Supplementary Information

Supplementary Table 1: Brief summary of the 21 therapeutic drug trials examined in Ampuero et al.'s 2022 meta-analysis of variables influencing the interpretation of clinical trial results in NAFLD[22]

Drug	First author and year	Noninvasive biomarkers used	Fibrosis changes reported by study	Brief summary	Included for review in Table 3
Alderfermin	Harrison SA et al.[1] (2021)	ELF™, PRO-C3	A trend toward fibrosis improvement.	Decrease in ELF™ and PRO-C3 scores, when compared to placebo p=0.15 and p=0.001 for ELF™ and PRO-C3 respectively.	Yes.
Aramchol	Ratzui V et al.[2] (2020)	FIB-4, NFS, ELF™	Fibrosis improvement by 1 stage or more was numerically higher in the 600 mg arm than in the placebo arm, without reaching statistical significance.	No data on ELF and limited data on FIB-4 and NFS is provided. Data supporting the findings of the study are owned by Galmet Research and Development and the article states the data is not publicly available.	Supplementary Table 2 only.
Belapectin	Chalasani N et al.[3] (2020)	ELF™, FibroTest®, VCTE	No improvement in fibrosis.	Study notes that reasons for no improvement in fibrosis include: (i) the duration of therapy was not sufficiently long and (ii) the study population included patients with established cirrhosis and portal hypertension, a group in who fibrosis reversal may not be possible.	Yes.
Cenicriviroc	Friedman SL et al.[4] (2018)	NFS, FIB-4, APRI, ELF™	Cenicriviroc shows a significant anti-fibrotic benefit at year 1.	Post-hoc analysis explored the relationship between change in fibrosis indices and improvement in liver histology. In general, more favourable changes (i.e. smaller mean increases or larger mean decreases) in fibrosis indices (NFS, FIB-4, APRI and ELF™) were observed in subjects in whom fibrosis improved by ≥1 stage at year 1 relative to subjects in whom fibrosis did not improve. However, the post-hoc analysis was not powered to demonstrate a difference for treatment (cenicriviroc or placebo) and/or subgroup (histological improvement or not).	Yes.
Cilofexor and Firsocostate	Loomba R et al.[5] 2020	ELF™, FibroTest®, VCTE	In patients with bridging fibrosis and cirrhosis, cilofexor/firsocostat may have an anti-fibrotic effect.	Cohort included ≥F3, therefore appropriate use of noninvasive biomarkers. Treatment with cilofexor/firsocostat for 48 weeks led to improvements in ELF and liver stiffness measured by VCTE. Post-hoc analyses of liver fibrosis, assessed by a machine learning approach, suggest fibrosis regression in patients with cilofexor/firsocostat.	Yes.
Efruxifermin	Harrison SA et al.[6] (2021)	ELF™, PRO-C3	Noninvasive measure of fibrogenesis (PRO-C3 and ELF™) corroborate the observed improvements in liver histopathology.	Cohort includes F1 and F2. ELF™ is currently only validated for ≥F3. The changes observed to ELF™ scores may not necessarily be an accurate representation to the changes in liver observed in histopathology.	Yes.

Elafibranor	Ratzui V et al.[7] (2016)	NFS, FibroTest®	Post-hoc analysis of data showed that elafibranor resolved NASH without worsening of fibrosis.	Limited data available. Cohort includes F0, F1 and F2. NFS and FibroTest® are both currently validated for ≥F3 only.	Yes.
Elafibranor	Harrison SA et al.[8] (2020)	Follow-up paper from Ratzui V et al. above	Elafibranor did not meet the key secondary endpoint of fibrosis improvement.	Conference report only.	No.
Emricasan	Harrison SA et al.[9] (2020)		Emricasan did not improve liver histology.	Noninvasive biomarkers not used (ALT and AST only)	No.
Lanifibranor	Franque S et al.[10] (2021)	ELF™, FIB-4, PRO-C3, VCTE	Markers of fibrosis (scores on the ELF™ and FIB-4) did not improve.	Authors' note that the changes in biomarkers are not fully validated as surrogates of histologic change and the results should be interpreted with caution, particularly in short-term trials.	Yes.
Liraglutide	Armstrong MJ et al.[11] (2016)	ELF™	Fewer patients receiving liraglutide had progression of fibrosis (when compared to placebo). The absence of a difference in mean change in fibrosis stage between intervention and placebo probably reflects the duration of treatment, and a longer treatment course should be assessed.	When compared to placebo, the mean change for ELF™ from baseline to 48 weeks was greater in the intervention arm (p=0.05). Cohort includes F0, F1 and F2. ELF™ is currently only validated for ≥F3. The changes observed to ELF™ scores may not necessarily be an accurate representation to the changes in liver observed in histopathology.	Yes.
MSDC-0602K	Harrison SA et al.[12] (2020)	APRI, ELF™, FIB-4, FibroTest®	MSDC-00602K did not demonstrate significant effects to liver histology with the biopsy techniques used.	Cohorts include F1 and F2. Serum biomarkers used are only validated for ≥F3. No follow up data showing the changes in biomarkers used was recorded in the supplementary information.	Yes.
Obeticholic acid	Neuschwander-Tetri BA et al.[13] (2015)		The improvement in fibrosis, although small, shows that this therapy might be beneficial in preventing progression to fibrosis.	Noninvasive biomarkers not used.	No.
Obeticholic acid	Younossi ZM et al.[14] (2019)		Obeticholic acid significantly improved fibrosis.	Noninvasive biomarkers not used (ALT and AST only).	No.
Pioglitazone	Sanyal AJ et al.[15] (2010)		Fibrosis scores were not significantly improved.	Noninvasive biomarkers not used.	No.
Pioglitazone	Cusi K et al.[16] (2016)		Pioglitazone treatment was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, -0.5 [CI, -0.9 to 0.0]; p=0.039.	Noninvasive biomarkers not used.	No.
Resmetirom	Harrison SA et al.[17] (2019)	ELF™, PRO-C3	Biomarkers of hepatic fibrogenesis (PRO-C3 and ELF™) were reduced.	Cohorts included F0, F1 and F2. ELF™ is currently only validated for ≥F3. The changes observed to ELF™ scores may not necessarily be	Yes

