Appendix 1. Search strategy

PubMed:

(("efruxifermin"[tiab] OR "AKR-001"[tiab] OR "AMG-876"[tiab] OR "EFX"[tiab])

AND

("metabolic dysfunction-associated fatty liver disease"[tiab] OR "nonalcoholic fatty liver disease"[tiab] OR "fatty liver"[tiab] OR "metabolic dysfunction-associated steatohepatitis"[tiab] OR "nonalcoholic steatohepatitis"[tiab] OR "NAFLD"[tiab] OR "MAFLD"[tiab] OR "MASLD"[tiab] OR "NASH"[tiab] OR "MASH"[tiab] OR "cirrhosis"[tiab]))

Scopus:

(TITLE-ABS ("efruxifermin" OR "AKR-001" OR "AMG-876" OR "EFX")) AND (TITLE-ABS ("metabolic dysfunction-associated fatty liver disease" OR "nonalcoholic fatty liver disease" OR "fatty liver" OR "metabolic dysfunction-associated steatohepatitis" OR "nonalcoholic steatohepatitis" OR "NAFLD" OR "MAFLD" OR "MASLD" OR "NASH" OR "MASH" OR "cirrhosis"))

Embase:

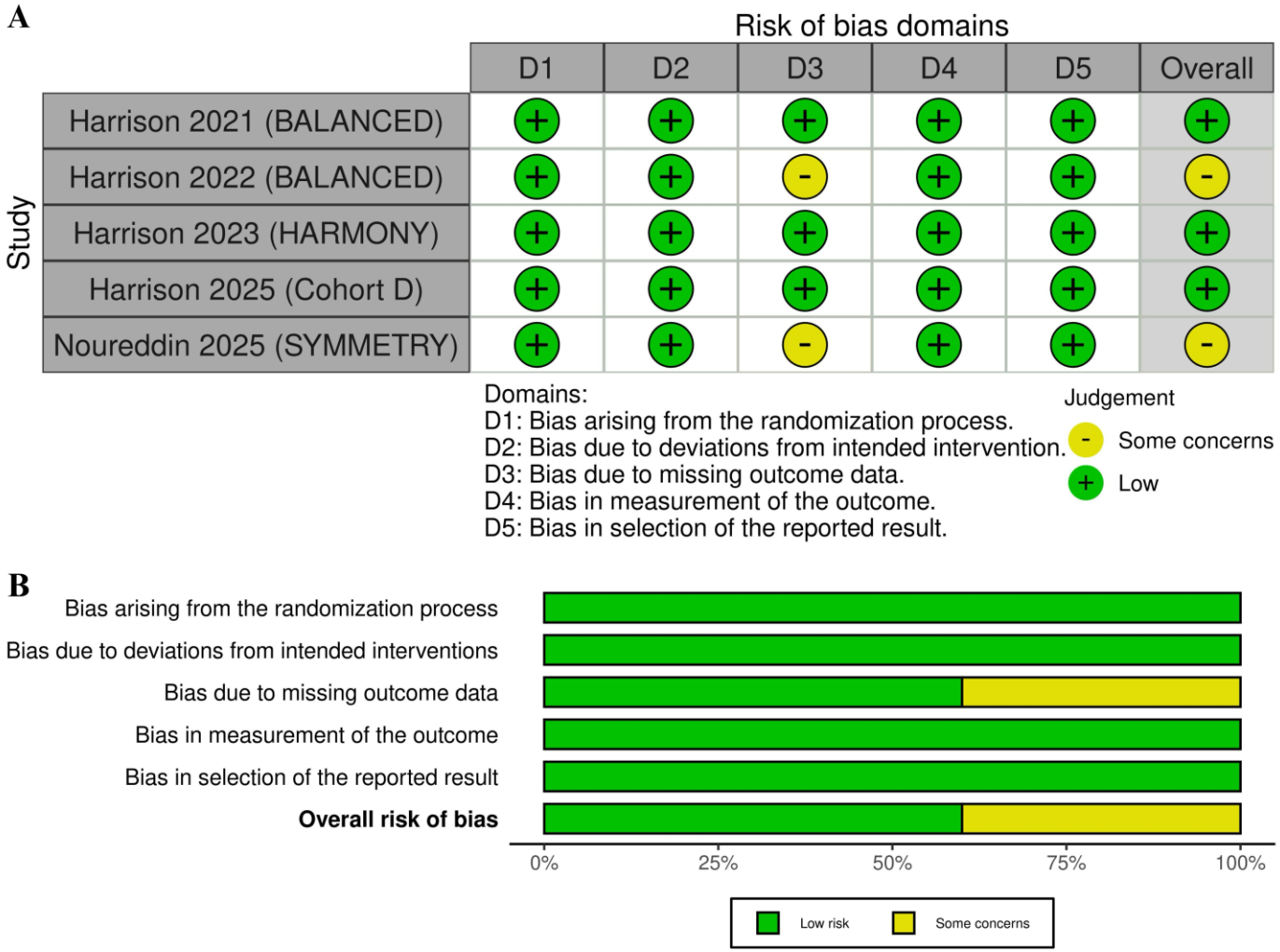
(('efruxifermin':ti,ab OR 'AKR-001':ti,ab OR 'AMG-876':ti,ab OR 'EFX':ti,ab) AND ('metabolic dysfunction-associated fatty liver disease':ti,ab OR 'nonalcoholic fatty liver disease':ti,ab OR 'fatty liver':ti,ab OR 'metabolic dysfunction-associated steatohepatitis':ti,ab OR 'nonalcoholic steatohepatitis':ti,ab OR 'NAFLD':ti,ab OR 'MAFLD':ti,ab OR 'MASLD':ti,ab OR 'NASH':ti,ab OR 'MASH':ti,ab OR 'cirrhosis':ti,ab))

