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Orforglipron, a novel non-peptide oral daily glucagon-like peptide-1 receptor agonist as an anti-obesity medicine: A systematic review and meta-analysis

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Abstract

Background: Orforglipron is a novel once-daily oral non-peptide glucagon-like peptide-1 receptor agonist with several recently published randomized controlled trials (RCTs) evaluating its role in diabetes and obesity. No meta-analysis has analyzed the efficacy and safety of orforglipron; this meta-analysis aimed to address this knowledge gap.

Methods: A systematic search was conducted in electronic databases to identify RCTs that included individuals with obesity who were administered orforglipron and compared to either a placebo or an active comparator. The primary outcome of interest was the percent change in body weight.

Results: From 12 initially screened articles, data from three RCTs involving 774 people were analyzed with a follow-up duration of up to 36 weeks. Compared to placebo, patients receiving orforglipron 12 mg/day (mean difference (MD), MD −5.48%, 95% CI [−7.64, −3.33], $p < 0.01$), 24 mg/day (MD −8.51%, 95% confidence interval (CI) [−9.88, −7.14], $p < 0.01$), 36 mg/day (MD −8.84%, 95% CI [−11.68, −6.00], $p < 0.01$) and 45 mg/day (MD −8.24%, 95% CI [−12.84, −3.63], $p < 0.01$) had a significantly greater percent reduction in body weight. The percentage of patients being able to achieve >15% weight loss from baseline was significantly higher with orforglipron 24 mg/day [Odds ratio (OR) 21.90 (95% CI [4.06, 118.15], $p = 0.0003$), 36 mg/day (OR 17.43, 95% CI [3.18, 95.66], $p = 0.001$) and 45 mg/day (OR 23.17, 95% CI [4.37, 123.03], $p = 0.0002$). Total but not severe adverse events were significantly higher with all the doses of orforglipron compared to placebo, with the hazard ratios being higher with higher doses. Gastrointestinal side-effects were predominant side effects, being dose-dependent, with nausea, vomiting, constipation, and gastroesophageal reflux being the predominant ones.

Conclusion: Orforglipron at 24–45 mg/day doses is an effective weight loss medication. The efficacy versus side effect profile suggests that 24–36 mg/day is the most optimal dose for orforglipron as an anti-obesity medicine.

1 | INTRODUCTION

Developing effective weight loss medications has been an unmet medical need for the last 50 years, becoming even more pertinent today with the increasing global prevalence of obesity.[1,2] Only a few medicines have proven effective as anti-obesity treatments and have gained approval from regulatory agencies like the European Medicine Agency or the US Food and Drug Administration. These medicines include orlistat, liraglutide, naltrexone-bupropion, and phentermine-topiramate and have been associated with only modest weight loss, typically in the range of 3%–5% from baseline body weight.[1–4] Glucagon-like peptide-1 receptor agonists (GLP1RA) have significantly revolutionized the field of obesity therapeutics in this particular context. Use of liraglutide 3 mg daily subcutaneous (s.c.) injections (Satiety and Clinical Adiposity-Liraglutide Evidence [SCALE trial])[5] and semaglutide 2.4 mg once weekly injections [Semaglutide Treatment Effect in People with obesity (STEP 1 trial)][6] over 56 and 68 weeks, respectively, was associated with an impressive mean body weight reduction of 9.2% and 16.9% respectively. Even more impressive weight loss has been noted with dual glucagon-like peptide-1 and gastric inhibitory polypeptide agonist (twincretin) tirzepatide.[7]

An oral formulation of semaglutide with an absorption enhancer has also gained popularity in certain parts of the globe for managing diabetes and obesity.[8] However, the weight loss observed with oral semaglutide, 14 mg taken orally daily, is lower than that of injectable semaglutide.[8] Therefore, there remains an unmet clinical need for oral GLP1RA-based therapy for obesity that offers efficacy similar to injectable GLP1RAs.

Orforglipron is a newly developed non-peptide GLP1RA that is taken orally once a day. Its effectiveness in managing diabetes and obesity has been assessed through a series of recently conducted randomized controlled trials (RCTs).[9–12] Orforglipron stands out due to its prolonged half-life of 29–49 h, which makes it a powerful partial agonist of the GLP-1 receptor. It has a stronger effect on cyclic AMP signaling than on β-arrestin recruitment, resulting in a lower risk of receptor desensitization than other GLP1Ras.[13] However, no systematic review or meta-analysis has analyzed the clinical efficacy, tolerability, safety, and positioning of this novel oral GLP1RA analog as an anti-obesity medicine. Hence, this meta-analysis aimed to evaluate the efficacy and safety of orforglipron as an anti-obesity medication.