				an accurate representation to the changes in liver observed in histopathology.	
Seladelpar	Harrison SA et al.[18] (2020)		No significant decrease in fibrosis	Conference report and poster presentation only.	No.
Selonsertib	Loomba R et al.[19] (2018)	ELF™, FibroTest®, VCTE	Improvement in fibrosis was associated with reduction in collagen content and lobular inflammation on liver biopsy as well as improvements in serum biomarkers.	Cohort included F3, therefore appropriate use of noninvasive biomarkers. Difference between baseline and follow up for biomarkers recorded only.	Yes.
Selonsertib	Harrison SA et al.[20] (2020)	ELF™, FibroTest®, APRI, FIB-4, NFS, VCTE	Selonsertib did not reduce fibrosis.	Cohort was F4, therefore appropriate use of noninvasive biomarkers.	Yes.
Semaglutide	Newsome PN et al.[21] (2021)	ELF™, VCTE	The trial did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage.	Cohort included F1 and F2. ELF™ is currently only validated for ≥F3. The changes observed to ELF™ scores may not necessarily be an accurate representation to the changes in liver observed in histopathology.	Yes.

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Supplementary Table 2: Comparison between change in noninvasive serum biomarkers and change in liver fibrosis assessed by liver histology, in therapeutic trials of nonalcoholic steatohepatitis (NASH)

First author (year)	Study design, duration & numbers recruited	Relevant drug for NASH	Patient group	Fibrosis marker	Fibrosis Stage	Baseline	Follow-up	Change in mean	Change in serum biomarker score
Newsome PN et al.[1] (2021)	Phase 2, double-blind, randomised, placebo-controlled; 72 weeks; *n*=320	Semaglutide	0.1mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=13 (16%)		
					F1	*n*=23 (29%)	*n*=22 (28%)		
					F2	*n*=18 (22%)	*n*=19 (24%)		
					F3	*n*=39 (49%)	*n*=18 (23%)		
					F4	*n*=0	*n*=2 (3%)		
				Mean fibrosis stage[a] (SD)		2.2 (0.6)	1.6 (0.3)	-0.6	
				Mean ELF™ score[f,h]		9.8 ±1.0	9.42[d]		-0.34[e]
				Mean VCTE reading, kPa[g]		10.4±78.5	8.04[i]		-2.0[d]
			0.2mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=9 (14%)		
					F1	*n*=19 (26%)	*n*=19 (30%)		
					F2	*n*=18 (24%)	*n*=11 (17%)		
					F3	*n*=41 (55%)	*n*=23 (36%)		
					F4	*n*=0	*n*=2 (3%)		
				Mean fibrosis stage[a] (SD)		2.3 (0.7)	1.8 (0.4)	-0.5	
				Mean ELF™ score[f,h]		9.8 ±0.9	9.37[d]		-0.39[e]
				Mean VCTE reading, kPa[g]		12.3±74.0	7.55[i]		-4.75[d]
			0.4mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=11 (16%)		
					F1	*n*=26 (32%)	*n*=21 (30%)		
					F2	*n*=14 (17%)	*n*=17 (25%)		
					F3	*n*=42 (51%)	*n*=20 (29%)		
					F4	*n*=0	*n*=0		
				Mean fibrosis stage[a]		2.2 (0.6)	1.7 (0.4)	-0.5	
				Mean ELF™ score[f,h]		9.9 ±1.0	9.2[d]		-0.56 [e]
				Mean VCTE reading, kPa[g]		11.5±87.1	7.68[i]		-3.82

