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Safety and efficacy of oral non-peptide GLP-1 receptor agonist in non-diabetic obese patients; systematic review and meta-analysis of randomized controlled trials

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Abbreviations

GLP-1 RAs– glucagon-like peptide-1 receptor agonists

RCT–Randomized Controlled Trial

PRISMA–Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RoB–Risk of Bias

RR–Risk Ratio

MD–Mean Difference

CI–Confidence Interval

PICO–Population, Intervention, Comparison, Outcome

BMI–Body Mass Index

ABSTRACT

Background

Oral glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been developed as a needle-free alternative of subcutaneous injectables GLP-1 RAs. This systematic review and meta-analysis evaluated whether oral GLP-1 receptor agonists improve body weight and metabolic outcomes, and characterized their safety and tolerability, compared with placebo in adults with obesity or overweight.

Methods

PubMed, Embase, the Cochrane Library, Scopus, and ClinicalTrials.gov were systematically searched for randomized controlled trials comparing oral GLP-1 receptor agonists with placebo in adults with obesity or overweight without diabetes. Study selection followed Cochrane handbook guidelines and PRISMA checklist 2020, and quality was assessed using the Cochrane RoB 2 tool. Analysis was done using random-effects models in R version 4.5.2 (meta package). Certainty of evidence was assessed using the GRADE framework.

Results

Six randomized controlled trials comprising 31 treatment arms of five oral GLP-1 receptor agonists (danuglipron, elecoglipron, lotiglipron, orforglipron, and aleniglipron) versus placebo were included, spanning phase 2 to phase 3 designs of 26 to 72 weeks. Four trials had a low risk of bias, one raised some concerns, and one had a high risk. Oral GLP-1 receptor agonists significantly reduced body weight from baseline compared with placebo (MD −7.61%, 95% CI −8.59 to −6.62; $p<0.0001$; $I^2=74.0\%$), an effect that remained stable on leave-one-out sensitivity analysis and differed significantly by drug, escalation intensity, and placebo run-in. Significant reductions were also observed for alanine aminotransferase (MD −9.53 U/L, 95% CI −11.88 to −7.18; $p<0.0001$; $I^2=0\%$), aspartate aminotransferase (MD −5.48 U/L, 95% CI −6.99 to −3.97; $p<0.0001$; $I^2=0\%$), systolic blood pressure (MD −5.49 mmHg, 95% CI −6.17 to −4.82; $p<0.0001$; $I^2=0\%$), and diastolic blood pressure (MD −1.54 mmHg, 95% CI −1.99 to −1.09; $p<0.0001$; $I^2=8.6\%$). However, oral GLP-1 receptor agonists were associated with an

increased risk of any adverse event (RR 1.07, 95% CI 1.04–1.11; p<0.0001), treatment discontinuation due to adverse events (RR 2.85, 95% CI 2.07–3.92; p<0.0001), nausea (RR 3.04, 95% CI 2.29–4.04; p<0.0001), vomiting (RR 3.38, 95% CI 2.19–5.21; p<0.0001), constipation (RR 2.48, 95% CI 1.64–3.75; p<0.0001), and gastroesophageal reflux (RR 1.92, 95% CI 1.15–3.19; p=0.0124), with no significant differences in diarrhea, dyspepsia, headache, or fatigue. Heterogeneity was low ($I^2 \leq 8.6\%$) for all outcomes except body weight. GRADE certainty of evidence was high for seven outcomes and moderate for the remaining eight, with no outcome rated below moderate certainty.

Conclusion

Oral GLP-1 receptor agonists significantly reduce body weight and improve liver enzymes and blood pressure compared with placebo in adults with obesity or overweight, but are associated with a higher incidence of gastrointestinal adverse events and treatment discontinuation.

INTRODUCTION

Obesity is a chronic, progressive, and relapsing disease whose prevalence has increased substantially worldwide over recent decades. It is associated with an increased risk of type 2 diabetes, hypertension, cardiovascular disease, fatty liver disease, obstructive sleep apnoea, osteoarthritis, and several cancers, thereby contributing to a decline in both the quality of life and life expectancy [1]. A rising prevalence of childhood obesity specifically imposes a substantial and growing burden on individuals and healthcare systems worldwide [2].

Lifestyle interventions involving dietary modification, physical activity, and behavioural support remain fundamental components of obesity management. However, obesity interventions commonly produce initial weight loss followed by a plateau and progressive weight regain, making long-term weight-loss maintenance particularly challenging [3]. Pharmacological therapy may therefore be required as an adjunct to lifestyle modification in individuals who do not achieve or sustain adequate weight loss through behavioural interventions alone [4].

Glucagon-like peptide-1 receptor agonists have emerged as effective pharmacological treatments for obesity because GLP-1 signalling regulates food intake, gastric emptying, and glucose-dependent insulin secretion [5]. Activation of the GLP-1 receptor reduces appetite and energy intake and delays gastric emptying, thereby supporting clinically meaningful reductions in body weight [5]. Randomized controlled trials have shown that the peptide GLP-1 receptor agonists liraglutide and semaglutide produce significantly greater weight loss than placebo when combined with lifestyle intervention in adults with overweight or obesity [4,6].

Despite their efficacy, established peptide GLP-1 receptor agonists used for obesity have traditionally required subcutaneous administration, which may be undesirable for individuals who prefer oral treatment [4,6]. Oral administration of peptide-based drugs like GLP-1 agonists is challenged by their degradation in the stomach due to low pH and proteolytic enzymes, and

by their limited permeability across the gastrointestinal epithelium [7]. Oral semaglutide addresses these limitations through co-formulation with the absorption enhancer salcaprozate sodium, but its systemic exposure is influenced by water volume and the duration of fasting after administration [7,8].

These limitations have encouraged the development of orally bioavailable, small-molecule non-peptide GLP-1 receptor agonists [9]. Unlike peptide analogues, these compounds are chemically synthesized small molecules that activate the GLP-1 receptor and are being investigated as oral treatments for obesity and type 2 diabetes [9,10]. Danuglipron was among the first oral small-molecule GLP-1 receptor agonists to demonstrate pharmacological activity and reductions in body weight in clinical studies [9]. More recent randomized studies have also evaluated lotiglipron and other investigational small-molecule agonists in populations with obesity, with or without diabetes [11,12].

Orforglipron is an orally administered non-peptide GLP-1 receptor agonist that has been evaluated specifically in adults with obesity or overweight without diabetes. In a phase 2 randomized controlled trial, once-daily orforglipron produced dose-dependent reductions in body weight, body mass index, and waist circumference compared with placebo [10]. The adverse-event profile was broadly consistent with that of the GLP-1 receptor agonist class, with gastrointestinal events occurring most frequently, particularly during dose escalation [10]. Subsequent phase 3 evidence demonstrated significantly greater weight reduction with orforglipron than with placebo after 72 weeks in adults with obesity [12].

Although individual randomized trials have reported promising findings, the evidence varies according to the investigated molecule, dose, treatment duration, participant characteristics, and reported efficacy and safety outcomes. A focused quantitative synthesis is therefore needed to estimate the overall effects of small-molecule non-peptide GLP-1 receptor agonists specifically in obese adults without diabetes and to assess the consistency of findings across available trials.

Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of small-molecule non-peptide GLP-1 receptor agonists in adults with obesity without diabetes. The principal efficacy outcomes included changes in body weight and other anthropometric or cardiometabolic measures, while safety outcomes included overall adverse events, serious adverse events, gastrointestinal adverse events, and treatment discontinuation.

METHODS

Literature search

This systematic review and meta-analysis are conducted and reported in accordance with Cochrane handbook guidelines and PRISMA checklist 2020 respectively. PubMed, Embase, Cochrane CENTRAL, Scopus, and ClinicalTrials.gov were searched from inception to August 1, 2026, we searched the terms for obesity and for oral, non-peptide GLP-1 receptor

agonists (danuglipron, elecoglipron, lotiglipron, orforglipron, aleniglipron; full strategies in the Supplement).

Eligibility criteria

Studies included if (1) randomized controlled trial; (2) evaluating safety and efficacy of oral, non-peptide GLP-1 receptor agonists; (3) in adults (>18 yrs old) with obesity or obesity related comorbidity without diabetes. Studies were excluded if they have (1) injectable agonists; (2) non-randomized designs; (3) pediatric populations; (4) type 1 or 2 diabetic participants; (5) without extractable outcome data.

Study selection and data extraction

Records were screened in Rayyan; primary screening (titles and abstracts) were done independently by A.A.C and A.H on the basis of inclusion and exclusion criteria, and duplicates were resolved by discussion with M.S, and full texts were screened and selected by M.S. Baseline data from all RCTs were extracted by A.H and cross checked by A.R.A, primary and secondary outcome data were extracted by A.R.A and cross checked by T.H.

Risk of Bias

Risk of bias was assessed for each RCT using the Cochrane RoB 2 tool across its five domains (Figures 2–3).

Outcomes

The primary outcome was percentage change in body weight from baseline. Secondary outcomes were change in ALT, AST, systolic and diastolic blood pressure, and the incidence of any adverse event, adverse event–related discontinuation, nausea, vomiting, diarrhea, constipation, dyspepsia, GERD, headache, and fatigue.

Statistical Analysis

All data were pooled using random-effects meta-analysis in R version 4.5.2 (meta package), with use of mean differences (MD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes. Between-study variability (τ^2) was estimated using restricted maximum likelihood (REML). Pooled treatment effects were reported with 95% confidence intervals (CIs) using the standard z-based method. 95% prediction intervals were calculated by Higgins–Thompson–Spiegelhalter method with k−2 degrees of freedom. Statistical heterogeneity between studies was assessed using I^2. For subgroup analyses by drug, mixed-effects models were used. A leave-one-out sensitivity analysis was performed for the primary outcome, and publication bias was assessed with contour-enhanced funnel plots. Certainty of

evidence was rated per outcome using Grading of Recommendations Assessment, Development and Evaluation (Table 2) [13].

RESULTS

Study Selection and Baseline Characteristics

A total of 1645 records were identified through database and register searches of PubMed (n = 180), Embase (n = 318), ClinicalTrials.gov (n = 95), Cochrane (n = 838), and Scopus (n = 214) (**Figure 1**). After 156 duplicates were removed, 1489 records were screened and 1448 were excluded on title and abstract. All 41 reports sought for retrieval were obtained and assessed for eligibility, of which 35 were excluded: 12 for wrong study design and 23 that were ongoing or without published results. Six randomized controlled trials met the inclusion criteria and were included in the meta-analysis [10,11,13–16].

The six trials randomized adults with obesity or overweight and without diabetes to one of five oral GLP-1 receptor agonists (danuglipron, elecoglipron, lotiglipron, orforglipron, or aleniglipron) or placebo, across phase 2 to phase 3 designs of 26 to 72 weeks (**Table 1**). Participants were largely middle-aged and predominantly female, with mean weight of roughly 102 to 118 kg, BMI near 37 to 40 kg/m², and near-normal HbA1c.