2 | METHODS

This meta-analysis strictly complied with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses checklists.[14] The predetermined protocol has been officially recorded in PROSPERO, with a registration number of CRD42023462990. All (RCTs) published up until August 2023 were taken into account. The PICOS criteria were employed for screening and selecting studies. The studies necessitate a minimum of two treatment groups/arms, with one group receiving orforglipron and the other group receiving either a placebo or another active comparator medication. The primary objective was to assess the percent changes in body weight. The secondary objectives of the study were to evaluate the proportion of patients who achieved weight loss greater than 15%, 10%, and 5%, as well as changes in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), waist circumference, body mass index(BMI), and adverse events, including hypoglycemia. The analysis of primary and secondary outcomes was conducted by comparing the control group that received an active comparator medicine, referred to as the active-control group (ACG), with the control group that received a placebo, referred to as the passive-control group (PCG).

PubMed (Medline) was systematically searched with keywords or MESH terms: (orforglipron) OR (LY3502970). Then, Embase, Cochrane database, CNKI database, clinicaltrials.gov, ctri.nic.in, and Google Scholar were searched to ensure any relevant articles were not missed. The authors have previously provided comprehensive methodological details in their published meta-analyses.[15,16] Three authors conducted a risk of bias assessment utilizing the risk of bias assessment tool in Review Manager (RevMan) Version 5.4 computer software. The authors provided a detailed analysis of the various forms of bias examined in previous meta-analyses.[15,16] The data were aggregated employing random effect models to analyze the primary as well as secondary outcomes. Heterogeneity was examined by utilizing forest plots generated for each distinct outcome of interest. The Chi-square test was conducted with N-1 degrees of freedom, adopting an alpha level of 0.05 to determine statistical significance, and the I^2 test was also employed.[17] The specifics of heterogeneity analysis have been expounded upon in previously published meta-analyses.[16] The evidence for the major outcomes was assessed by deploying the Grades of Recommendation, Assessment, Development, and Evaluation approach,[18] with procedural details elaborated in a previous publication by the authors.[16] Funnel plots served as a means to measure publication bias.[18,19]

3 | RESULTS

3.1 | Study selection and study characteristics

The initial search revealed 12 articles. Following screening titles and abstracts, the search was down to 4 RCTs evaluated in detail[9–12]

(Figure S1). Data from three RCTs involving 774 people with diabetes and obesity, which fulfilled all criteria, were analyzed.[9–11] This included 602 individuals who received different doses of orforglipron and 172 individuals in the control group. The RCT by Pratt et al. was excluded from the analysis as it was a phase 1 study in healthy individuals.[12] The baseline characteristics of the study population are included in Table 1.

3.2 | Risk of bias in the included studies

Summaries of the risk of bias of the three studies included in the meta-analysis have been elaborated in Figures 2a and 2b. Random sequence generation, allocation concealment bias, performance bias, detection bias, and reporting bias were found to be at low risk in all three studies. Attrition bias was found to be high in all three studies. Sources of funding, especially funding from pharmaceutical organizations and conflicts of interest, were considered "other bias." All three studies had high "other bias" risk.

Orforglipron versus PCG

3.3 | Effect on body weight and body mass index

Orforglipron (in 2 RCTs, 211 subjects) was superior to placebo in percent reductions of the body weight after 26 weeks of clinical use at all doses- 12 mg/day [mean difference (MD) −5.48% (95% CI: −7.64, −3.33)] [Figure 1A], 24 mg/day [MD −8.51% (95% CI: −9.88, −7.14)] [Figure 1B], 36 mg/day [MD −8.84% (95% CI: −11.68, −6.00)] [Figure 1C], and 45 mg/day [MD -8.24% (95% CI: −12.84, −3.63)] [Figure 1D] (p-values are significant for all).