			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=8 (11%)	
					F1	*n*=22 (28%)	*n*=17 (24%)	
					F2	*n*=22 (28%)	*n*=16 (23%)	
					F3	*n*=36 (45%)	*n*=26 (37%)	
					F4	*n*=0	*n*=3 (4%)	
				Mean fibrosis stage[a] (SD)		2.2 (0.6)	2.0 (0.4)	-0.2
				Mean ELF™ score[f,h]		9.6±0.9	9.77 [d]	0.01[e]
				Mean VCTE reading, kPa[g]		8.7±90.0	10.84[i]	2.14[d]
Friedman SL et al.[2] (2018)	Phase 2b, double-blind, randomised, placebo-controlled; 52 weeks; *n*=288	Cenicriviroc	150mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=10 (7%)	
					F1	*n*=47 (32%)	*n*=44 (32%)	
					F2	*n*=42 (29%)	*n*=35 (25%)	
					F3	*n*=56 (39%)	*n*=47 (34%)	
					F4	*n*=0	*n*=2 (1%)	
				Mean fibrosis stage (SD)		2.1 (0.5)	1.9 (0.4)	-0.2
				Median NFS score (min, max)		–0.942 (–4.55, 1.27)	–0.942 (–4.55, 1.27)	–0.942 (–4.55, 1.27)
				Mean NFS score for subjects with improvement (SD)		–1.28 (1.24)	–1.24 (1.21)	0.05 (0.52)
				Mean NFS score for subjects without improvement (SD)		–0.99 (1.09)	–0.80 (1.21)	0.19 (0.49)
				Median FIB-4 score (min, max)		1.239 (0.38, 4.20)	1.375 (0.42, 5.26)	0.080 (–1.81, 2.38)
				Mean FIB-4 for subjects with improvement, (SD)		1.27 (0.59)	1.29 (0.63)	0.02 (0.41)
				Mean FIB-4 for subjects without improvement, (SD)		1.44 (0.72)	1.61 (0.82)	0.16 (0.54)
				Median APRI score, (min, max)		0.470 (0.20, 3.12)	0.539 (0.15, 3.45)	0.024 (–1.30, 1.49)
				Mean APRI for subjects with improvement, (SD)		0.52 (0.29)	0.57 (0.49)	0.05 (0.41)
				Mean APRI for subjects without improvement, (SD)		0.61 (0.43)	0.72 (0.50)	0.11 (0.38)
				Median ELF™◊ (min, max)		–0.892 (–2.70, 1.27)	–0.828 (–2.50, 1.08)	0.023 (–1.98, 1.65)
				Mean ELF™ for subjects with improvement, (SD)		–1.06 (0.65)	–1.10 (0.60)	–0.04 (0.66)
				Mean ELF™ for subjects without improvement, (SD)		–0.72 (0.73)	–0.66 (0.76)	0.06 (0.53)
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=5 (4%)	
					F1	*n*=48 (35%)	*n*=42 (31%)	
					F2	*n*=40 (28%)	*n*=34 (25%)	
					F3	*n*=50 (38%)	*n*=50 (37%)	
					F4	*n*=0	*n*=5 (4%)	
				Mean fibrosis score (SD)		2.0 (0.5)	2.1 (0.4)	0.1
				Median NFS score (min, max)		–1.223 (–4.81, 2.46)	–1.190 (–4.27, 2.34)	0.102 (–1.74, 1.37)
				Mean NFS score for subjects with improvement (SD)		–1.26 (1.46)	–1.24 (1.61)	0.02 (0.64)
				Mean NFS score for subjects without improvement (SD)		–1.13 (1.48)	–0.99 (1.41)	0.15 (0.48)
				Median FIB-4 score (min, max)		1.303 (0.40, 4.14)	1.242 (0.36, 5.32)	0.006 (–1.18, 3.11)
				Mean FIB-4 for subjects with improvement, (SD)		1.31 (0.63)	1.17 (0.60)	–0.14 (0.49)

