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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	Study	Noninvasive biomarkers used	Fibrosis changes reported by study	Brief summary	Included for review in Table 3
Alderfermin	Harrison 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 et al.[2] (2018)	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 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 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 et al.[5] (2021)	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

Supplementary Table 1. Continued

Drug	Study	Noninvasive biomarkers used	Fibrosis changes reported by study	Brief summary	Included for review in Table 3
Efruxifermin	Harrison 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	Ratziu 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 et al.[8] (2020)	Follow-up paper from Ratziu et al.[7] above	Elafibranor did not meet the key secondary endpoint of fibrosis improvement.	Conference report only.	No
Emricasan	Harrison et al.[9] (2020)		Emricasan did not improve liver histology.	Noninvasive biomarkers not used (ALT and AST only)	No
Lanifibranor	Francque 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 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 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 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

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Supplementary Table 1. Continued

Drug	Study	Noninvasive biomarkers used	Fibrosis changes reported by study	Brief summary	Included for review in Table 3
Obeticholic acid	Younossi et al.[14] (2019)		Obeticholic acid significantly improved fibrosis.	Noninvasive biomarkers not used (ALT and AST only).	No
Pioglitazone	Sanyal et al.[15] (2010)		Fibrosis scores were not significantly improved.	Noninvasive biomarkers not used.	No
Pioglitazone	Cusi et al.[16] (2016)		Pioglitazone treatment was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, -0.5 [95% CI, -0.9 to 0.0]; P=0.039).	Noninvasive biomarkers not used.	No
Resmetirom	Harrison 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 an accurate representation to the changes in liver observed in histopathology.	Yes
Seladelpar	Harrison et al.[18] (2020)		No significant decrease in fibrosis	Conference report and poster presentation only.	No
Selonsertib	Loomba 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 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 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

NAFLD, non-alcoholic fatty liver disease; ELF™, enhanced liver fibrosis; FIB-4, fibrosis-4; PRO-C3, Type III collagen marker of the N-terminal pro-peptide; NFS, NAFLD fibrosis score; VCTE, vibration controlled transient elastography; APRI, aspartate transaminase to platelet ratio index; NASH, nonalcoholic steohepatitis; AST, aspartate transaminase; ALT, alanine transaminase; CI, confidence interval.

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