Although a similar proportion of patients receiving orforglipron 12 mg and placebo achieved at least 15% weight loss [OR 6.95 (95% CI: 0.43, 112.32)], the same dose was superior to placebo in achieving weight loss by at least 10% [OR 11.04 (95% CI: 1.93, 63.09)] and at least 5% [OR 7.53 (95% CI: 4.07, 13.95)] at 26 weeks. Within a similar time frame, orforglipron 24, 36, and 45 mg outperformed placebo in achieving at least 15% weight loss [for 24 mg: OR 21.90 (95% CI: 4.06, 118.15); for 36 mg: OR 17.43 (95% CI: 3.18, 95.66); for 45 mg: OR 23.17 (95% CI: 4.37, 123.03)], at least 10% weight loss [for 24 mg: OR 22.66 (95% CI: 4.47, 114.93); for 36 mg: OR 29.83 (95% CI: 2.56, 347.41); for 45 mg: OR 27.75 (95% CI: 2.44, 315.66)], and at least 5% weight loss [for 24 mg: OR 17.46 (95% CI: 8.59, 35.49); for 36 mg: OR 20.32 (95% CI: 10.15, 40.67); for 45 mg [OR 14.13 (95% CI: 7.44, 26.85)] (p-values are significant for all) [Table 2]. Furthermore, orforglipron (in 2 RCTs, 211 subjects)[9,10] at all doses used in the trials was superior in reductions of BMI [for 12 mg: MD −1.95 kg/m2 (95% CI: −2.83, −1.06); for 24 mg: MD −3.00 kg/m2 (95% CI: −3.78, −2.22); for 36 mg MD −3.15 kg/m2 (95% CI: −4.42, −1.88); and 45 mg MD −4.11 kg/m2 (95% CI: −4.50, −3.72)] had a significantly greater reduction in BMI (p-values are significant for all) [Table 2].

The decline in body weight was dose-dependent and was noted to be maximum with orforglipron 45 mg/day and least with 12 mg/day. The percent reduction in body weight was highest at 36 mg and least with a 12 mg daily dose of orforglipron. Orforglipron at 45 mg/day performed best in achieving at least 15% weight loss, whereas the best results of achieving weight loss by at least 10% and 5% were observed with a 36 mg/day dose. BMI reduction was also dose-dependent maximally seen with orforglipron 45 mg/day.

One study (Wharton 2023) reported weight changes after 36 weeks of treatment. Weight reduction continued through week 36, with the placebo-corrected percentage change from baseline in body weight ranging from 7.1% to 12.3%. The placebo-corrected change in body weight ranged from −7.4 kg to −13.0 kg at week 36. Weight reduction did not appear to have plateaued by week 36. The weight reduction observed at week 36 was greater than at week 26.

3.4 | Waist circumference

Greater reductions in waist circumference were also achieved with all doses of orforglipron compared to placebo [for 12 mg: MD −3.43 cm (95% CI: −5.29, −1.56), p < 0.0003, I^2 = 74%; for 24 mg MD −5.51 cm (95% CI: −7.47, −3.55), p < 0.0001, I^2 = 81%; for 36 mg: MD −5.54 cm (95% CI: −6.48, −4.60), p < 0.0001, I^2 = 0%; and for 45 mg: MD −6.49 cm (95% CI: −10.60, −2.37), p = 0.002, I^2 = 95%] [Table 2] (in 2 RCTs, 211 subjects).[9,10] The reduction in waist circumference, again, was dose-dependent and most pronounced with orforglipron 45 mg/day.

3.5 | Glycemic parameters

Frias et al. assessed changes in HbA1c and FPG.[9] Orforglipron, compared to placebo, achieved significantly greater reductions in HbA1c (MD −1.48% for 12 mg, −1.36% for 24 mg, −1.60% for 36 mg, and −1.67% for 45 mg), and FPG (MD −2.36 mmol/L for 12 mg, −2.28 mmol/L for 24 mg, −2.37 mmol/L for 36 mg, and −1.29 mmol/L for 45 mg) in all the doses.[9]

3.6 | Safety

Three studies reported the safety data of orforglipron versus placebo, summarized in Table 3[9–11] Compared to placebo, the occurrence of total adverse events was significantly higher with orforglipron 12 mg [OR 2.49 (95% CI: 1.25, 4.98), p = 0.01, I^2 = 12%], 24 mg [OR 2.23 (95% CI: 1.13, 4.43), p = 0.02, I^2 = 10%], 36 mg [OR 2.04 (95% CI: 1.08, 3.84), p = 0.03, I^2 = 0%] and 45 mg [OR 2.96 (95% CI: 1.41, 6.21), p = 0.004, I^2 = 17%] daily doses; the highest rates seen with orforglipron 45 mg [Table 3].