				Mean FIB-4 for subjects without improvement, (SD)		1.55 (0.76)	1.55 (0.76)		0.17 (0.73)
				Median APRI score, (min, max)		0.568 (0.15, 2.26)	0.538 (0.13, 3.71)		–0.031 (–0.82, 3.46)
				Mean APRI for subjects with improvement, (SD)		0.51 (0.26)	0.42 (0.26)		–0.09 (0.26)
				Mean APRI for subjects without improvement, (SD)		0.70 (0.41)	0.81 (0.71)		0.11 (0.61)
				Median ELF™ (Min, max)		–0.893 (–2.20, 1.62)	–1.003 (–2.53, 2.07)		–0.113 (–1.21, 1.60)
				Mean ELF™ for subjects with improvement, (SD)		–1.10 (0.73)	–1.12 (0.68)		–0.02 (0.44)
				Mean ELF™ for subjects without improvement, (SD)		–0.74 (0.73)	–0.81 (0.84)		–0.08 (0.59)
Francque SM et al.[3] (2021)	Phase 2b, double-blind, randomised, placebo-controlled; 24 weeks; *n*=247	Lanifibranor	800mg	Mean fibrosis score (SD)[f j]		2.1±0.8	NR	NR	
				Median ELF™ score[L] (IQR)		NR	NR		-0.19 (-0.35 to -0.04)
				Median FIB-4[h] (IQR)		NR	NR		0 (-0.17 to 0.16)
				Median PRO-C3, ug/l (IQR)		NR	NR		-3.93 (-5.26 to -2.61)
				Mean VCTE reading, kPa (SD)		10.31 (4.73)	NR	-1.70 (3.23)	
			1200mg	Mean fibrosis score (SD)[f j]		2.1±0.8	NR	NR	
				Median ELF™ score[L] (IQR)		NR	NR		0.11 (-0.04 to 0.26)
				Median FIB-4[h] (IQR)		NR	NR		0.03 (-0.13 to 0.19)
				Median PRO-C3, ug/l (IQR)		NR	NR		-1.79 (-3.07 to -0.52)
				Mean VCTE reading, kPa (SD)		9.99 (5.46)	NR	-1.01 (3.88)	
			Placebo	Mean fibrosis score (SD)[f j]		2.0±0.8	NR	NR	
				Median ELF™ score[L] (IQR)		NR	NR		-0.08 (-0.23 to 0.06)
				Median FIB-4[h] (IQR)		NR	NR		0.03 (-0.19 to 0.13)
				Median PRO-C3, ug/l (IQR)		NR	NR		-1.01 (-2.30 to 0.28)
				Mean VCTE reading, kPa (SD)		9.96 (4.89)	NR	-0.66 (3.04)	
Harrison et al.[4] (2020)	Phase 2b,double-blind, randomised, placebo-controlled; 52 weeks; *n*=392	MSDC-0602K	62.5mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	NR		Follow-up data was not recorded in the supplementary information. In the report the following information was provided regarding the performance of noninvasive biomarkers: The average effect of the combined highest doses relative to placebo on ELF™, FIB-4, FibroTest®, and CK-18 was a reduction of 0.21 (95% CI −0.39 to −0.03) SDs at 6 months and 0.17 (95% CI −0.37 to 0.02) SDs at 12 months.
					F1	*n*=37 (37.4%)	NR		
					F2	*n*=16 (16.2%)	NR		
					F3	*n*=47 (46.5%)	NR		
					F4	*n*=0	NR		
				Mean fibrosis stage[a] (SD)		2.12 (0.59)	NR	0.1	
				Mean APRI score (SD)		0.581 (0.3253)	NR		
				Mean ELF™ score (SD)		9.83 (0.986)	NR		
				Mean FIB-4 score (SD)		1.54 (0.686)	NR		
				Mean FibroTest® (SD)		0.31 (0.226)	NR		
			125mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	NR		
					F1	*n*=37 (36.7%)	NR		
					F2	*n*=16 (16.3%)	NR		
					F3	*n*=47 (45.9%)	NR		
					F4	*n*=0	NR		
				Mean fibrosis stage[a] (SD)		2.14 (0.59)	NR	-0.1	
				Mean APRI score (SD)		0.516 (0.2331)	NR		
				Mean ELF™ score (SD)		9.74 (0.953)	NR		
				Mean FIB-4 score (SD)		1.49 (0.755)	NR		

				Mean FibroTest® (SD)		0.31 (0.204)	NR		
			250mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	NR		
					F1	*n*=40 (40.6%)	NR		
					F2	*n*=16 (15.8%)	NR		
					F3	*n*=44 (43.6%)	NR		
					F4	*n*=0	NR		
				Mean fibrosis stage[a] (SD)		2.10 (0.53)	NR	-0.1	
				Mean APRI score (SD)		0.604 (0.4385)	NR		
				Mean ELF™ score (SD)		9.80 (1.052)	NR		
				Mean FIB-4 score (SD)		1.58 (0.909)	NR		
				Mean FibroTest® (SD)		0.33 (0.192)	NR		
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	NR		
					F1	*n*=36 (38.3%)	NR		
					F2	*n*=15 (16.0%)	NR		
					F3	*n*=43 (45.7%)	NR		
					F4	*n*=0	NR		
				Mean fibrosis stage[a] (SD)		2.2 (0.6)	NR	0.1	
				Mean APRI score (SD)		0.540 (0.2896)	NR		
				Mean ELF™ score (SD)		9.6 (0.850)	NR		
				Mean FIB-4 score (SD)		1.38 (0.688)	NR		
				Mean FibroTest® (SD)		0.31 (0.197)	NR		
Armstrong MJ et al.[5] (2016)	Phase 2, double-blind, randomised, placebo-controlled; 48 weeks; *n*=52	Liraglutide	1.8mg	Biopsy confirmed fibrosis stages using Kleiner scoring system:	F0-F2	*n*=14 (54%)	NR		
					F3-F4	*n*=12 (46%)	NR		
				Mean fibrosis stage (SD)		2.3 (0.9)	NR	-0.2 (0.8)	
				Mean ELF™ score (SD)		9.3 (SD)			-0.3 (0.8)
			Placebo	Biopsy confirmed fibrosis stages using Kleiner scoring system:	F0-F2	*n*=11 (42%)	NR		
					F3-F4	*n*=15 (58%)	NR		
				Mean fibrosis stage (SD)		2.3 (1.3)	NR	0.2 (1.0)	
				Mean ELF™ score (SD)		9.4 (1.3)			0.1 (0.8)
Chalasani N et al.[6] (2020)	Phase 2b, double-blind, randomised, placebo-controlled; 52 weeks; *n*=162	Belapectin	2mg/kg	Biopsy confirmed cirrhosis using Ishak scoring system:	F3	0	*n*=15[m] (31.5%)		
					F4	*n*=54 (100%)	*n*=31[m] (68.5%)		
				Mean fibrosis stage[a] (SD)		4.0[d]	3.7[a] (1.2)	-0.3[d]	
				Mean ELF™ score (SD)		10.73 (1.26)	NR		0.49 (0.83)
				Mean Fibrotest® score (SD)					0.02 (0.02)
				Mean VCTE reading, kPa (SD)		32.4 (17.7)	NR		-1.3 (12.5)
			8mg/kg	Biopsy confirmed cirrhosis using Ishak scoring system:	F3	*n*=0	*n*=10[m] (24.1%)		
					F4	*n*=54 (100%)	*n*=31[m] (75.9%)		
				Mean fibrosis stage[a] (SD)		4.0[d]	3.75[a] (1.3)	-0.25[d]	
				Mean ELF™ score (SD)		10.64 (1.16)			0.50 (0.78)
				Mean Fibrotest® score (SD)					0.01 (0.02)
				Mean VCTE reading, kPa (SD)		29.3 (14.9)			-2.34 (10.8)
			Placebo		F3	*n*=0	*n*=12[m] (1.3)		

