.5 (2)	18.5 (9)	53.5 (5)
AASLD-5017	24 weeks	62.0 (3)	46.4 (7)	34.7 (8)	51.7 (5)	91.6 (1)	48.4 (6)	87.3 (2)	19.4 (9)	53.7 (4)
Siddiqui MS, 2021	24 weeks	61.9 (3)	40.8 (7)	33.8 (8)	50.8 (6)	92.4 (1)	57.9 (4)	86.4 (2)	19.8 (9)	52.1 (5)
NCT03008070	24 weeks	62.5 (3)	44.2 (7)	34.2 (8)	49.7 (6)	90.6 (1)	55.8 (4)	85.3 (2)	20.0 (9)	53.4 (5)
NCT02443116	24 weeks	60.9 (3)	43.1 (7)	33.2 (8)	49.5 (6)	90.2 (1)	55.5 (5)	86 (2)	19.2 (9)	57.9 (4)
NCT03912532	24 weeks	63.1 (3)	43.9 (7)	35.7 (8)	50.9 (5)	90.2 (1)	57.1 (4)	87.3 (2)	19.9 (9)	46.8 (6)
NCT04929483	24 weeks	64.0 (3)	46.5 (6)	35.4 (8)	52.9 (5)	93.3 (1)	40.8 (7)	87.9 (2)	19.2 (9)	55.8 (4)
NCT02912260	36 weeks	58.8 (4)	41.0 (7)	31.9 (8)	63.5 (3)	92.0 (1)	55.3 (5)	87.0 (2)	15.7 (9)	50.7 (6)
NCT04321343	36 weeks	58.6 (3)	38.3 (7)	29.5 (8)	45.2 (6)	91.5 (1)	52.8 (4)	85.2 (2)	--	48.3 (5)
NCT04771273	48 weeks	69.2 (2)	47.7 (6)	37.7 (7)	55.9 (5)	95.1 (1)	61.5 (3)	--	20.4 (8)	57.9 (4)
NCT01237119	48 weeks	60.8 (3)	43.1 (7)	33.5 (8)	49.8 (6)	91.2 (1)	55.9 (4)	87.6 (2)	20.3 (9)	53.7 (5)

Excluding trials	Omitting durations	GLP-1 RA	PPAR agonist	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)- Pioglitazone	FGF19 analogue
NCT03486899	48 weeks	59.2 (4)	40.6 (7)	32.0 (8)	48.8 (6)	90.6 (1)	69.8 (3)	86.4 (2)	17.9 (9)	50.9 (5)
NCT04173065	52 weeks	62.9 (3)	45.3 (6)	36.0 (8)	40.4 (7)	92.5 (1)	58.1 (4)	86.5 (2)	19.6 (9)	54.4 (5)
NCT04166773	52 weeks	68.4 (2)	48.2 (6)	37.3 (7)	56.3 (5)	--	63.8 (3)	93.0 (1)	20.4 (8)	58.1 (4)
NCT01694849	52 weeks	62 (3)	45.5 (7)	35.8 (8)	46.9 (6)	90.9 (1)	55.2 (4)	86.2 (2)	19.4 (9)	53.4 (5)
NCT03900429	52 weeks	63.3 (3)	44.7 (7)	34.0 (8)	47.4 (6)	91.1 (1)	56.4 (4)	86.0 (2)	20.2 (9)	52.3 (5)
AASLD-5018	72 weeks	73.3 (3)	42.1 (7)	32.8 (8)	48.8 (6)	90.4 (1)	54.2 (4)	85.8 (2)	18.6 (9)	49.9 (5)
NCT02548351	72 weeks	60.8 (3)	41.9 (8)	44.5 (7)	48.0 (6)	90.1 (1)	54.4 (4)	85.1 (2)	18.9 (9)	51.7 (5)
NCT01265498	72 weeks	63.1 (3)	43.9 (7)	28.3 (8)	50.6 (6)	90.7 (1)	56.3 (4)	86.9 (2)	20.1 (9)	53.9 (5)
NCT00994682	72 weeks	63.6 (3)	32.5 (8)	35.6 (7)	52.8 (6)	92.8 (1)	57.7 (4)	88.2 (2)	19.0 (9)	53.7 (5)
NCT02970942	72 weeks	54.8 (4)	44.9 (7)	34.1 (8)	52.2 (6)	91.1 (1)	57.3 (3)	87.7 (2)	19.1 (9)	54.5 (5)

Note: Values are SUCRA (%). Numbers in parentheses indicate the corresponding rank.