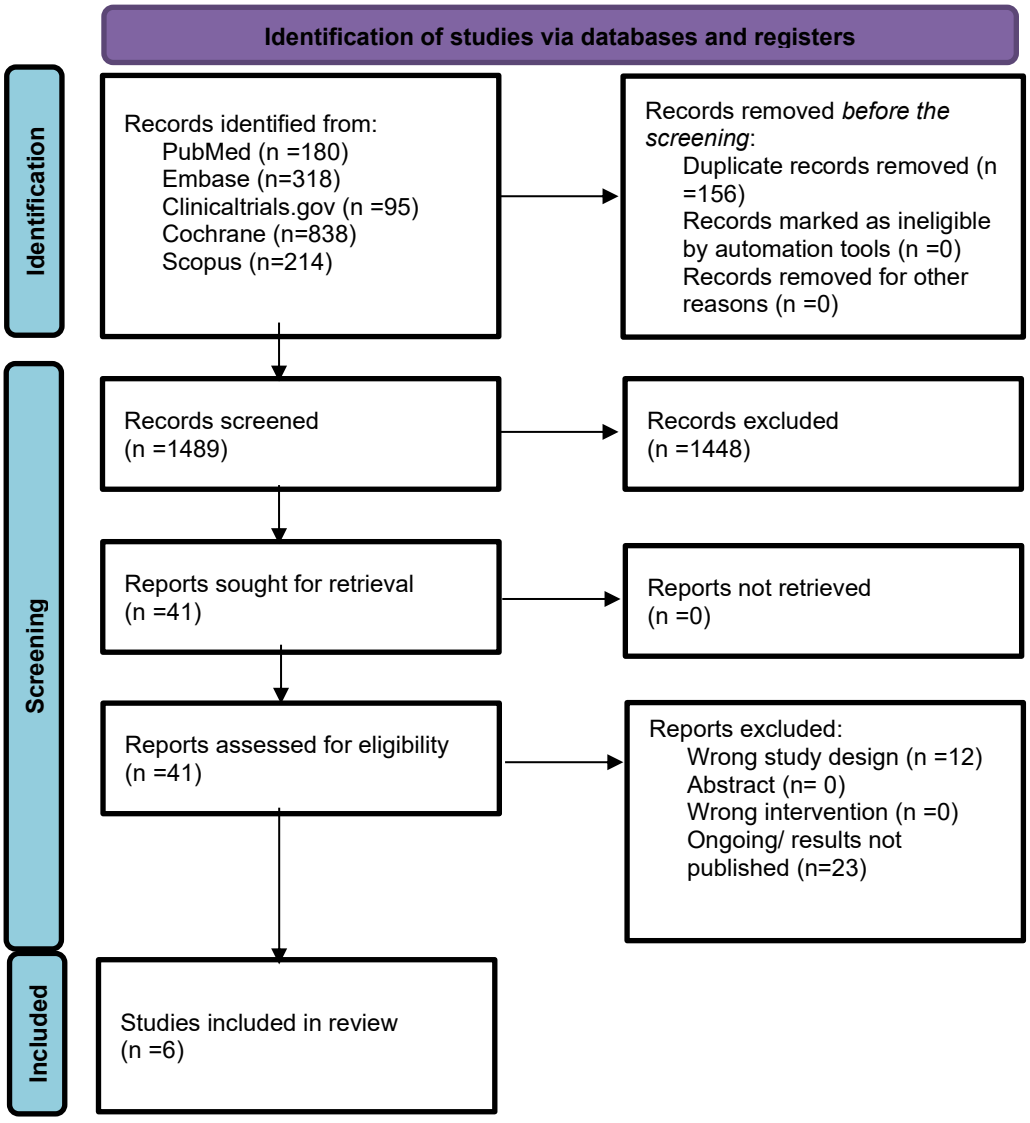

Identification of studies via databases and registers
Identification
Records identified from:
PubMed (n =180)
Embase (n=318)
Clinicaltrials.gov (n =95)
Cochrane (n=838)
Scopus (n=214)
Records removed *before the screening*:
Duplicate records removed (n =156)
Records marked as ineligible by automation tools (n =0)
Records removed for other reasons (n =0)
Screening
Records screened
(n =1489)
Records excluded
(n =1448)
Reports sought for retrieval
(n =41)
Reports not retrieved
(n =0)
Reports assessed for eligibility
(n =41)
Reports excluded:
Wrong study design (n =12)
Abstract (n= 0)
Wrong intervention (n =0)
Ongoing/ results not published (n=23)
Included
Studies included in review
(n =6)

Figure 1. *PRISMA 2020 flow diagram of study identification, screening, and inclusion.*

Risk of Bias

Cochrane RoB 2 tool was used to assess risk of bias across six RCTs. Four trials (wharton 2023, Davies 2026, Wharton 2025, and Rosenstock 2026) were assessed to be of low risk of bias (figure R2 and R3). Amin 2025 raised some concerns arising from deviations from the intended intervention (D2). Buckeridge 2025 was at high risk of bias, with concerns in the domains of deviations from the intended intervention, missing outcome data, and selection of the reported result (D2, D3, D5). The randomization process (D1) and measurement of the outcome (D4) were at low risk across every trial.

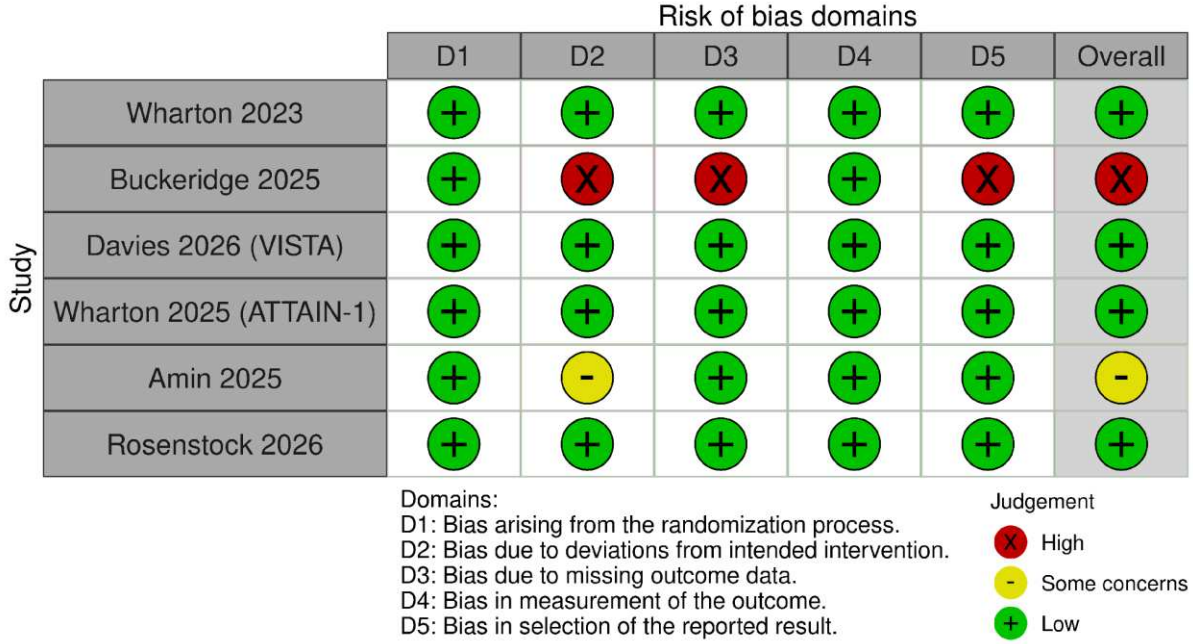


Figure 2. *Risk of bias summary (RoB 2) for each included trial across the five domains.*

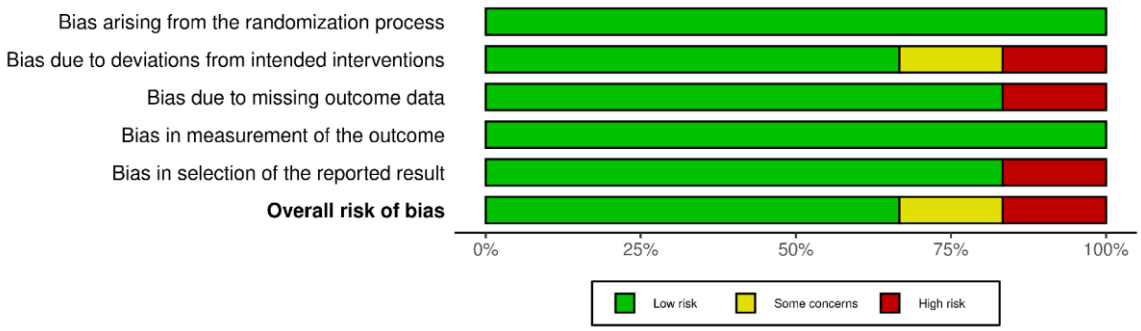


Figure 3. *Weighted risk of bias across trials for each RoB 2 domain*

Study	Group	N	Age, mean (SD), y	Female, n (%)	Weight, kg	BMI, kg/m^2	HbA1c, %	SBP, mmHg	DBP, mmHg	Dur, wk	Phase
Buckeridge 2025	danu 40 mg qwt	62	48.2 (10.1)	40 (65%)	109.6 (24.0)	38.7 (7.0)	5.5 (0.3)	126.3 (10.9)	79.0 (9.0)	26	2b
	danu 80 mg qwt	64	46.5 (12.0)	41 (65%)	107.6 (22.2)	38.8 (5.9)	5.5 (0.4)	125.2 (10.8)	78.1 (7.3)	26	2b
	danu 120 mg qwt	64	48.8 (10.5)	42 (66%)	103.8 (16.4)	37.5 (5.1)	5.5 (0.4)	126.5 (14.7)	79.1 (8.5)	26	2b
	danu 160 mg qwt	63	46.5 (11.2)	41 (65%)	106.0 (20.1)	38.4 (5.8)	5.5 (0.4)	124.0 (12.8)	78.0 (8.4)	26	2b
	danu 200 mg qwt	64	47.2 (10.9)	41 (65%)	106.9 (18.8)	38.2 (6.4)	5.5 (0.5)	126.9 (10.8)	79.0 (7.6)	26	2b
	danu 120 mg q2wt	38	48.5 (12.6)	22 (58%)	113.2 (22.9)	39.4 (6.5)	5.5 (0.3)	126.5 (10.3)	80.6 (7.2)	26	2b
	danu 160 mg q2wt	37	43.2 (10.1)	22 (59%)	113.4 (26.8)	38.6 (8.1)	5.4 (0.4)	123.5 (12.2)	80.4 (6.7)	26	2b
	danu 200 mg q2wt	36	51.0 (11.4)	23 (64%)	114.6 (28.5)	40.1 (7.0)	5.6 (0.4)	126.4 (10.4)	79.6 (7.9)	26	2b
	danu 80 mg q4wt	37	47.5 (9.4)	23 (62%)	112.5 (19.5)	39.2 (4.7)	5.5 (0.4)	125.6 (12.7)	81.5 (6.9)	32	2b
	danu 140 mg q4wt	37	47.2 (9.6)	23 (62%)	115.1 (28.3)	39.9 (9.3)	5.4 (0.4)	128.6 (12.4)	81.2 (7.1)	32	2b
	danu 200 mg q4wt	36	48.2 (11.1)	22 (61%)	117.6 (20.2)	40.5 (6.4)	5.4 (0.4)	127.7 (12.9)	80.4 (7.5)	32	2b
Davies 2026	Eleco 5 mg	32	50.7 (12.2)	26 (81%)	107.5 (20.7)	38.7 (5.8)	NR	125.3 (14.2)	81.0 (8.4)	36	2
	Eleco 15 mg	49	46.7 (13.3)	33 (67%)	109.7 (21.6)	39.0 (6.8)	NR	121.4 (14.7)	78.5 (10.5)	36	2
	Eleco 50 mg q4wt	50	51.0 (12.7)	40 (80%)	104.4 (20.8)	37.8 (5.9)	NR	127.4 (14.0)	83.6 (9.9)	36	2
	Eleco 75 mg q1wt	49	48.0 (11.9)	28 (57%)	106.7 (27.5)	37.4 (8.4)	NR	124.1 (12.3)	80.9 (6.9)	36	2
	Eleco 75 mg q2wt	49	48.9 (15.7)	41 (84%)	103.5 (28.1)	37.3 (8.3)	NR	124.6 (14.7)	80.3 (8.2)	36	2
Amin 2024	Loti 80 mg q4wt	66	49.3 (13.0)	38 (58%)	105.7 (22.3)	37.1 (5.7)	5.37 (0.37)	NR	NR	32	2
	Loti 140 mg q4wt	64	48.1 (12.4)	45 (70%)	106.7 (25.3)	38.4 (7.1)	5.54 (0.38)	NR	NR	32	2
	Loti 200 mg (4-step) q4wt	66	50.0 (10.7)	42 (64%)	104.1 (15.9)	37.0 (4.5)	5.42 (0.38)	NR	NR	32	2
	Loti 260 mg q4wt	64	48.5 (11.7)	40 (63%)	109.3 (24.9)	38.3 (7.3)	5.46 (0.41)	NR	NR	32	2
Wharton 2023	orfo 12 mg	50	49.8 (10.5)	31 (62%)	107.5 (25.3)	37.7 (7.7)	5.5 (0.4)	129.4 (12.1)	82.9 (6.8)	36	2
	orfo 24 mg	53	57.0 (9.1)	30 (57%)	112.1 (30.2)	38.1 (7.7)	5.7 (0.3)	129.7 (10.8)	82.1 (7.4)	36	2
	orfo 45 mg (pooled)	61	53.8 (11.9)	35 (57%)	108.0 (24.5)	37.7 (6.6)	5.65 (0.35)	127.7 (11.3)	79.3 (8.5)	36	2
Wharton 2025	orfo 6 mg q4wt	723	44.9 (12.1)	469 (65%)	103.2 (21.7)	37.0 (6.5)	5.6 (0.4)	125.4 (14.1)	81.0 (9.3)	72	3
	orfo 12 mg q4wt	725	45.4 (12.6)	467 (64%)	102.2 (21.6)	36.7 (6.5)	5.6 (0.3)	125.1 (13.7)	81.2 (9.4)	72	3
	orfo 36 mg q4wt	730	44.9 (11.9)	465 (64%)	103.1 (23.2)	36.9 (6.7)	5.6 (0.3)	125.8 (15.9)	80.9 (10.1)	72	3
Rosenstock 2026	aleni 45 mg	45	49.0 (12.7)	25 (56%)	115.6 (24.7)	39.7 (6.9)	5.7 (0.3)	127.0 (11.3)	83.3 (7.9)	36	2b
	aleni 90 mg	65	47.9 (12.5)	35 (54%)	117.9 (23.6)	39.8 (7.5)	5.7 (0.4)	126.4 (12.6)	81.9 (8.0)	36	2b
	aleni 120 mg	64	52.3 (13.9)	35 (55%)	113.1 (20.5)	39.0 (6.4)	5.7 (0.3)	125.3 (14.8)	80.2 (8.8)	36	2b