				Biopsy confirmed cirrhosis using Ishak scoring system:	F4	*n*=54 (100%)	*n*=33[m] (74.1%)		
				Mean fibrosis stage[a] (SD)		4.0[d]	3.7[a] (1.3)	-0.3[d]	
				Mean ELF™ score (SD)		10.81 (1.1)	NR		0.37 (0.63)
				Mean Fibrotest®score (SD)		NR	NR		0.03 (0.02)
				Mean VCTE reading, kPa (SD)		29.9 (17.8)	NR		-0.47 (18.6)
Harrison SA et al.[7] (2021)	Phase 2, double blind, randomised, placebo-controlled; 24 weeks; *n*=78	Aldafermin	1mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F2 F3	*n*=29 (55%) *n*=24 (45%)	NR NR		
				Mean fibrosis stage (SD)		2.5[a] (0.7)	NR	NR[N]	
				Mean ELF™ score (SD)		9.8 (0.8)	NR		-0.2 (0.5)
				Mean PRO-C3 score, ug/l (SD)		17.5 (8.4)	NR		-5.4 (6.2)
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F2 F3	*n*=15 (60%) *n*=10 (40%)	NR NR		
				Mean fibrosis stage[a] (SD)		2.4 (0.7)	NR	NR[N]	
				Mean ELF™ score (SD)		9.9 (1.0)	NR		0 (0.6)
				Mean PRO-C3 score, ug/l (SD)		17.1 (7.0)	NR		-1.2 (6.2)
Harrison SA et al.[8] (2021)	Phase 2a, double blind, randomised, placebo-controlled; 12 weeks; *n*=80	Efruxifermin	28mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F1 F2 F3	*n*=7 (37%) *n*=7 (37%) *n*=5 (26%)	NR NR NR		
				Mean fibrosis stage[a] (SD)		1.9 (0.4)	NR	NR[N]	
				Mean ELF™ score (SD)		9.5 (0.6)	NR		8.8[d o]
				Mean PRO-C3 score, ug/l (SD)		19.2 (10.7)	NR		12.0[d o]
			50mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F1 F2 F3	*n*=7 (35%) *n*=8 (40%) *n*=5 (25%)	NR NR NR	NR[N]	
				Mean fibrosis stage[a] (SD)		1.9 (0.4)	NR		
				Mean ELF™ score (SD)		9.5 (0.9)	NR		8.8[d o]
				Mean PRO-C3 score, ug/l (SD)		16.2 (5.8)	NR		11.0[d o]
			70mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F1 F2 F3	*n*=7 (35%) *n*=6 (30%) *n*=7 (35%)	NR NR NR	NR[N]	
				Mean fibrosis stage[a] (SD)		2.0 (0.4)	NR		
				Mean ELF™ score (SD)		9.5 (0.8)	NR		9.3[d o]
				Mean PRO-C3 score, ug/l (SD)		17.2 (5.9)	NR		10.0[d o]
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F1 F2 F3	*n*=8 (38%) *n*=5 (24%) *n*=8 (38%)	NR NR NR	NR[N]	
				Mean fibrosis stage[a] (SD)		2.0 (0.5)	NR		
				Mean ELF™ score (SD)		9.5 (1.0)	NR		9.5[d o]
				Mean PRO-C3 score, ug/l (SD)		16.1 (6.7)	NR		15.0[d o]
	Phase 2b, double blind, randomised,	Cilofexor Firsocostat	Selonsertib 18mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2 F3	*n*=0 *n*=18 (46%)	Study arm discontinued		