Supplementary Table 10.4 The comparisons between different therapeutic targets and placebo for steatohepatitis improvement without fibrosis worsening

Excluding trials	Omitting durations	GLP-1 RA	PPAR agonist	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)- Pioglitazone	FGF19 analogue
NCT03976401	16 weeks	4.58 (2.17, 9.65)	3.12 (1.55, 6.27)	2.48 (1.09, 5.65)	3.56 (1.74, 7.28)	14.33 (3.36, 61.16)	4.64 (1.67, 12.87)	10.67 (3.04, 37.46)	1.41 (0.29, 6.77)	3.84 (1.02, 14.39)
AASLD-5017	24 weeks	4.61 (2.14, 9.90)	3.13 (1.53, 6.40)	2.47 (1.06, 5.77)	3.55 (1.71, 7.40)	14.33 (3.28, 62.73)	3.38 (0.89, 12.90)	10.67 (2.95, 38.57)	1.41 (0.29, 6.93)	3.84 (1.01, 14.59)
Siddiqui MS, 2021	24 weeks	4.57 (2.18, 9.57)	2.94 (1.46, 5.93)	2.48 (1.09, 5.61)	3.56 (1.75, 7.25)	14.33 (3.39, 60.67)	4.06 (1.55, 10.66)	10.67 (3.07, 37.11)	1.41 (0.29, 6.72)	3.84 (1.03, 14.32)
NCT03008070	24 weeks	4.66 (2.09, 10.42)	3.11 (1.22, 7.89)	2.47 (1.01, 6.04)	3.54 (1.64, 7.66)	14.33 (3.10, 66.26)	4.07 (1.48, 11.14)	10.67 (2.77, 41.06)	1.41 (0.27, 7.29)	3.84 (0.98, 15.05)
NCT02443116	24 weeks	4.61 (2.15, 9.89)	3.13 (1.53, 6.39)	2.47 (1.01, 6.04)	3.55 (1.71, 7.40)	14.33 (3.28, 62.66)	4.06 (1.52, 10.83)	10.67 (2.95, 38.52)	1.41 (0.29, 6.93)	4.69 (0.70, 31.47)
NCT03912532	24 weeks	4.61 (2.15, 9.89)	3.13 (1.53, 6.39)	2.47 (1.01, 6.04)	3.55 (1.71, 7.40)	14.33 (3.28, 62.66)	4.06 (1.52, 10.83)	10.67 (2.95, 38.52)	1.41 (0.29, 6.93)	3.16 (0.48, 20.57)
NCT04929483	24 weeks	4.53 (2.21, 9.28)	3.10 (1.58, 6.08)	2.48 (1.12, 5.48)	3.57 (1.79, 7.11)	14.33 (3.48, 58.96)	2.78 (0.98, 7.87)	10.67 (3.17, 35.90)	1.41 (0.30, 6.55)	3.84 (1.04, 14.10)
NCT02912260	36 weeks	4.46 (2.26, 8.81)	3.07 (1.62, 5.83)	2.49 (1.18, 5.24)	4.89 (2.31, 10.37)	14.33 (3.66, 56.06)	4.06 (1.61, 10.25)	10.67 (3.36, 33.84)	1.41 (0.32, 6.25)	3.84 (1.07, 13.72)
NCT04321343	36 weeks	4.57 (2.18, 9.55)	3.11 (1.56, 6.22)	3.11 (1.56, 6.22)	3.56 (1.75, 7.24)	14.33 (3.39, 60.57)	4.06 (1.55, 10.65)	10.67 (3.07, 37.04)	--	3.84 (1.03, 14.31)