Table 1. *Baseline characteristics of the included treatment groups.*

Outcomes

Primary Outcome: Percentage Change in Body Weight from Baseline

Six studies favoured the GLP-1 receptor agonist (**Figure 1**; **Supplementary Figures S1 to S3**): pooled MD −7.61 (95% CI −8.59 to −6.62; z = −15.15, p < 0.0001; I^2 = 74.0%), with a prediction interval (−12.32 to −2.89) below null. Only elecoglipron 5 mg and lotiglipron 80 mg q4wt crossed the null. The effect differed by drug (p = 0.0005; largest for aleniglipron −9.20 and orforglipron −8.62, smallest for lotiglipron −4.58). On leave-one-out analysis the pooled estimate stayed between −7.42 and −7.79 and remained significant when each estimate was omitted in turn (**Supplementary Figure S1**), so the result was robust. The funnel plot showed some asymmetry, but with substantial heterogeneity (I^2 = 74.0%) this most likely reflects genuine between-study variability rather than publication bias.

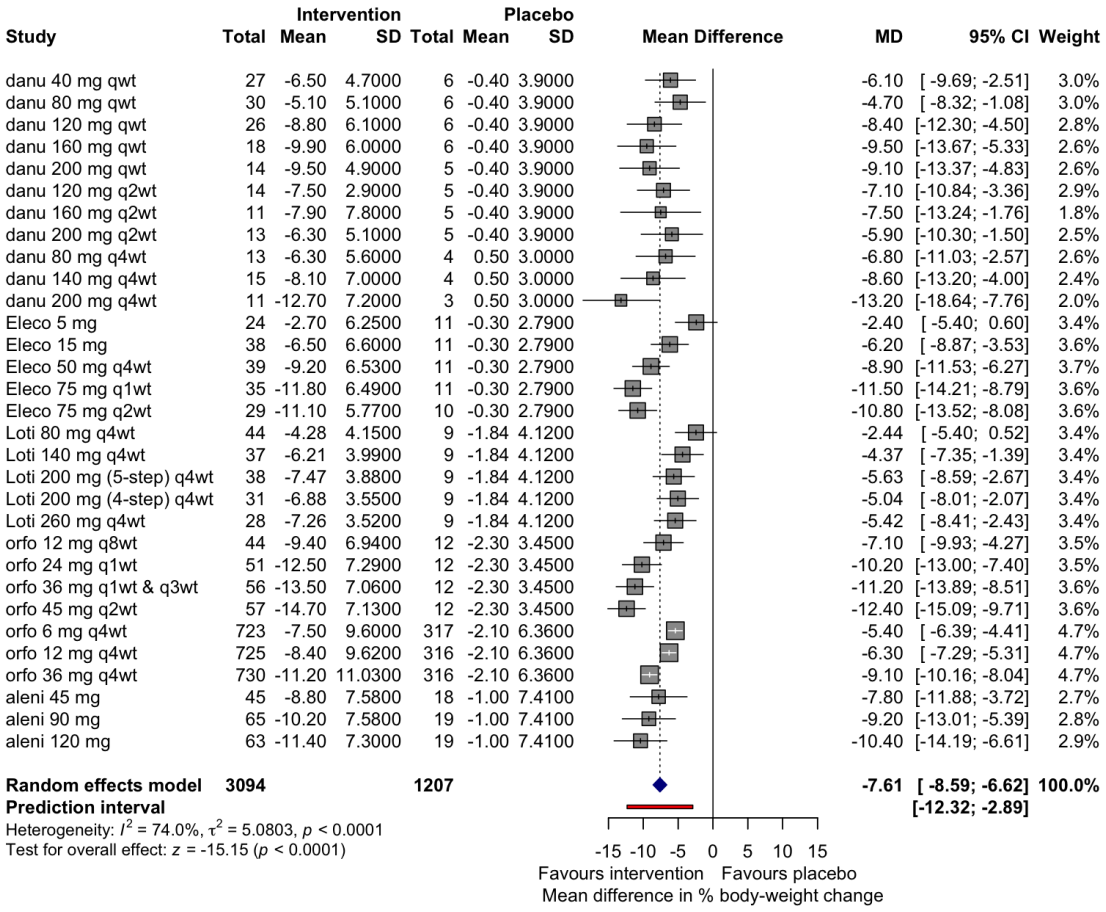


Figure 1. *Forest plot of percentage change in body weight from baseline.*

Change in Alanine Aminotransferase (ALT)

Four studies favoured the GLP-1 receptor agonist (**Figure 2**; **Supplementary Figures S4 and S5**): MD −9.53 (95% CI −11.88 to −7.18; p < 0.0001; I^2 = 0%; prediction interval −14.63 to −4.43). The reduction was greatest with orforglipron (drug p = 0.0088). The funnel plot was broadly symmetric.

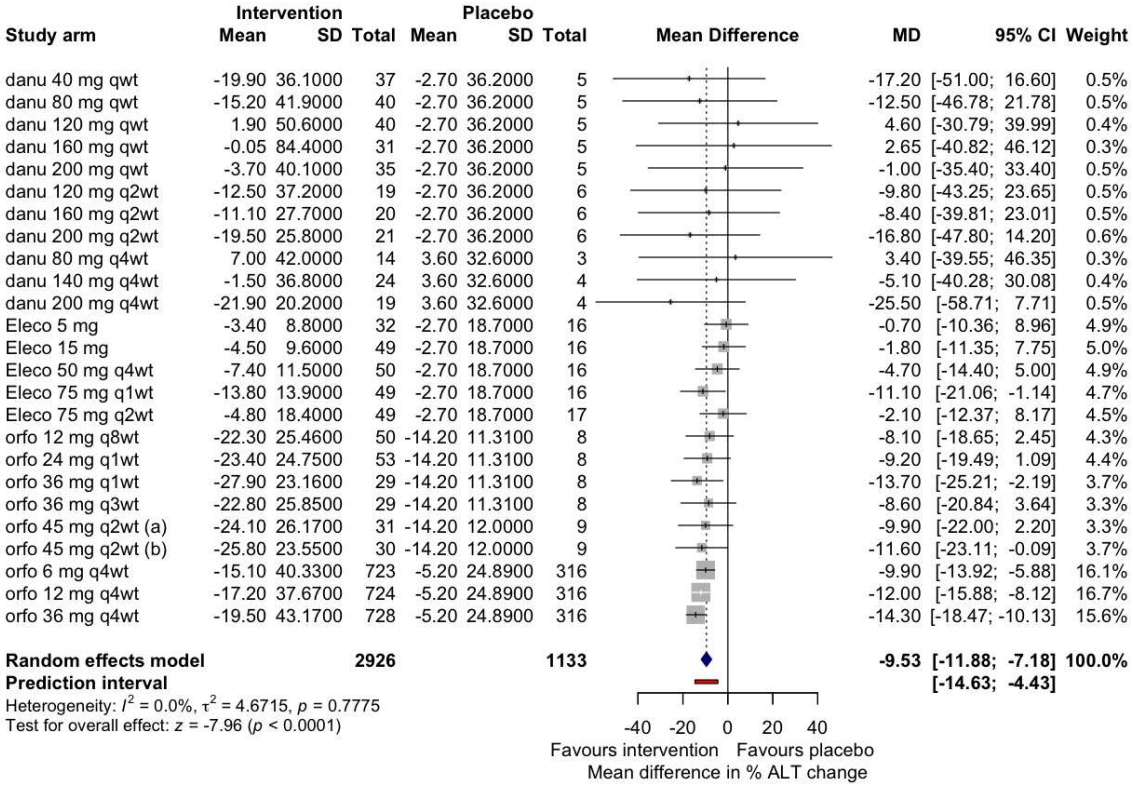


Figure 2. *Forest plot of change in ALT.*

Change in Aspartate Aminotransferase (AST)

Four studies favoured the GLP-1 receptor agonist (**Figure 3**; **Supplementary Figures S6 and S7**): MD −5.48 (95% CI −6.99 to −3.97; p < 0.0001; I^2 = 0%; prediction interval −7.07 to −3.89). The drug difference was borderline (p = 0.0572). The funnel plot was broadly symmetric.