Loomba R et al.[9] (2021)	placebo-controlled; 48 weeks; *n*=392	and Selonsertib			F4	*n*=21 (54%)			
				Median ELF™ score (IQR)		9.6 (8.9, 11.4)			
				Median VCTE reading, kPa (IQR)		16.3 (12.3, 23.2)			
			Firsocostat 20mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2	*n*=2 (5%)	NR	Data not available to calculate change	
					F3	*n*=16 (40%)	NR		
					F4	*n*=22 (55%)	NR		
				Median ELF™ score (IQR)		10.2 (9.7, 10.6)	NR		-0.1 (-0.4, 0.1)
				Median VCTE reading, kPa (IQR)		17.1 (13.2, 22.2)	NR		-6.3 (-9.6, -3.0)
			Cilofexor 30mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2	*n*=1 (3%)	NR	Data not available to calculate change	
					F3	*n*=17 (43%)	NR		
					F4	*n*=22 (55%)	NR		
				Median ELF™ score (IQR)		10.1 (9.7, 10.7)	NR		0.2 (-0.1, 0.4)
				Median VCTE reading, kPa (IQR)		16.0 (12.8, 21.7)	NR		-4.3 (-7.5, -1.0)
			Firsocostat 20mg Selonsertib 18mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2	*n*=1 (1%)	NR	Data not available to calculate change	
					F3	*n*=32 (42%)	NR		
					F4	*n*=46 (58%)	NR		
				Median ELF™ score (IQR)		10.0 (9.4, 10.9)	NR		0.1 (-0.1, 0.20)
				Median VCTE reading, kPa (IQR)		16.5 (11.0, 25.1)	NR		-2.4 (-4.7, -2.0)
			Cilofexor 30mg Selonsertib 18mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2	*n*=2 (3%)	NR	Data not available to calculate change	
					F3	*n*=29 (38%)	NR		
					F4	*n*=46 (60%)	NR		
				Median ELF™ score (IQR)		10.1 (9.6, 10.8)	NR		0.1 (-0.1, 0.30
				Median VCTE reading, kPa (IQR)		14.9 (10.2, 20.6)	NR		-3.1 (-5.5, -0.7)
			Cilofexor 30mg Firsocostat 20mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2	*n*=2 (3%)	NR	Data not available to calculate change	
					F3	*n*=34 (44%)	NR		
					F4	*n*=42 (54%)	NR		
				Median ELF™ score (IQR)		10.0 (9.4, 10.7)	NR		-0.0 (-0.2, 0.20)
				Median VCTE reading, kPa (IQR)		15.7 (10.9, 22.2)	NR		-4.2 (-6.5, -1.9)
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0-F2	*n*=0	NR	Data not available to calculate change	
					F3	*n*=17 (44%)	NR		
					F4	*n*=22 (56%)	NR		
				Median ELF™ score (IQR)		10.1 (9.2, 11.0)	NR		0.3 (0.1, 0.6)
				Median VCTE reading, kPa (IQR)		17.1 (14.3, 23.2)	NR		-1.2 (-4.1, 1.8)
Harrison SA et al.[10] (2019)	Phase 2, double blind, randomised, placebo-controlled; 36 weeks; *n*=125	Resmetriom	80mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=1 (1%)	NR	Reported as Fibrosis responder = 28.8%	
					F1	*n*=47 (56%)	NR		
					F2	*n*=18 (21%)	NR		
					F3	*n*=18 (21%)	NR		
					F4	*n*=0	NR		
				Mean fibrosis stage[a] (SD)		1.6 (0.3)	NR		
				Mean ELF™ score (SD)		9.2 (0.9)	NR		-0.38[Q] (0.09)
				Mean PRO-C3 score, ug/l (SD)		17.8 (10.3)	NR		-2.2[T] (2.1); -6.5[U] (3.5)
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=2 (5%)		Reported as Fibrosis	
					F1	*n*=19 (46%)			