Severe adverse events was comparable in all daily dose of orforglipron [for 12 mg: OR 0.37 (95% CI: 0.06, 2.44), p = 0.30, I^2 = 0%; for 24 mg: OR 1.99 (95% CI: 0.58, 6.87), p = 0.28, I^2 = 0%; for 36 mg: OR

TABLE 1 Characteristics of patients with key outcomes of the randomized controlled trials analyzed in this meta-analysis.

|	Frias 2023[9]		Wharton 2023[10]		Pratt 2023[11]	
	Orforglipron	Placebo	Orforglipron	Placebo	Orforglipron	Placebo
Parameter	(n = 278)	(n = 55)	(n = 222)	(n = 50)	(n = 17)	(n = 51)
Age (years)	57.12 (9.2)	58.3 (9.5)	54.1 (10.93)	54 (8.8)	58.5 (6.3)	56 (6)
Male	61.09%	51%	40.5%	50%	62.7%	58.8%
Weight (kg)	100.22 (21.8)	102 (18.8)	100.9 (25.8)	107.6 (25.2)	88.4 (15.06)	90.29 (20.04)
BMI (kg/m^2)	23.7 (6.9)	35.8 (6.2)	37.8 (5.76)	37.8 (6.5)	30.89 (4.09)	31.31 (4.86)
HBA1c (%)	8.09 (0.8)	8.1 (0.9)	5.62 (0.46)	5.6 (0.4)	8.03 (0.91)	8.09 (0.75)
Duration of T2D (years)	6.1 (5.6)	7.8 (6.2)	-	-	11.1 (7.64)	8.63 (4.89)
eGFR (mL/min/1·73 m^2)	89 (17.5)	90.2 (17.7)	83.46 (14.7)	85 (14.5)	-	-
Metformin use	90.6%	93%	-	-	90.2%	88.2%
SBP	133.5 (12.62)	135.2 (14.6)	129.5 (11.5)	128.5 (9.5)	-	-
DBP	79.8 (8.24)	81.5 (7.1)	81.3 (7.8)	81.5 (7.2)	-	-

Note: Data presented as percentages (%) or mean (SD).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus.
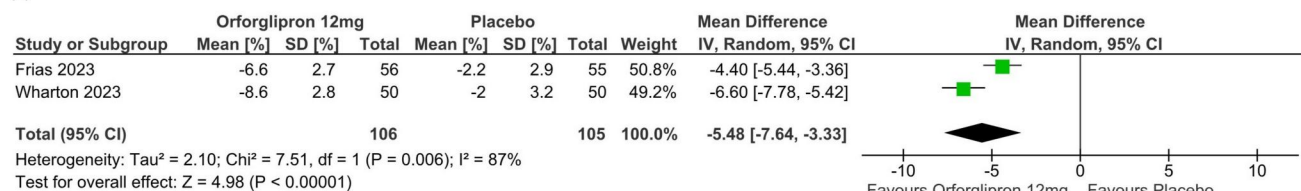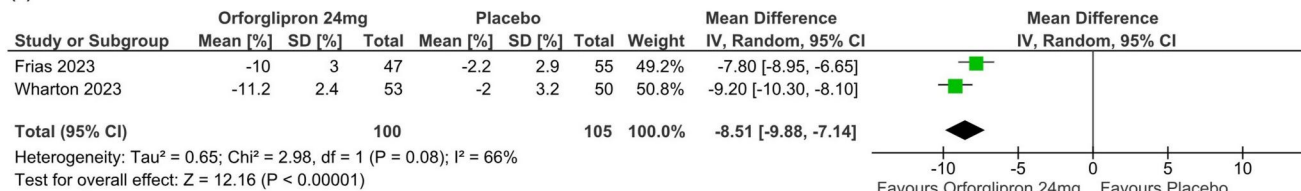
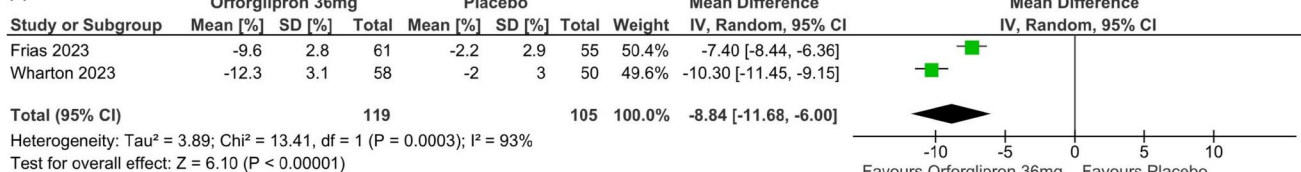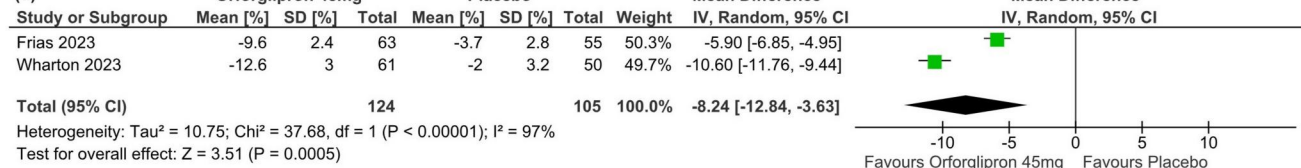**FIGURE 1** Forest plot highlighting (A) percent reduction in body weight with orforglipron 12 mg as compared to PCG (B) percent reduction in body weight with orforglipron 24 mg as compared to PCG; (C) percent reduction in body weight with orforglipron 36 mg as compared to PCG; (D) percent reduction in body weight with orforglipron 45 mg as compared to PCG. PCG, passive-control group.