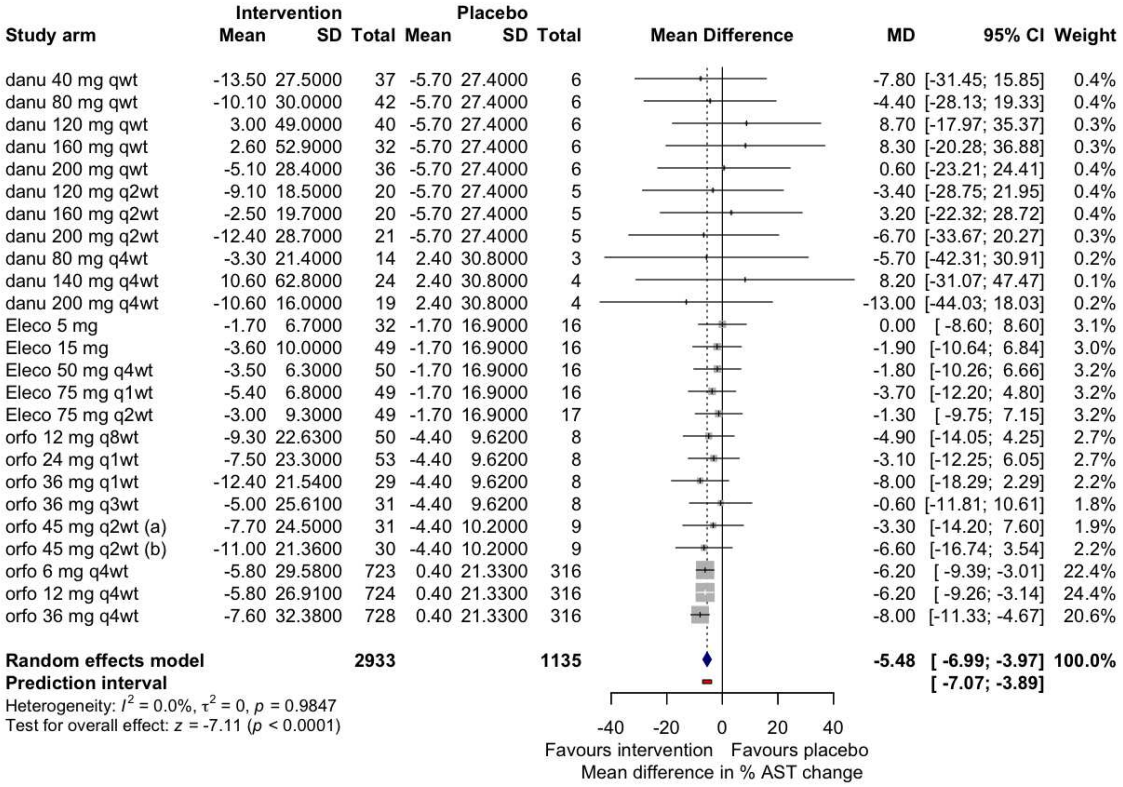


Figure 3. *Forest plot of change in AST.*

Change in Systolic Blood Pressure

Three studies of orforglipron and aleniglipron favoured the GLP-1 receptor agonist (**Figure 4**; **Supplementary Figures S8 and S9**): MD −5.49 (95% CI −6.17 to −4.82; z = −15.97, p < 0.0001; I^2 = 0%; prediction interval −6.27 to −4.71). The drug subgroups did not differ (p = 0.3392). The funnel plot was broadly symmetric.

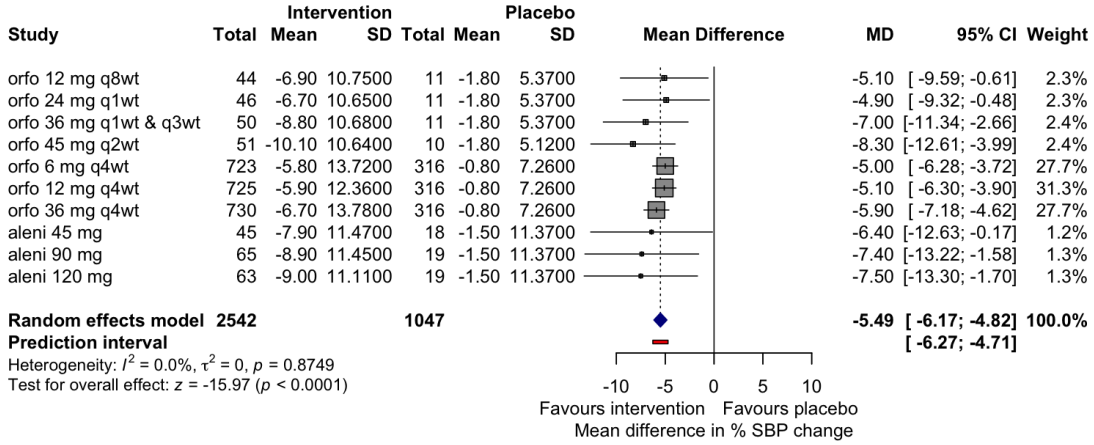


Figure 4. *Forest plot of percentage change in systolic blood pressure.*

Change in Diastolic Blood Pressure

Three studies of orforglipron and aleniglipron favoured the GLP-1 receptor agonist (**Figure 5**; **Supplementary Figures S10 and S11**): MD −1.54 (95% CI −1.99 to −1.09; z = −6.69, p < 0.0001; I^2 = 8.6%; prediction interval −2.06 to −1.02). The drug subgroups did not differ (p = 0.1055). The funnel plot was broadly symmetric.

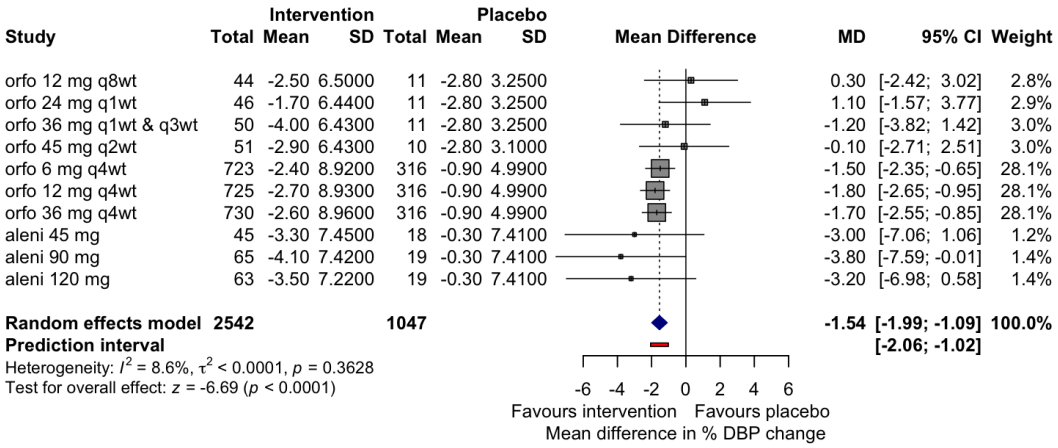


Figure 5. *Forest plot of percentage change in diastolic blood pressure.*

Any Adverse Event

Five studies favoured placebo (**Figure 6**; **Supplementary Figures S12 and S13**): RR 1.07 (95% CI 1.04 to 1.11; p < 0.0001; I^2 = 0%; prediction interval 1.04 to 1.11), a small excess of

events on the drug. The excess was largest with lotiglipron (drug p = 0.0106). The funnel reflected the pooled effect and sparse-event imprecision rather than publication bias.

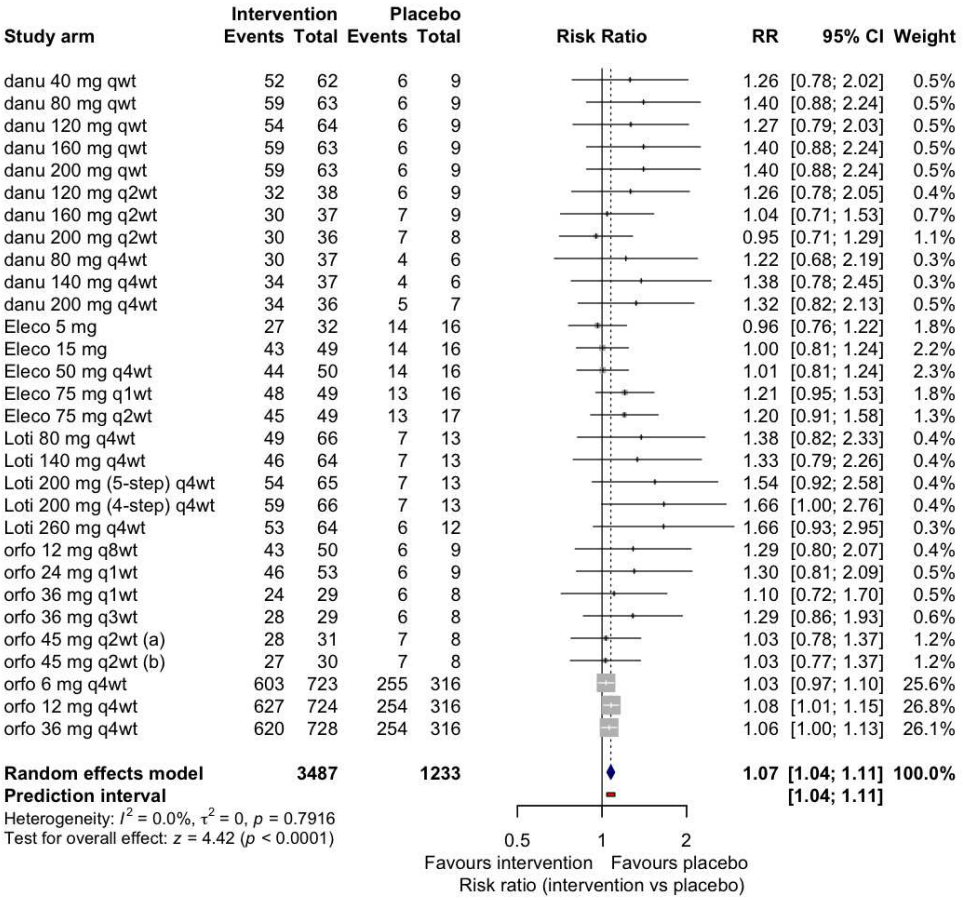


Figure 6. *Forest plot of any adverse event.*

Adverse Event Leading to Treatment Discontinuation

Four studies favoured placebo (**Figure 7**; **Supplementary Figures S14 and S15**): RR 2.85 (95% CI 2.07 to 3.92; p < 0.0001; I^2 = 0%; prediction interval 2.04 to 3.99), roughly a three-fold increase on the drug. Danuglipron carried the highest risk (drug p = 0.0583, borderline). The funnel reflected the pooled effect and sparse-event imprecision rather than publication bias.

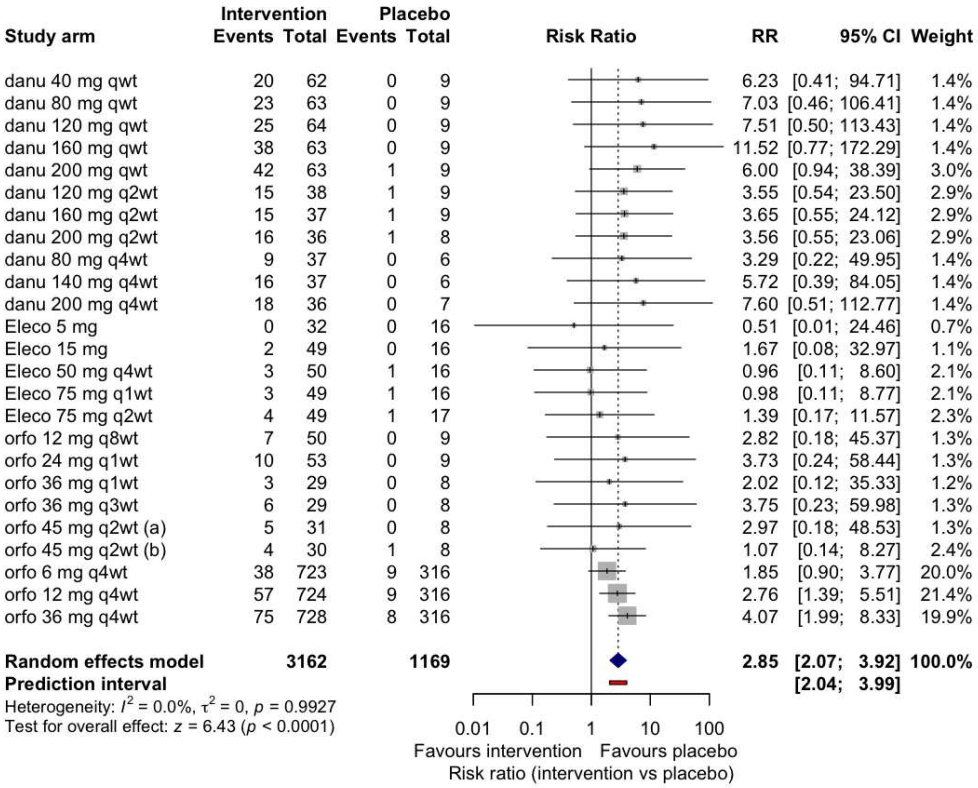


Figure 7. *Forest plot of adverse event leading to discontinuation.*

Nausea

Five studies favoured placebo (**Figure 8**; **Supplementary Figures S16 and S17**): RR 3.04 (95% CI 2.29 to 4.04; z = 7.70, p < 0.0001; I^2 = 0%; prediction interval 2.26 to 4.09). Every drug subgroup was significantly elevated except the small aleniglipron subgroup (1.21, crossing the null), the drug subgroups did not differ (p = 0.4531), and elecoglipron 5 mg (0.38) remained a single protective outlier. The funnel reflected the pooled effect and sparse-event imprecision rather than publication bias.