					F2	*n*=13 (32%)		responders = 16.7%	
					F3	*n*=7 (17%)			
					F4	*n*=0			
				Mean fibrosis stage[a] (SD)		1.6 (0.3)			
				Mean ELF™ score (SD)		9.2 (1.0)			0.02[P] (0.12)
				Mean PRO-C3 score, ug/l (SD)		16.2 (59.0)			7.4[R] (3.1); 14.9[S] (5.6)
Ratziu V et al.[11] (2016)	Phase 2, double blind, randomised, placebo-controlled; 52 weeks; *n*=276	Elafibranor	80mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=20 (21.5%)		Data not available to calculate change	
					F1	*n*=28 (30.1%)			
					F2	*n*=22 (23.7%)			
					F3[V]	*n*=23 (24.7%)			
					F4	*n*=0			
				Mean fibrosis stage (SD)		1.5 (1.1)			
				Mean NFS score (SD)		NR	NR		
				Mean Fibrotest® (SD)		NR	NR		
			120mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=5 (5.6%)		Mean change: Responders = -0.7[d] Non-responders = 0.25[d]	
					F1	*n*=39 (43.8%)			
					F2	*n*=25 (28.1%)			
					F3[V]	*n*=20 (22.5%)			
					F4	*n*=0			
				Mean fibrosis stage (SD)		1.7 (0.9)			
				Mean NFS score (SD)		NR	NR		-0.25[d]
				Mean Fibrotest® (SD)		NR	NR		-0.07[d]
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=15 (16.3%)		Data not available to calculate change	
					F1	*n*=32 (34.8%)			
					F2	*n*=25 (27.2%)			
					F3[V]	*n*=20 (21.7%)			
					F4	*n*=0			
				Mean fibrosis stage (SD)		1.5 (1.0)			
				Mean NFS score (SD)		NR	NR		-0.01[d]
				Mean Fibrotest® (SD)		NR	NR		-0.01[d]
Harrison SA et al.[12] (2020)	Phase III (STELLAR-4), double blind, randomised, placebo-controlled; 48 weeks; *n*=877	Selonsertib	6mg	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=1 (0.3%)		
					F1	*n*=0	*n*=1 (0.3%)		
					F2	*n*=0	*n*=2 (0.6%)		
					F3	*n*=0	*n*=55 (15.7%)		
					F4	*n*=351 (100%)	*n*=292 (83.2%)		
				Mean fibrosis stage[a] (SD)		4.0 (1.8)	3.8 (1.4)		
				Median ELF™ score (IQR)		10. 64 (10.01-11.34)	10.84 (10.08-11.52)		-0.2[d]
				Median Fibrotest® (IQR)		0.58 (0.41-0.73)	0.58 (0.39-0.73)		NC
				Median APRI score (IQR)		0.8 (0.5-1.3)	0.8 (0.5-1.3)		NC
				Median FIB-4 score (IQR)		2.48 (1.74-3.65)	2.58 (1.65-3.99)		0.10[d]
				Median NFS score (IQR)		0.629 (-0.215-1.629)	0.984 (-0.031-1.814)		0.355[d]
				Median VCTE reading, kPa (IQR)		21.30 (14.0-29.8)	20.40 (13.9-29.8)		-0.9[d]
			18mg		F0	*n*=0	*n*=0		

				Biopsy confirmed fibrosis using NASH CRN criteria:	F1	*n*=0	*n*=2 (0.6%)	
					F2	*n*=0	*n*=1 (0.3%)	
					F3	*n*=0	*n*=64 (18.1%)	
					F4	*n*=354 (100%)	*n*=281 (81.1%)	
				Mean fibrosis stage[a] (SD)		4.0 (1.8)	3.7 (1.4)	-0.3[d]
				Median ELF™ score (IQR)		10.61 (10.04-11.34)	10.73 (10.07-10.51)	0.10[d]
				Median Fibrotest® (IQR)		0.58 (0.44-0.73)	0.58 (0.40-0.75)	NC
				Median APRI score (IQR)		0.8 (0.6-1.2)	0.8 (0.5-1.3)	NC
				Median FIB-4 score (IQR)		2.55 (1.76-3.62)	2.65 (1.74-3.76)	0.10[d]
				Median NFS score (IQR)		0.659 (-0.119-1.472)	0.816 (0.031-1.574)	0.157[d]
				Median VCTE reading, kPa (IQR)		21.10 (14.7-28.8)	19.4 (14.3-27.3)	-1.7[d]
			Placebo	Biopsy confirmed fibrosis using NASH CRN criteria:	F0	*n*=0	*n*=0	
					F1	*n*=0	*n*=0	
					F2	*n*=0	*n*=0	
					F3	*n*=1 (0.6%)	*n*=27 (15.7%)	
					F4	*n*=171 (99.4%)	*n*=145 (84.3%)	
				Mean fibrosis stage[a] (SD)		3.7 (1.4)	3.8 (1.5)	0.10[d]
				Median ELF™ score (IQR)		10.67(10.05-11.16)	10.66 (10.14-11.26)	-0.01[d]
				Median Fibrotest® (IQR)		0.59 (0.40-0.77)	0.57 (0.39-0.73)	-0.02[d]
				Median APRI score (IQR)		0.8 (0.6-1.2)	0.7 (0.5-1.2)	-0.1[d]
				Median FIB-4 score (IQR)		2.50 (1.81-3.66)	2.50 (1.65-3.67)	NC
				Median NFS score (IQR)		0.682 (-0.304-1.450)	0.774 (-0.241-1.595)	0.092[d]
				Median VCTE reading, kPa (IQR)		20.00 (14.4-26.7)	19.30 (13.8-26.7)	0.70[d]
Loomba R et al.[13] (2018)	Phase 2, double blind, randomised, *de facto* placebo-controlled; 24 weeks; *n*=72	Selonsertib ±Simtuzumab	Selonsertib 6mg ±Simtuzumab	Biopsy confirmed F3 using NASH CRN criteria		*n*=20 (67%)	Improvement *n*=8 (30%) Cirrhosis *n*=2 (7%)	
				Median ELF™ score (IQR)		NR	NR	-0.07 (-0.46-0.36)
				Median Fibrotest® (IQR)		NR	NR	0.02 (-0.03-0.08)
				Median VCTE reading, kPa (IQR)		NR	NR	-0.80 (-1.90-2.30)
			Selonsertib 18mg ±Simtuzumab	Biopsy confirmed F3 using NASH CRN criteria		*n*=21 (66%)	Improvement *n*=13 (43%) Cirrhosis *n*=1 (3%)	
				Median ELF™ score (IQR)		NR	NR	0.02 (-0.34-0.52)
				Median Fibrotest® (IQR)		NR	NR	-0.01 (-0.03-0.03)
				Median VCTE reading, kPa (IQR)		NR	NR	0.2 (-3.50 – 1.40)
			Simtuzumab	Biopsy confirmed F3 using NASH CRN criteria		*n*=6 (60%)	Improvement *n*=2 (20%) Cirrhosis *n*=2 (20%)	
				Median ELF™ score (IQR)		NR	NR	-0.13 (-0.35-0.05)
				Median Fibrotest® (IQR)		NR	NR	0.01 (-0.04-0.05)
				Median VCTE reading, kPa (IQR)		NR	NR	-0.50 (-3.80-3.4)
Ratzui V et al.[14] (2020)	Phase 2b, double blinde, randomised, placebo-controlled; 52 weeks; *n*=247	Aramachol	400mg	Biopsy confirmed fibrosis using NASH CRN staging system	F2	18.8%	NR	
					F3	45.7%	NR	
				FIB-4 change from baseline to week 52		NR	NR	−0.05 ± 0.06