Supplementary Table S1. Summary of the excluded studies

Authors, Publication year [References]	**Reason for exclusion**	**Study design**	**Summary of outcomes**
Tillman et al., 2021 [9]	Animal study	• Study subjects: Male and female Sprague Dawley rats • Sample size: 160 (80 male and 80 female) • Intervention: EFX was administered weekly for 4 or 26 weeks.	• Efruxifermin significantly reduced body weight gain after 4 and 26 weeks, despite increasing food intake. • Changes in tissue pathology, clinical chemistry and serum biomarkers generally appeared to be associated with weight loss, except for a significant decrease in urine volume in both males and females without perturbed electrolyte balance. • Markers of sympathetic activation, urinary corticosterone and ratio of adrenal-to-body weight were unchanged.
Kaufman et al., 2021 [26]	Phase 1, Pharmacodynamic study	• Study subjects: Adults (18-65 years) with T2D with BMI of 25.0-40.0 kg/m^2, HbA1c 6.5%–10%, and fasting C-peptide ≥0.8 ng/mL • Sample size: 69 • Intervention: Study subjects were randomized to receive AKR-001 (EFX) or a placebo at a ratio of 3:1. AKR-001 (7, 21,70, or 140 mg) was administered s.c. Q2W or QW for 4 weeks.	• With a half-life of 3-3.5 days, the peak-to-trough ratio under steady-state conditions is approximately 2 following QW dosing. AKR-001 appears to demonstrate pharmacodynamic effects on serum markers of insulin sensitivity and acceptable tolerability up to and including 70 mg QW. • Positive trends in lipoprotein profile, including TG, non-HDL-C, HDL-C, and apolipoproteins B and C3 are consistent with other FGF-21 analogs.

BMI, Body mass index; EFX, Efruxifermin; HbA1c, Glycated hemoglobin; T2D, HDL-C, High-density lipoprotein cholesterol; QW; Once weekly; Q2W, Once every 2 weeks; Type 2 diabetes.

Supplementary Figure S1. A. Risk of bias summary: Review authors' judgments about each risk of bias item for each included study using RoB2; B. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.



Supplementary Table S2. Leave-one-out sensitivity analysis for the main outcomes with high heterogeneity in the meta-analysis

Variable	EFX dose	Study omitted	MD [95% CI]	P	I^2 (%)
ALT (U/L)	28 mg	Harrison 2021 (BALANCED)	-11.45 [-26.64, 3.74]	0.14	83
		Harrison 2023 (HARMONY)	-15.04 [-36.85, 6.77]	0.18	94
		Noureddin 2025 (SYMMETRY)	-23.28 [-29.76, -16.80]	<0.00001	31
	50 mg	Harrison 2021 (BALANCED)	-12.92 [-22.91, -2.92]	0.01	86
		Harrison 2022 (BALANCED)	-18.97 [-33.04, -4.90]	0.008	93
		Harrison 2023 (HARMONY)	-13.79 [-26.50, -1.08]	0.03	93
		Harrison 2025 (Cohort D)	-18.92 [-32.91, -4.93]	0.008	93
		Noureddin 2025 (SYMMETRY)	-19.97 [-32.77, -7.16]	0.002	93
AST (U/L)	50 mg	Harrison 2021 (BALANCED)	-12.26 [-19.09, -5.44]	0.005	86
		Harrison 2022 (BALANCED)	-15.51 [-24.18, -6.84]	0.0005	88
		Harrison 2023 (HARMONY)	10.45 [-17.64, -3.27]	0.004	86
		Harrison 2025 (Cohort D)	-15.11 [-24.47, -5.76]	0.002	90
		Noureddin 2025 (SYMMETRY)	-14.29 [-23.59, -4.99]	0.003	91
ALP (U/L)	28 mg	Harrison 2021 (BALANCED)	1.78 [-7.12, 10.67]	0.70	67
		Harrison 2023 (HARMONY)	-1.44 [-16.53, 13.65]	0.85	92
		Noureddin 2025 (SYMMETRY)	-6.09 [-12.15, -0.02]	0.05	71
GGT (U/L)	28 mg	Harrison 2021 (BALANCED)	-11.45 [-26.64, 3.74]	0.14	83
		Harrison 2023 (HARMONY)	-15.04 [-36.85, 6.77]	0.18	94
		Noureddin 2025 (SYMMETRY)	-23.28 [-29.76, -16.80]	<0.00001	31
	50 mg	Harrison 2021 (BALANCED)	-15.26 [-25.33, -5.20]	0.01	86
		Harrison 2022 (BALANCED)	-18.97 [-33.04, -4.90]	0.008	93
		Harrison 2023 (HARMONY)	-13.79 [-26.50, -1.08]	0.03	93
		Harrison 2025 (Cohort D)	-18.92 [-32.91, -4.93]	0.008	93
		Noureddin 2025 (SYMMETRY)	-19.97 [-32.77, -7.16]	0.002	93

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; CI, Confidence interval; GGT, Gamma-glutamyl transferase; MD, Mean difference