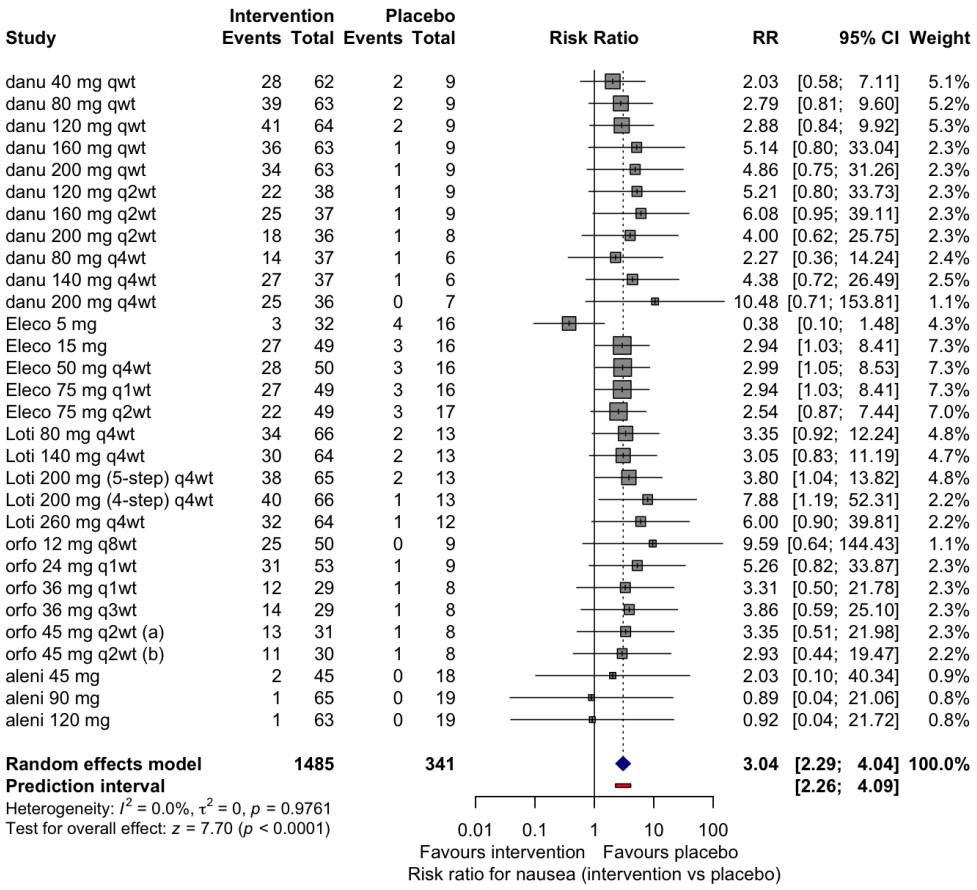


Figure 8. *Forest plot of nausea.*

Vomiting

Five studies favoured placebo (**Figure 9**; **Supplementary Figures S18 and S19**): RR 3.38 (95% CI 2.19 to 5.21; z = 5.51, p < 0.0001; I^2 = 0%; prediction interval 2.15 to 5.31). Danuglipron, elecoglipron, and lotiglipron subgroups were significant while orforglipron and aleniglipron crossed the null, and the drug subgroups did not differ (p = 0.7547). The funnel reflected the pooled effect and sparse-event imprecision rather than publication bias.

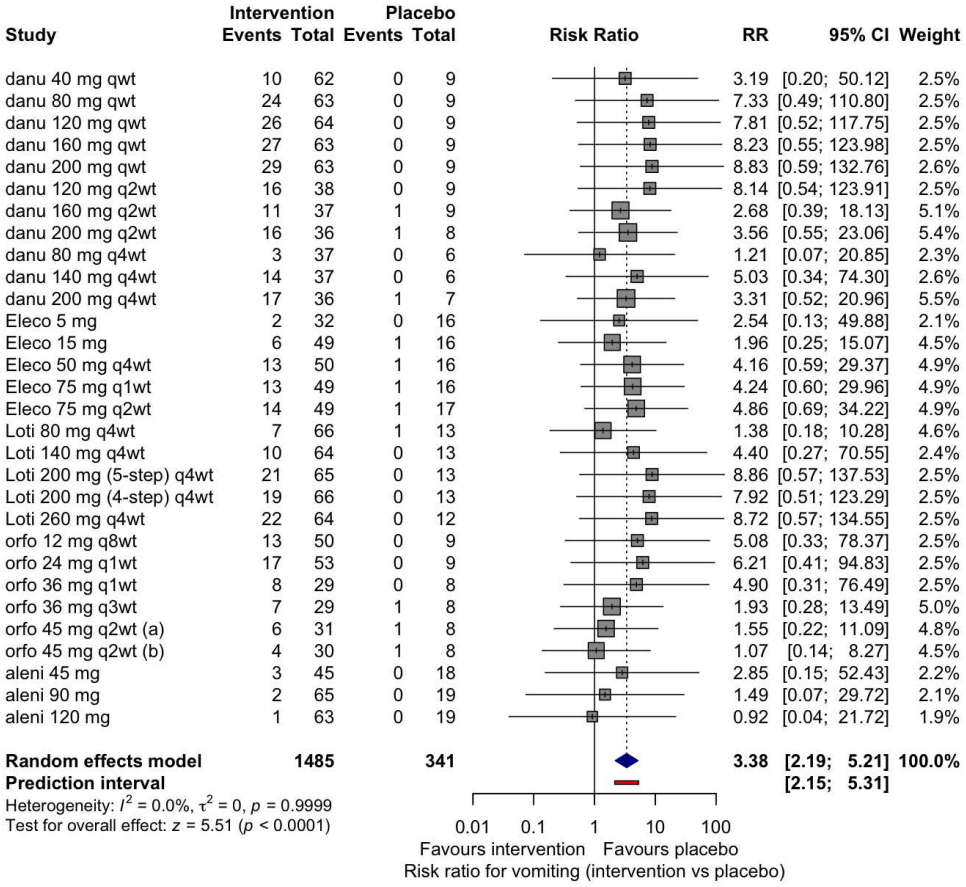


Figure 9. *Forest plot of vomiting.*

Diarrhea

Four studies favoured neither group (**Figure 10**; **Supplementary Figures S20 and S21**): RR 1.23 (95% CI 0.92 to 1.64; p = 0.1643; I^2 = 0%; prediction interval 0.91 to 1.66), numerically more on the drug but not significant. The drug subgroups did not differ (p = 0.4566). The funnel plot was near-symmetric.

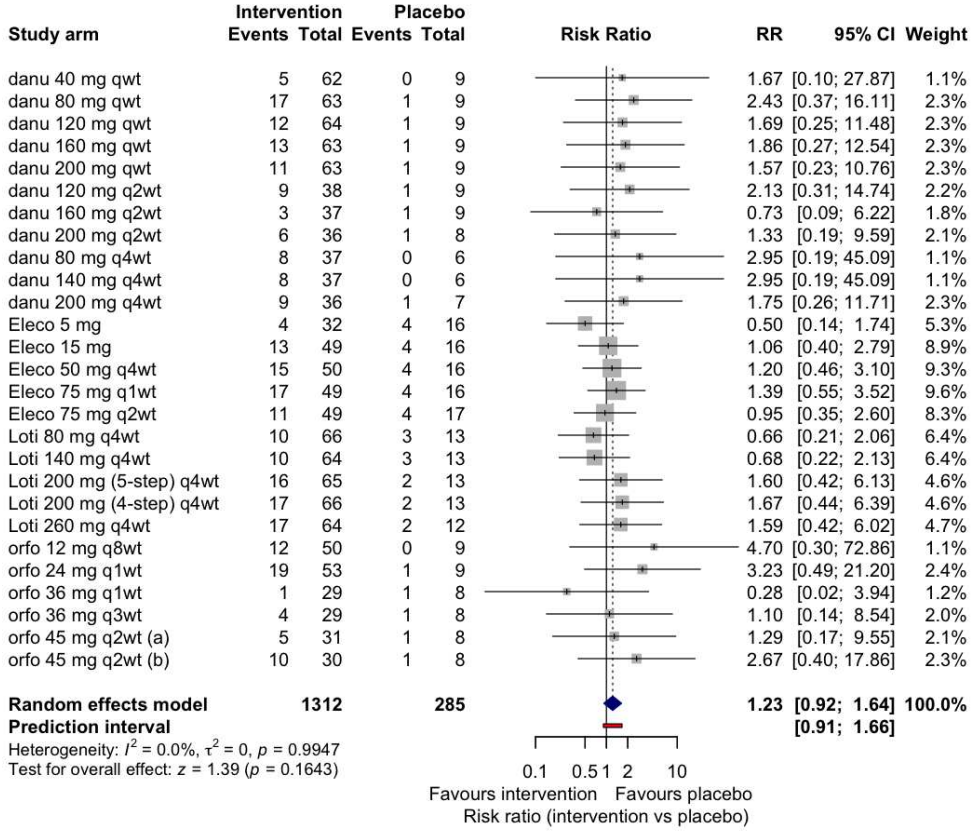


Figure 10. *Forest plot of diarrhea.*

Constipation

Four studies favoured placebo (**Figure 11**; **Supplementary Figures S22 and S23**): RR 2.48 (95% CI 1.64 to 3.75; p < 0.0001; I^2 = 0%; prediction interval 1.60 to 3.82). Elecoglipron and lotiglipron were individually significant, and the drug subgroups did not differ (p = 0.2880). The funnel reflected the pooled effect and sparse-event imprecision rather than publication bias.

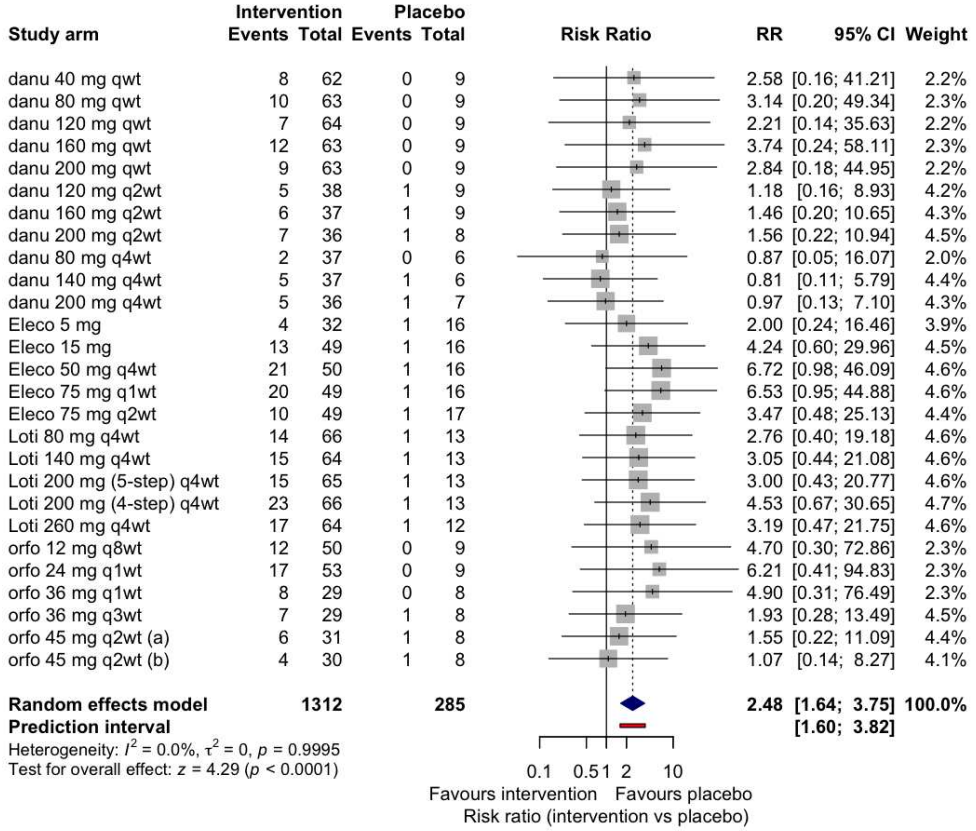


Figure 11. *Forest plot of constipation.*

Dyspepsia

Five studies favoured neither group (**Figure 12**; **Supplementary Figures S24 and S25**): RR 1.58 (95% CI 0.98 to 2.55; z = 1.87, p = 0.0608; I^2 = 0%; prediction interval 0.96 to 2.60), again narrowly missing significance. Only elecoglipron was elevated, the drug subgroups did not differ (p = 0.4058), and the aleniglipron 45 mg group was dropped as a double-zero. The funnel plot was near-symmetric.