TABLE 2 Summary of secondary outcome findings.

Outcome variables	Orforglipron arm	Control arm	I² (%)	Pooled effect size	p value
Participants achieving ≥15% weight loss	Orforglipron 12 mg/day	Placebo	55	OR 6.95 (95% CI: 0.43, 112.32)	0.17
	Orforglipron 24 mg/day	Placebo	0	OR 21.90 (95% CI: 4.06, 118.15)	0.0003
	Orforglipron 36 mg/day	Placebo	1	OR 17.43 (95% CI: 3.18, 95.66)	0.001
	Orforglipron 45 mg/day	Placebo	0	OR 23.17 (95% CI: 4.37, 123.03)	0.0002
Participants achieving ≥10% weight loss	Orforglipron 12 mg/day	Placebo	56	OR 11.04 (95% CI: 1.93, 63.09)	0.007
	Orforglipron 24 mg/day	Placebo	50	OR 22.66 (95% CI: 4.47, 114.93)	0.0002
	Orforglipron 36 mg/day	Placebo	77	OR 29.83 (95% CI: 2.56, 347.41)	0.007
	Orforglipron 45 mg/day	Placebo	77	OR 27.75 (95% CI: 2.44, 315.66)	0.007
Participants achieving ≥5% weight loss	Orforglipron 12 mg/day	Placebo	0	OR 7.53 (95% CI: 4.07, 13.95)	<0.001
	Orforglipron 24 mg/day	Placebo	0	OR 17.46 (95% CI: 8.59, 35.49)	<0.001
	Orforglipron 36 mg/day	Placebo	0	OR 20.32 (95% CI: 10.15, 40.67)	<0.001
	Orforglipron 45 mg/day	Placebo	0	OR 14.13 (95% CI: 7.44, 26.85)	<0.001
Body mass index (kg/m²)	Orforglipron 12 mg/day	Placebo	91	MD −1.95 kg/m² (95% CI: −2.83, −1.06)	<0.0001
	Orforglipron 24 mg/day	Placebo	86	MD −3.00 kg/m² (95% CI: −3.78, −2.22)	<0.0001
	Orforglipron 36 mg/day	Placebo	95	MD −3.15 kg/m² (95% CI: −4.42, −1.88)	<0.0001
	Orforglipron 45 mg/day	Placebo	56	MD −4.11 kg/m² (95% CI: −4.50, −3.72)	<0.0001
Waist circumference (cm)	Orforglipron 12 mg/day	Placebo	74	MD −3.43 (95% CI: −5.29, −1.56)	<0.0003
	Orforglipron 24 mg/day	Placebo	81	MD −5.51 cm (95% CI: −7.47, −3.55)	<0.0001
	Orforglipron 36 mg/day	Placebo	0	MD −5.54 cm (95% CI: −6.48, −4.60)	<0.0001
	Orforglipron 45 mg/day	Placebo	95	MD −6.49 cm (95% CI: −10.60, −2.37)	0.002

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio.