Excluding trials	Omitting durations	GLP-1 RA	PPAR agonist	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)- Pioglitazone	FGF19 analogue
NCT04771273	48 weeks	4.57 (2.18, 9.55)	3.11 (1.56, 6.22)	3.11 (1.56, 6.22)	3.56 (1.75, 7.24)	14.33 (3.39, 60.57)	4.06 (1.55, 10.65)	--	1.41 (0.29, 6.71)	3.84 (1.03, 14.31)
NCT01237119	48 weeks	4.35 (1.91, 9.87)	3.13 (1.53, 6.40)	2.47 (1.06, 5.76)	3.55 (1.71, 7.40)	14.33 (3.28, 62.65)	4.06 (1.52, 10.83)	10.67 (2.95, 38.51)	1.41 (0.29, 6.93)	3.84 (1.01, 14.58)
NCT03486899	48 weeks	4.53 (2.21, 9.30)	3.10 (1.58, 6.08)	2.48 (1.12, 5.48)	3.57 (1.79, 7.12)	14.33 (3.48, 59.02)	6.23 (2.03, 19.15)	10.67 (3.17, 35.94)	1.41 (0.30, 6.55)	3.84 (1.04, 14.11)
NCT04173065	52 weeks	4.57 (2.18, 9.56)	3.11 (1.56, 6.22)	2.48 (1.10, 5.61)	2.71 (1.16, 6.33)	14.33 (3.39, 60.60)	4.06 (1.55, 10.66)	10.67 (3.07, 37.06)	1.41 (0.29, 6.72)	3.84 (1.03, 14.32)
NCT04166773	52 weeks	4.57 (2.18, 9.55)	3.11 (1.56, 6.22)	2.48 (1.10, 5.60)	3.56 (1.75, 7.24)	--	4.06 (1.55, 10.65)	10.67 (3.07, 37.04)	1.41 (0.29, 6.71)	3.84 (1.03, 14.31)
NCT01694849	52 weeks	4.66 (2.08, 10.45)	3.16 (1.49, 6.70)	2.47 (1.01, 6.05)	3.24 (1.15, 9.15)	14.33 (3.09, 66.47)	4.07 (1.48, 11.16)	10.67 (2.76, 41.20)	1.41 (0.27, 7.32)	3.84 (0.98, 15.07)
NCT03900429	52 weeks	4.66 (2.08, 10.45)	3.16 (1.49, 6.70)	2.47 (1.01, 6.05)	3.24 (1.15, 9.15)	14.33 (3.09, 66.47)	4.07 (1.48, 11.16)	10.67 (2.76, 41.20)	1.41 (0.27, 7.32)	3.84 (0.98, 15.07)
AASLD-5018	72 weeks	6.74 (2.33, 19.54)	3.11 (1.55, 6.24)	2.48 (1.09, 5.61)	3.56 (1.75, 7.25)	14.33 (3.38, 60.70)	4.06 (1.55, 10.66)	10.67 (3.06, 37.13)	1.41 (0.29, 6.73)	3.84 (1.03, 14.33)
NCT02548351	72 weeks	4.64 (2.11, 10.19)	3.14 (1.51, 6.56)	3.12 (0.94, 10.27)	3.55 (1.67, 7.55)	14.33 (3.18, 64.67)	4.06 (1.50, 11.01)	10.67 (2.85, 39.94)	1.41 (0.28, 7.13)	3.84 (0.99, 14.84)
NCT01265498	72 weeks	4.64 (2.11, 10.19)	3.14 (1.51, 6.56)	1.89 (0.53, 6.81)	3.55 (1.67, 7.55)	14.33 (3.18, 64.67)	4.06 (1.50, 11.01)	10.67 (2.85, 39.94)	1.41 (0.28, 7.13)	3.84 (0.99, 14.84)

Excluding trials	Omitting durations	GLP-1 RA	PPAR agonist	FXR agonist	THR- β agonist	GLP-1/GIP dual RA	FGF21 analogue	GLP-1/GCG dual RA	d-(R)- Pioglitazone	FGF19 analogue
NCT00994682	72 weeks	4.46 (2.25, 8.83)	2.33 (1.11, 4.91)	2.49 (1.18, 5.24)	3.59 (1.87, 6.88)	14.33 (3.67, 55.97)	4.06 (1.61, 10.24)	10.67 (3.37, 33.78)	1.41 (0.32, 6.24)	3.84 (1.07, 13.71)
NCT02970942	72 weeks	3.78 (1.52,9.38)	3.12 (1.54,6.32)	2.48 (1.08,5.69)	3.56 (1.73,7.33)	14.33 (3.33,61.68)	4.06 (1.54,10.75)	10.67 (3.01,37.83)	1.41 (0.29,6.83)	3.84 (1.02,14.46)

Note: Values are odds ratios (95% confidence interval).