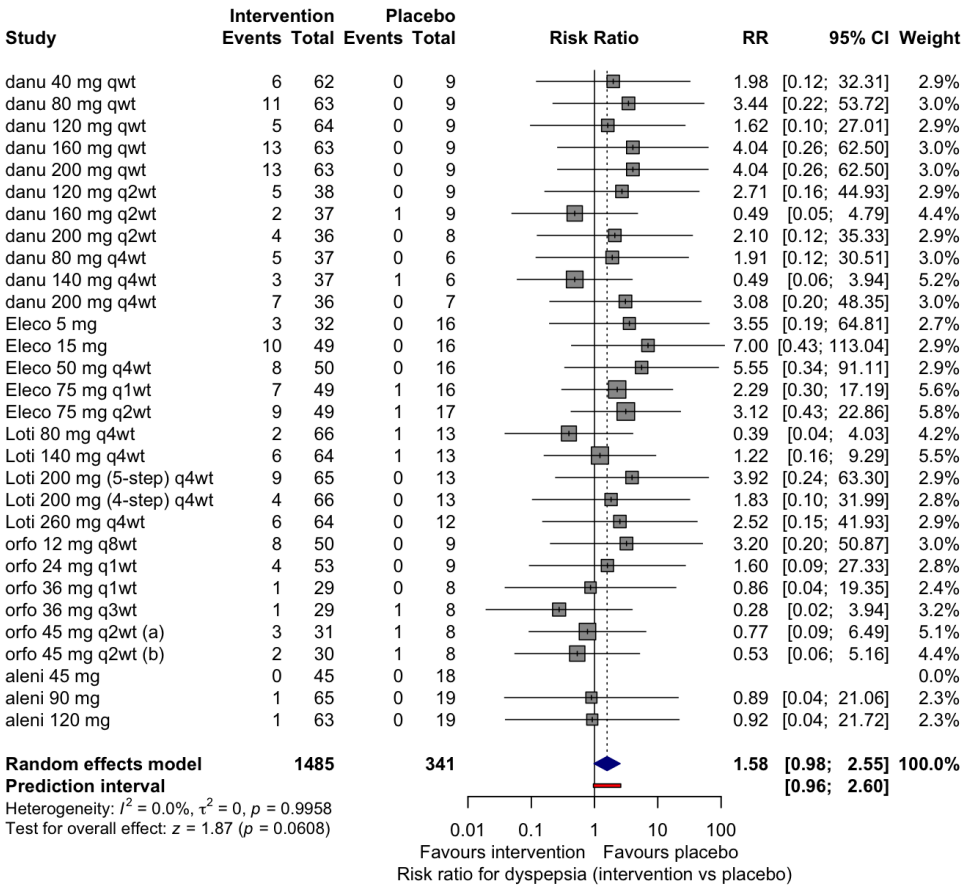


Figure 12. *Forest plot of dyspepsia.*

Gastroesophageal Reflux (GERD)

Four studies favoured placebo (**Figure 13**; **Supplementary Figures S26 and S27**): RR 1.92 (95% CI 1.15 to 3.19; p = 0.0124; I^2 = 0%; prediction interval 1.12 to 3.27). Every drug crossed the null individually yet the pooled effect was significant, and the drug subgroups did not differ (p = 0.9674). The funnel reflected the pooled effect and sparse-event imprecision rather than publication bias.

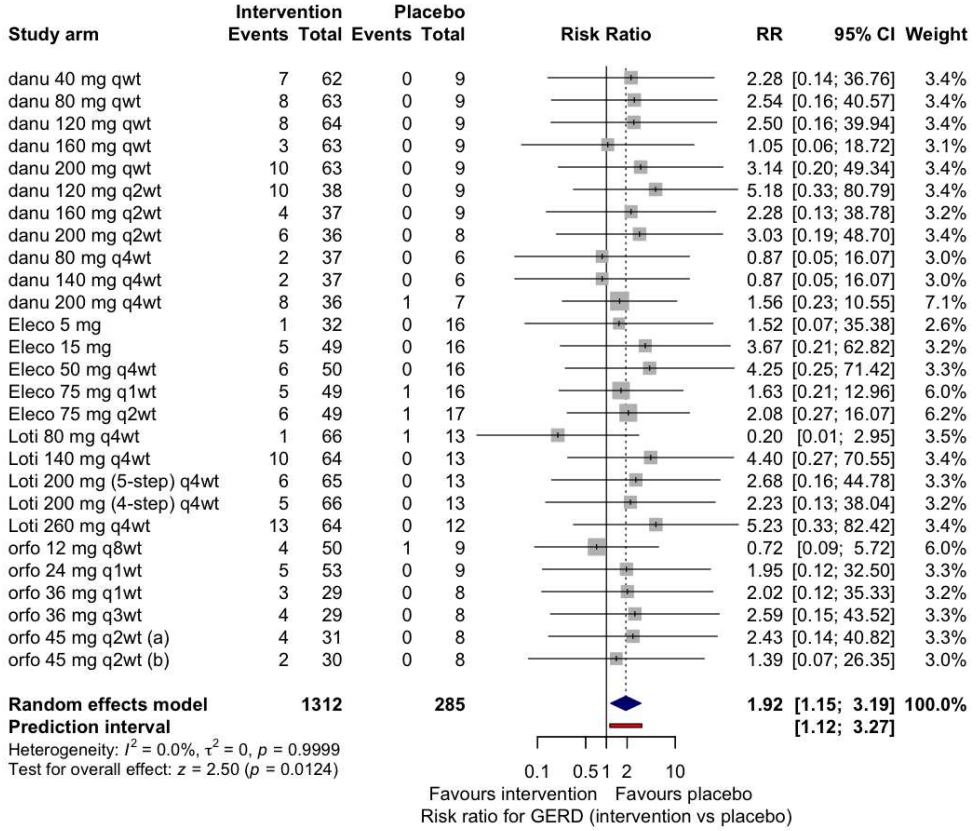


Figure 13. *Forest plot of GERD.*

Headache

Four studies favoured neither group (**Figure 14**; **Supplementary Figures S28 and S29**): RR 1.14 (95% CI 0.80 to 1.63; p = 0.4699; I^2 = 0%; prediction interval 0.78 to 1.66). The drug subgroups did not differ (p = 0.9021). The funnel plot was near-symmetric.

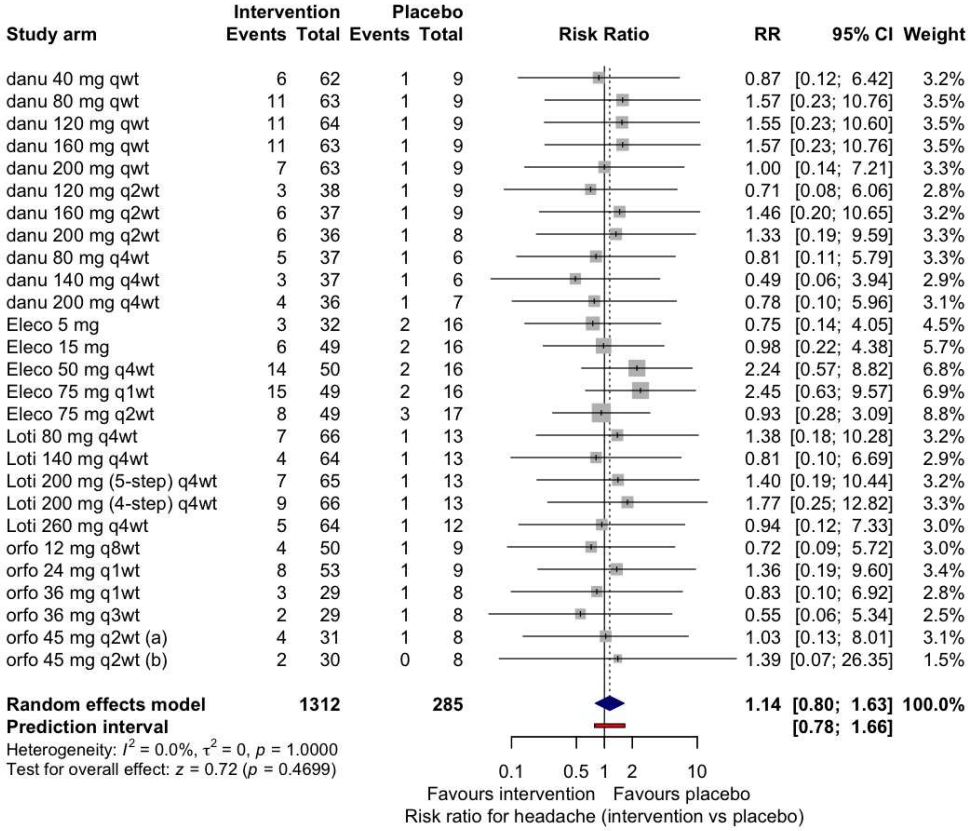


Figure 14. *Forest plot of headache.*

Fatigue

Four studies favoured neither group (**Figure 15**; **Supplementary Figures S30 and S31**): RR 1.12 (95% CI 0.73 to 1.74; p = 0.6019; I^2 = 0%; prediction interval 0.71 to 1.78). The drug subgroups did not differ (p = 0.5938). The funnel plot was near-symmetric.

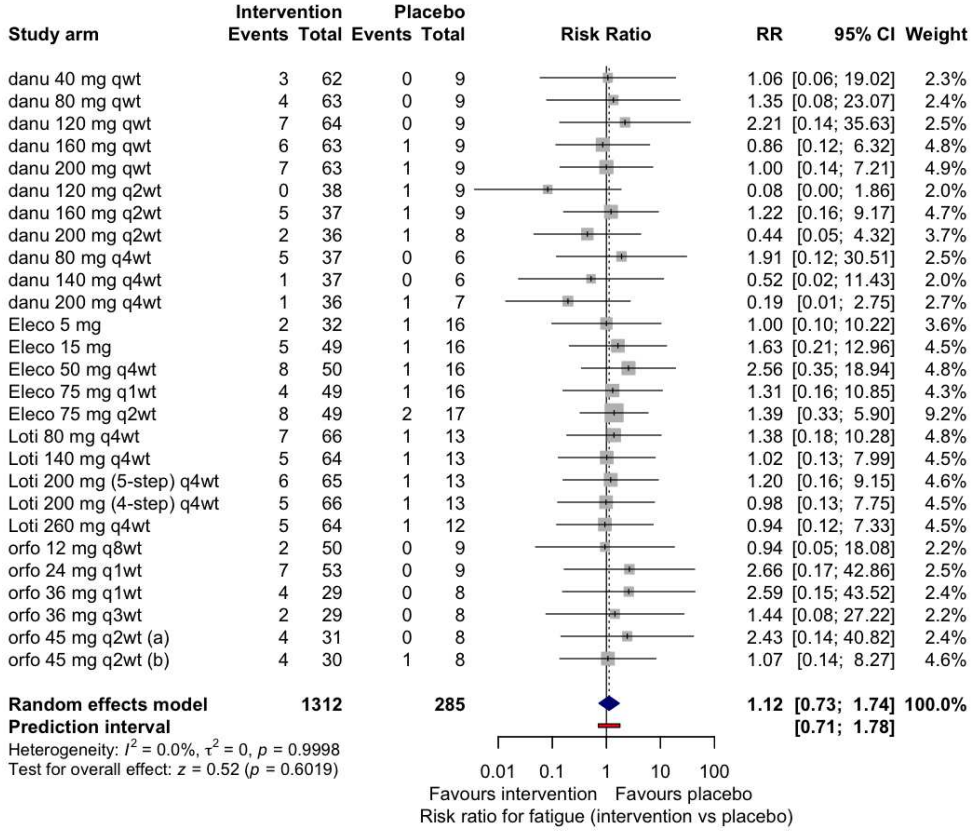


Figure 15. *Forest plot of fatigue.*

Certainty of Evidence (GRADE)

Certainty of evidence was assessed with the GRADE framework (**Table 2**). Because all evidence came from randomized controlled trials, every outcome started at high certainty and was then considered for downgrading across risk of bias, inconsistency, indirectness, imprecision, and publication bias. Seven outcomes retained high certainty (ALT, AST, any adverse event, adverse-event discontinuation, nausea, vomiting, and constipation), each supported by no heterogeneity, large samples, and an effect estimate that excluded the null.