1.44 (95% CI: 0.14, 14.62), $p = 0.76$, $I^2 = 46\%$; and for 45 mg: OR 0.70 (95% CI: 0.14, 3.48), $p = 0.66$, $I^2 = 0\%$] and placebo groups [Table 3].

Compared to placebo, patients receiving orforglipron at any dose experienced higher occurrences of nausea, vomiting, and constipation. A higher risk of diarrhea was found with 24 and 45 mg daily doses but not with 12 and 36 mg daily doses. All but 12 mg/day doses increased the risk of gastroesophageal reflux. An increased risk of decreased appetite was found only with 24/day dose [Table 3].

3.6.1 | Orforglipron versus ACG

As data were available from only one study, which compared different doses of orforglipron with once-weekly dulaglutide 1.5 mg, no meta-analysis could be done comparing their efficacy and safety.[9] The comparison of the effectiveness and safety of orforglipron with once-weekly dulaglutide is available as Supporting Information S2.

TABLE 3 The results of safety outcomes in meta-analysis.

Outcome variables	Orforglipron arm	Control arm	I^2 (%)	Pooled effect size, OR (95% CI)	p value
Total adverse events	Orforglipron 12 mg/day	Placebo	12	2.49 (1.25, 4.98)	0.01
	Orforglipron 24 mg/day	Placebo	10	2.23 (1.13, 4.43)	0.02
	Orforglipron 36 mg/day	Placebo	0	2.04 (1.08, 3.84)	0.03
	Orforglipron 45 mg/day	Placebo	17	2.96 (1.41, 6.21)	0.04
Severe adverse events	Orforglipron 12 mg/day	Placebo	0	0.37 (0.06, 2.44)	0.30
	Orforglipron 24 mg/day	Placebo	0	1.99 (0.58, 6.87)	0.28
	Orforglipron 36 mg/day	Placebo	46	1.44 (0.14, 14.62)	0.76
	Orforglipron 45 mg/day	Placebo	0	0.70 (0.14, 3.48)	0.66
Nausea	Orforglipron 12 mg/day	Placebo	0	9.77 (4.60, 20.74)	<0.0001
	Orforglipron 24 mg/day	Placebo	0	10.67 (4.86, 23.42)	<0.0001
	Orforglipron 36 mg/day	Placebo	0	7.52 (3.32, 17.03)	<0.0001
	Orforglipron 45 mg/day	Placebo	24	8.00 (3.10, 20.63)	<0.0001
Vomiting	Orforglipron 12 mg/day	Placebo	0	8.81 (3.08, 25.19)	<0.0001
	Orforglipron 24 mg/day	Placebo	0	11.68 (4.13, 32.99)	<0.0001
	Orforglipron 36 mg/day	Placebo	38	7.27 (1.61, 32.81)	0.01
	Orforglipron 45 mg/day	Placebo	0	10.41 (3.71, 29.26)	<0.0001
Constipation	Orforglipron 12 mg/day	Placebo	0	5.60 (1.92, 16.33)	0.002
	Orforglipron 24 mg/day	Placebo	0	7.53 (2.47, 22.95)	<0.001
	Orforglipron 36 mg/day	Placebo	0	5.85 (1.92, 17.81)	0.002
	Orforglipron 45 mg/day	Placebo	0	3.45 (1.09, 10.86)	0.03
Diarrhea	Orforglipron 12 mg/day	Placebo	0	2.23 (1.01, 4.91)	0.05
	Orforglipron 24 mg/day	Placebo	0	3.60 (1.57, 8.27)	0.002
	Orforglipron 36 mg/day	Placebo	8	1.40 (0.55, 3.56)	0.48
	Orforglipron 45 mg/day	Placebo	27	3.04 (1.25, 7.37)	0.01
Gastroesophageal reflux	Orforglipron 12 mg/day	Placebo	0	4.53 (0.75, 27.45)	0.10
	Orforglipron 24 mg/day	Placebo	0	7.16 (1.54, 33.39)	0.01
	Orforglipron 36 mg/day	Placebo	0	9.46 (1.71, 52.47)	0.01
	Orforglipron 45 mg/day	Placebo	0	3.54 (1.08, 11.56)	0.04
Decreased appetite	Orforglipron 12 mg/day	Placebo	0	3.34 (0.95, 11.74)	0.06
	Orforglipron 24 mg/day	Placebo	0	2.87 (0.78, 10.54)	0.11
	Orforglipron 36 mg/day	Placebo	0	1.81 (0.43, 7.65)	0.42
	Orforglipron 45 mg/day	Placebo	0	6.12 (1.31, 28.46)	0.02

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio.