	NFS change from baseline to week 52		NR	NR	−0.12 ± 0.08
600mg	Biopsy confirmed fibrosis using NASH CRN staging system	F2 F3	22.4% 36.7%		
	FIB-4 change from baseline to week 52		NR	NR	−0.10 ± 0.06
	NFS change from baseline to week 52		NR	NR	−0.04 ± 0.08
Placebo	Biopsy confirmed fibrosis using NASH CRN staging system	F2 F3	16.7% 33.3%		
	FIB-4 change from baseline to week 52		NR	NR	-0.12 ± 0.08
	NFS change from baseline to week 52		NR	NR	0.23 ± 0.11

NR, not reported; kPa, kilopascal; ug/l, micrograms per litre; mg, milligram; NC, no change; ELF™, enhanced liver fibrosis; FIB-4, fibrosis-4; NFS, NAFLD fibrosis score; APRI, aspartate transaminase to platelet ratio index; PRO-C3, Type III collagen marker of the N-terminal pro-peptide; SD, standard deviation; IQR, interquartile range; VCTE, vibration controlled transient elastography; [◊]Data for baseline, follow-up and change in ELF™ score taken from Table S6, supplementary information;[2] [a]Mean not provided, calculation made using data provided in the manuscript tables and supplementary information; [b]Manufacturers published cut off thresholds for fibrosis;[14] [c]Biopsy validated cut-off thresholds for fibrosis;[3] [d]No standard deviation/IQR reported; [e]Change in biomarker score is the change reported in the research paper and not the exact difference between baseline and follow-up; [f]Plus-minus values are means ±SD; [g]Plus-minus values are geometric means ±coefficient of variation; [h]An ELF™ score greater than 9.8 indicates a moderate risk of advanced fibrosis, and a score of greater than 11.3 denotes a high risk of advanced fibrosis; [i]No geometric means ±coefficient of variation reported; [j]Fibrosis stage was classified according to the SAF-NASH CRN staging system; [k]A Fibrosis-4 index score of less than 1.45 indicates low probability of stage F3 or F4 fibrosis, and a score greater than 3.25 indicates a high probability of stage F3 or F4 fibrosis; [L]An ELF™ score of less than 7.7 indicates none to mild fibrosis, and a score of 11.3 or greater indicates cirrhosis; [M]*n* value is approximate and was calculated from the % improvement recorded in Table 4 of the manuscript;[6] [N]improvement/no improvement or worsening reported, unable to calculate changes in fibrosis stage as data is not provided; [O]Estimated values only, exact values not recorded, data taken from manuscript[8] Figure 3, (f) and (g); [P]Mean difference reported for subjects with ELF™≥9.0 only (*n*=21) at week 12; [Q]Mean difference reported for subjects with ELF™≥9.0 only (*n*=40) at week 12; [R]Mean difference reported for subjects with Baseline ≥10.00 ng/ml (*n*=25); [S]Mean difference reported for subjects with Baseline ≥17.50 ng/ml (*n*=12); [T]Mean difference reported for subjects with Baseline ≥10.00 ng/ml (*n*=53); [U]Mean difference reported for subjects with Baseline ≥17.50 ng/ml (*n*=29); [v]Bridging fibrosis.

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