The remaining eight were rated moderate: body weight for substantial heterogeneity; systolic and diastolic blood pressure for indirectness, because few of the five agents contributed blood-pressure data; GERD for imprecision from sparse events with a fragile lower confidence bound; and diarrhea, dyspepsia, headache, and fatigue for imprecision, their confidence intervals crossing the null. No outcome was downgraded for publication bias, and risk of bias was not judged serious because the low-risk phase 3 trials dominated the pooled weight. No outcome fell below moderate certainty.

Table 2. *GRADE Summary of Findings.*

Outcome	Pooled effect (95% CI)	Participants (studies)	Certainty	Downgraded for
Body weight, % change	MD −7.61 (−8.59 to −6.62)	4301 (6)	⨁⨁⨁◯ Moderate	a
ALT change	MD −9.53 (−11.88 to −7.18)	4059 (4)	⨁⨁⨁⨁ High	—
AST change	MD −5.48 (−6.99 to −3.97)	4068 (4)	⨁⨁⨁⨁ High	—
Systolic BP, % change	MD −5.49 (−6.17 to −4.82)	3589 (3)	⨁⨁⨁◯ Moderate	b
Diastolic BP, % change	MD −1.54 (−1.99 to −1.09)	3589 (3)	⨁⨁⨁◯ Moderate	b
Any adverse event	RR 1.07 (1.04 to 1.11)	4720 (5)	⨁⨁⨁⨁ High	—
AE discontinuation	RR 2.85 (2.07 to 3.92)	4331 (4)	⨁⨁⨁⨁ High	—
Nausea	RR 3.04 (2.29 to 4.04)	1826 (5)	⨁⨁⨁⨁ High	—
Vomiting	RR 3.38 (2.19 to 5.21)	1826 (5)	⨁⨁⨁⨁ High	—
Constipation	RR 2.48 (1.64 to 3.75)	1597 (4)	⨁⨁⨁⨁ High	—
GERD	RR 1.92 (1.15 to 3.19)	1597 (4)	⨁⨁⨁◯ Moderate	d
Diarrhea	RR 1.23 (0.92 to 1.64)	1597 (4)	⨁⨁⨁◯ Moderate	c
Dyspepsia	RR 1.58 (0.98 to 2.55)	1826 (5)	⨁⨁⨁◯ Moderate	c
Headache	RR 1.14 (0.80 to 1.63)	1597 (4)	⨁⨁⨁◯ Moderate	c
Fatigue	RR 1.12 (0.73 to 1.74)	1597 (4)	⨁⨁⨁◯ Moderate	c

All outcomes began at high certainty because the evidence came from randomized controlled trials. MD, mean difference; RR, risk ratio.

a. Downgraded one level for inconsistency: substantial statistical heterogeneity (I^2 = 74.0%).

b. Downgraded one level for indirectness: only orforglipron and aleniglipron, two of the five agents, contributed blood-pressure data, limiting generalisability to the drug class.

c. Downgraded one level for imprecision: the 95% confidence interval crosses the null.

d. Downgraded one level for imprecision: a significant estimate but with a wide interval whose lower bound lies close to the null, from sparse events.

e. Risk of bias was not judged serious: four of six trials were low risk, while Buckeridge 2025 (high risk) and Amin 2025 (some concerns) contributed mainly to the smaller phase 2 pools and carried little weight.

Discussion:

In our systematic review and meta-analysis, we analyzed the efficacy and safety of oral small-molecule (non-peptide) GLP-1 receptor agonists in adults with obesity without diabetes. We found that oral non-peptide GLP-1 receptor agonists resulted in clinically meaningful improvements in several cardiometabolic outcomes. Oral GLP-1 receptor agonists significantly decreased body weight [−7.61% (95% CI: −8.59 to −6.62)], ALT, AST, systolic blood pressure (SBP) and diastolic blood pressure (DBP) while increasing gastrointestinal adverse events.

Patients taking oral GLP-1 receptor agonists lost an average of 7.61% more of their body weight than patients taking a placebo. This degree of weight loss is clinically meaningful as 5–10% loss of baseline body weight has been associated with improvements in insulin sensitivity, blood pressure, dyslipidemia, hepatic steatosis and cardiovascular risk [17]. Our findings are in line with previous studies by Lütkemeyer et al [18], Dutta et al [19], and Pandey et al [20] which also reported significant reduction in weight (6% to 9%), body mass index, and waist circumference in participants receiving orforglipron in comparison with placebo. Despite the robust overall effect, substantial heterogeneity was observed across studies (I^2 = 74%), indicating variability in treatment response. The wide prediction interval (−12.32 to −2.89) also indicates that the magnitude of weight loss may vary considerably across clinical settings. Subgroup analyses offer useful insights into potential drivers of this variability, with greater weight reduction seen in trials assessing orforglipron, utilizing high-intensity dose escalation protocols, and those without a placebo run-in period.

Subgroup analysis demonstrated significant differences in weight reduction according to the individual oral GLP-1 receptor agonist, with the largest pooled reduction observed for aleniglipron, followed by orforglipron, whereas lotiglipron showed the smallest effect. Several factors may account for this finding. The greater weight reduction observed with aleniglipron may be partly attributable to its dose-dependent efficacy [16]. Orforglipron has favorable pharmacokinetics with high oral bioavailability and prolonged receptor occupancy, allowing for sustained GLP-1 receptor activation over the dosing interval. Unlike peptide-based oral GLP-1 receptor agonists that need absorption enhancers and strict fasting conditions, orforglipron is a small molecule, non-peptide that can be administered without

complex dosing requirements. A simpler administration may enhance patient adherence and result in more consistent receptor stimulation [21]. Moreover, studies with higher intensity dose escalation had greater weight loss. This is consistent with previous studies on orforglipron that have shown a clear dose-response relationship, with more weight loss at higher doses. However, the increased efficacy observed with higher doses is associated with a greater incidence of gastrointestinal adverse events, particularly nausea, vomiting, diarrhea and constipation, the majority of which occur during the dose escalation period [10,22]. These findings underscore the need for individual dose titration in clinical practice to strike a balance between maximal weight reduction and acceptable tolerability.

Weight loss was found to be greater in studies without a placebo run-in. Placebo run-in phases may enrich the randomized population by excluding poorly adherent participants and permitting early lifestyle modifications that attenuate between-group differences after randomization. However, there is little evidence on the effect of run-in periods on weight-loss outcomes. A systematic review of 311 randomized controlled trials of obesity by Affuso et al [23] found that pre-randomization run-in periods were associated with lower overall weight loss.

The observed weight-loss effect is biologically plausible and reflects multiple complementary mechanisms of GLP-1 receptor activation. Activation of hypothalamic GLP-1 receptors reduces appetite by stimulating anorexigenic pro-opiomelanocortin neurons and inhibiting orexigenic neuropeptide Y/agouti-related peptide neurons, leading to decreased hunger and spontaneous energy intake [24]. At the same time, delayed gastric emptying causes increased postprandial fullness, decreased meal size and increased satiety. GLP-1 receptor agonists also improve the body's sensitivity to insulin and reduce the secretion of glucagon, which helps the body use energy more efficiently and reduces the buildup of fat tissue [25,26]. Together these mechanisms produce a persistent negative energy balance, resulting in progressive weight loss with continued treatment.

In addition to weight loss, oral small-molecule GLP-1 receptor agonists resulted in significant reductions in ALT and AST levels, suggestive of potential liver benefit. Given the close association between obesity and MASLD, these improvements may be ascribed to reductions in hepatic steatosis and hepatocellular injury mediated by weight loss, improved insulin sensitivity, reduced hepatic lipogenesis, increased fatty acid oxidation and reduced hepatic inflammation. The longer duration of treatment and the greater reductions are consistent with the gradual reversal of hepatic steatosis. Hence, oral GLP-1 receptor agonists may improve liver health in patients with obesity, although the relative contribution of weight loss and direct hepatic effects remains incompletely understood [27–29]. Significant reductions in systolic and diastolic blood pressure was also observed in trials including orforglipron and aleniglipron [30]. The reductions in blood pressure observed are likely multifactorial, reflecting both weight loss–mediated mechanisms, including reductions in sympathetic nervous system and renin–angiotensin–aldosterone system activity, and direct GLP-1 receptor–mediated effects such as improved endothelial function, increased nitric oxide bioavailability,

natriuresis, and reduced vascular inflammation [31]. Studies have similarly reported improvements in cardiometabolic risk factors accompanying weight reduction [32].

Our findings revealed a statistically significant increase in overall adverse events among participants receiving oral GLP-1 receptor agonists compared with placebo (RR 1.07). This suggests that most adverse events were mild to moderate, consistent with previous studies where gastrointestinal events predominated without a substantial increase in serious adverse events [33]. This could be explained by the fact that GLP-1 receptors are widely expressed throughout the gastrointestinal tract and central nervous system. Their activation delays gastric emptying, suppresses appetite, modulates gastrointestinal motility, and activates vagal afferent pathways involved in satiety, mechanisms that underlie both their therapeutic effects and the characteristic gastrointestinal adverse events [34].

An increase in adverse events leading to treatment discontinuation of about threefold was a particularly important finding. Danuglipron showed the highest point estimate for treatment discontinuation, although the between-drug subgroup difference did not reach statistical significance. Although the absolute rates of discontinuation were low, early discontinuation of treatment could jeopardize the long-term effectiveness of obesity therapy that depends on continued treatment. This finding is consistent with studies that have identified gastrointestinal intolerance, particularly nausea, vomiting, abdominal discomfort and early satiety, as the main reason for discontinuation. These effects are related to the pharmacologic actions of GLP-1 RA on gastric emptying and central satiety pathways and are most prominent during dose escalation before physiologic adaptation [9,35].

Nausea was the most common and consistent GI symptom and occurred more than three times more frequently in treated participants than in placebo, as found in previous studies [35,36]. Vomiting was significantly increased with danuglipron, elecoglipron, and lotiglipron but not with orforglipron individually, although subgroup analysis did not demonstrate statistically significant differences between drugs. Underlying mechanism includes the stimulation of GLP-1 receptors delays gastric emptying and stimulates vagal afferent pathways to the emetic centers in the brainstem, leading to nausea, especially at the beginning of treatment and when doses are increased. Importantly, these symptoms often diminish over time with gastric and central neural adaptation. Constipation was also significantly increased, probably due to reduced gastrointestinal motility and decreased stool bulk secondary to appetite suppression [35,37]. Conversely, diarrhea did not differ significantly from placebo, although there was a numerical increase that may reflect milder effects on lower gastrointestinal motility, variability in study conditions, or limited statistical power. This finding differs somewhat from previous analyses that reported increased diarrhea with certain GLP-1 receptor agonists [37]. There was no significant increase in other adverse events, including dyspepsia, headache, and fatigue, but there was a modest but significant increase in gastroesophageal reflux disease (GERD).

There are several important strengths to this systematic review. One such strength is that it is focused on oral small molecule (non-peptide) GLP-1 receptor agonists in adults with obesity without diabetes, reducing clinical heterogeneity and improving applicability to a population

for whom weight loss is the primary therapeutic goal. The sole inclusion of RCTs improves the internal validity, and the overall evaluation of efficacy and safety outcomes provides a balanced assessment of the benefit-risk profile. Most of the included trials were at low risk of bias but one trial was considered to have some concerns and one was at high risk of bias. The larger phase 3 trials contributed most of the weight to the pooled estimates. GRADE assessments suggested moderate- to high-certainty evidence across key outcomes. Sensitivity analyses confirmed the robustness of primary findings despite heterogeneity. Nevertheless, some limitations need to be acknowledged. The evidence base remains relatively small with only six trials limiting precision for less common or long-term outcomes. Variability in the effect estimates was likely due to clinical heterogeneity in drug types, dosing strategies, and study designs. In addition, some of the secondary outcomes, such as blood pressure, were based on a small number of studies including only orforglipron and aleniglipron, which may limit generalizability. Finally, relatively short follow-up durations prevent conclusions regarding long-term efficacy, safety, and durability of weight loss, highlighting the need for larger, longer-term comparative trials. Future research should include adequately powered head-to-head randomized trials of individual oral small-molecule GLP-1 receptor agonists, particularly orforglipron, danuglipron, elecoglipron, lotiglipron, and aleniglipron, to determine if differences in efficacy and tolerability are true pharmacological differences or differences in study design. Longer duration trials are also required to evaluate sustained weight maintenance, cardiovascular outcomes, quality of life and hepatic endpoints such as imaging confirmed metabolic dysfunction-associated steatotic liver disease. In addition, research examining predictors of gastrointestinal intolerance and individualized dose-escalation strategies may help to optimize adherence while maintaining therapeutic efficacy.

Conclusion:

Oral small-molecule (non-peptide) GLP-1 receptor agonists are effective in weight management in adults with obesity without diabetes with clinically meaningful weight loss and improvements in liver enzymes and blood pressure. These benefits are associated with an increased risk of discontinuation of treatment and mostly gastrointestinal adverse events and underline the importance of individualized dose escalation. The current evidence is derived predominantly from randomized controlled trials at low risk of bias; however, the evidence base remains limited by the small number of studies and relatively short follow-up durations. Comparative efficacy, safety and durability of weight loss require confirmation in larger, longer-term head-to-head trials, optimizing treatment tolerability and adherence.

References:

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15(5):288-298. doi:10.1038/s41574-019-0176-8
2. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. *PharmacoEconomics*. 2015;33(7):673-689. doi:10.1007/s40273-014-0243-x
3. Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. *Med Clin North Am*. 2018;102(1):183-197. doi:10.1016/j.mcna.2017.08.012

4. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med*. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
5. Müller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). *Mol Metab*. 2019;30:72-130. doi:10.1016/j.molmet.2019.09.010
6. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
7. Aroda VR, Blonde L, Pratley RE. A new era for oral peptides: SNAC and the development of oral semaglutide for the treatment of type 2 diabetes. *Rev Endocr Metab Disord*. 2022;23(5):979-994. doi:10.1007/s11154-022-09735-8
8. Bækdal TA, Breitschaft A, Donsmark M, Maarbjerg SJ, Søndergaard FL, Borregaard J. Effect of Various Dosing Conditions on the Pharmacokinetics of Oral Semaglutide, a Human Glucagon-Like Peptide-1 Analogue in a Tablet Formulation. *Diabetes Ther*. 2021;12(7):1915-1927. doi:10.1007/s13300-021-01078-y
9. Saxena AR, Frias JP, Gorman DN, et al. Tolerability, safety and pharmacodynamics of oral, small-molecule glucagon-like peptide-1 receptor agonist danuglipron for type 2 diabetes: A 12-week, randomized, placebo-controlled, Phase 2 study comparing different dose-escalation schemes. *Diabetes Obes Metab*. 2023;25(10):2805-2814. doi:10.1111/dom.15168
10. Wharton S, Blevins T, Connery L, et al. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med*. 2023;389(10):877-888. doi:10.1056/NEJMoa2302392
11. Amin NB, Frederich R, Tsamandouras N, et al. Evaluation of an oral small-molecule glucagon-like peptide-1 receptor agonist, lotiglipron, for type 2 diabetes and obesity: A dose-ranging, phase 2, randomized, placebo-controlled study. *Diabetes Obes Metab*. 2025;27(1):215-227. doi:10.1111/dom.16005
12. Buckeridge C, Cobain S, Bays HE, et al. Efficacy and safety of danuglipron (PF - 06882961) in adults with obesity: A randomized, placebo-controlled, dose-ranging phase 2b study. *Diabetes Obes Metab*. 2025;27(9):4915-4926. doi:10.1111/dom.16534
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
14. Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment. *N Engl J Med*. 2025;393(18):1796-1806. doi:10.1056/NEJMoa2511774
15. Davies MJ, Aroda VR, Rosenstock J, et al. Elecoglipron, an oral small molecule GLP-1 receptor agonist in adults with obesity or overweight (VISTA): a multicentre, phase 2, randomised, placebo-controlled clinical trial. *The Lancet*. 2026;407(10547):2503-2514. doi:10.1016/S0140-6736(26)00748-8
16. Rosenstock J, Lingvay I, Ryan D, et al. Oral small molecule GLP-1 receptor agonist aleniglipron in people with overweight or obesity: a randomized, double-blind, placebo-controlled phase 2b trial. *Nat Med*. 2026;32(8):2941-2947. doi:10.1038/s41591-026-04476-6

17. Wing RR, Lang W, Wadden TA, et al. Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals With Type 2 Diabetes. *Diabetes Care*. 2011;34(7):1481-1486. doi:10.2337/dc10-2415
18. Lütkemeyer C, Pasqualotto E, Ferreira ROM, et al. Effects of once-daily oral orforglipron on weight and metabolic markers: a systematic review and meta-analysis of randomized controlled trials. *Arch Endocrinol Metab*. 2024;68:e230469. doi:10.20945/2359-4292-2023-0469
19. Dutta D, Nagendra L, Anne B, Kumar M, Sharma M, Kamrul-Hasan ABM. Orforglipron, a novel non-peptide oral daily glucagon-like peptide-1 receptor agonist as an anti-obesity medicine: A systematic review and meta-analysis. *Obes Sci Pract*. 2024;10(2):e743. doi:10.1002/osp4.743
20. Pandey RK, Jan M, Mohammad A, et al. Efficacy and Safety of Orforglipron in Obese Adults With or Without Diabetes: A Systematic Review and Meta-Analysis. *Endocrinol Diabetes Metab*. 2025;8(6):e70134. doi:10.1002/edm2.70134
21. Ma X, Liu R, Pratt EJ, Benson CT, Bhattachar SN, Sloop KW. Effect of Food Consumption on the Pharmacokinetics, Safety, and Tolerability of Once-Daily Orally Administered Orforglipron (LY3502970), a Non-peptide GLP-1 Receptor Agonist. *Diabetes Ther*. 2024;15(4):819-832. doi:10.1007/s13300-024-01554-1
22. Rosenstock J, Hsia S, Nevarez Ruiz L, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes. *N Engl J Med*. 2025;393(11):1065-1076. doi:10.1056/NEJMoa2505669
23. Affuso O, Kaiser KA, Carson TL, et al. Association of run-in periods with weight loss in obesity randomized controlled trials. *Obes Rev*. 2014;15(1):68-73. doi:10.1111/obr.12111
24. Dong Y, Carty J, Goldstein N, et al. Time and metabolic state-dependent effects of GLP-1R agonists on NPY/AgRP and POMC neuronal activity in vivo. *Mol Metab*. 2021;54:101352. doi:10.1016/j.molmet.2021.101352
25. Camilleri M. Gastrointestinal hormones and regulation of gastric emptying. *Curr Opin Endocrinol Diabetes Obes*. 2019;26(1):3-10. doi:10.1097/MED.0000000000000448
26. Park JS, Kim KS, Choi HJ. Glucagon-Like Peptide-1 and Hypothalamic Regulation of Satiation: Cognitive and Neural Insights from Human and Animal Studies. *Diabetes Metab J*. 2025;49(3):333-347. doi:10.4093/dmj.2025.0106
27. Wang X, Lu G, Zhou Y, Zhao G. GLP-1 receptor agonists in metabolic dysfunction–associated steatotic liver disease: mechanistic networks and translational implications: a review. *J Endocrinol Invest*. 2026;49(9):2167-2189. doi:10.1007/s40618-026-02891-7
28. Zafer M, Tavaglione F, Romero-Gómez M, Loomba R. Review Article: GLP -1 Receptor Agonists and Glucagon/ GIP / GLP -1 Receptor Dual or Triple Agonists—Mechanism of Action and Emerging Therapeutic Landscape in MASLD. *Aliment Pharmacol Ther*. 2025;61(12):1872-1888. doi:10.1111/apt.70196
29. Potter KJ, Phinney J, Kulai T, Munro V. Effects of GLP-1 receptor agonist therapy on resolution of steatohepatitis in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Can Assoc Gastroenterol*. 2025;8(2):47-57. doi:10.1093/jcag/gwae057
30. Alper A, Peleg G, Fagin A, et al. Efficacy and safety of orforglipron, an oral small-molecule GLP-1 receptor agonist, on cardiometabolic outcomes: a meta-analysis and

systematic review. *Cardiovasc Diabetol – Endocrinol Rep*. 2026;12(1):9. doi:10.1186/s40842-025-00270-4
31. Kansakar U, Jankauskas SS, Pande S, Mone P, Varzideh F, Santulli G. Orforglipron: A Comprehensive Review of an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity and Type 2 Diabetes. *Int J Mol Sci*. 2026;27(3):1409. doi:10.3390/ijms27031409
32. Li L, Shui D, Zhang X, Tan B, Deng Y. Investigation into the efficacy and safety profile of oral small-molecule GLP-1 receptor agonists in type 2 diabetes and obesity: a systematic review and meta-analysis. *Front Endocrinol*. 2026;17:1854779. doi:10.3389/fendo.2026.1854779
33. Chiang CH, Jaroenlapnopparat A, Colak SC, et al. Glucagon-Like Peptide-1 Receptor Agonists and Gastrointestinal Adverse Events: A Systematic Review and Meta-Analysis. *Gastroenterology*. 2025;169(6):1268-1281. doi:10.1053/j.gastro.2025.06.003
34. Horowitz M, Aroda VR, Han J, Hardy E, Rayner CK. Upper and/or lower gastrointestinal adverse events with glucagon-like peptide-1 receptor agonists: I ncidence and consequences. *Diabetes Obes Metab*. 2017;19(5):672-681. doi:10.1111/dom.12872
35. Bhattarai HB, Paudel BS, Parajuli SR, et al. Gastrointestinal side effects of the non-peptide GLP-1 receptor agonists: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2025;104(52):e46671. doi:10.1097/MD.0000000000046671
36. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials. *Diabetes Obes Metab*. 2017;19(3):336-347. doi:10.1111/dom.12824
37. Ismaiel A, Scarlata GGM, Boitos I, et al. Gastrointestinal adverse events associated with GLP-1 RA in non-diabetic patients with overweight or obesity: a systematic review and network meta-analysis. *Int J Obes*. 2025;49(10):1946-1957. doi:10.1038/s41366-025-01859-6

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Clinical Trial Number

Not applicable.

Use of A.I

We did not use A.I for generative purposes, we used it to correct grammar and to refine the language.

Ethics Statement

This study is a secondary analysis of published data and did not require ethical approval.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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