The grades of the certainty of the evidence of the results are given in the summary of findings table [Table 4].

4 | DISCUSSION

GLP1RAs and GLP1 receptor-based therapies have been the game changers in weight loss medicines. The novel twincretin tirzepatide, which combines a dual glucose-dependent insulinotropic polypeptide

(GIP) and GLP1RA, has demonstrated a reduction in body weight of 11.9% and 12.4% at doses of 10 and 15 mg per week injection, respectively, over 6–18 months of clinical use. However, it is worth noting that gastrointestinal side effects, including nausea, vomiting, and diarrhea, have been the primary limiting factors associated with tirzepatide use.[7] Retatrutide is a single peptide with agonist activity at the GIP, glucagon-like peptide (GLP)-1, and glucagon receptors. Initial phase 2 RCTs have documented a 16.81% and 16.94% weight loss with retatrutide at doses of 8 mg/week and 12 mg/week,

TABLE 4 Summary of findings of the key outcomes of this meta-analysis.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with orforglipron 24 mg			
Percent reduction in weight (26 weeks)	The mean percent reduction in weight (26 weeks) was −2.1%	MD 8.51 lower (9.88 lower to 7.14 lower)	-	205 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Total adverse events (TAEs)	648 per 1000	804 per 1000 (675–891)	OR 2.23 (1.13–4.43)	231 (3 RCTs)	⊕⊕⊕⊕ High

Outcomes	Anticipated absolute effects* (95% CI)		Relative (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with orforglipron 36 mg			
Percent reduction in weight (26 weeks)	The mean percent reduction in weight (26 weeks) was −2.1%	MD 8.84 lower (11.68 lower to 6 lower)	-	224 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Total adverse events (TAEs)	686 per 1000	817 per 1000 (702–893)	OR 2.04 (1.08–3.84)	224 (2 RCTs)	⊕⊕⊕⊕ High

Outcomes	Anticipated absolute effects* (95% CI)		Relative (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with orforglipron 45 mg			
Percent reduction in weight (26 weeks)	The mean percent reduction in weight (26 weeks) was −2.9%	MD 8.24 lower (12.84 lower to 3.63 lower)	-	229 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Total adverse events (TAEs)	648 per 1000	845 per 1000 (721–919)	OR 2.96 (1.41–6.21)	255 (3 RCTs)	⊕⊕⊕⊕ High

[a]$I^2 > 50\%$ suggest considerable heterogeneity in data.

[b]The funnel plot is suggestive of the presence of most of the studies outside the plot; hence, it is likely that a significant publication bias is present.

respectively, escalated over 24 weeks of therapy.[20] Another RCT documented a 22.8% and 24.2% weight loss with retatrutide at 8 mg/week doses and 12 mg/week over 48 weeks of therapy.[21] Again, gastrointestinal adverse events were the most common issues noted, which were found to be dose-dependent and primarily seen at higher doses used for weight loss. This impressive weight reduction with the various long-acting gut peptide-based therapies is largely believed to result from a reduced food/calorie intake, which results from decreased appetite and earlier and increased satiety, coupled with controlled and mindful eating.

Evidence published to date suggests that the weight loss potential of injectable GLP1RAs tends to be better than that of oral GLP1RAs. The Peptide Innovation for Early Diabetes Treatment 1-8 series of studies showed that oral semaglutide at doses of 14 mg/day was associated with a 4.4%–5.2% weight loss from baseline over 1.5 years of clinical use,[22] which is much lower than 9.2% and 16.9% noted with liraglutide 3 mg/day and injectable semaglutide 2.4 mg/week respectively.[7] This meta-analysis showed that oral orforglipron at 24 mg/day and 36 mg/day were associated with 8.51% and 8.84% weight loss from baseline over 6 months of clinical use, respectively. Hence, the initial weight loss data with orforglipron is encouraging, appearing to be better than oral semaglutide at 14 mg/day and comparable to injectable liraglutide at 3 mg/day. Interestingly,

further increasing the orforglipron dose to 45 mg/day from 36 mg/day was not associated with additional benefits in weight loss. Notably, weight loss and reduction in HbA1c and FPG were better with orforglipron 12, 24, 36, and 45 mg/day compared to injectable dulaglutide 1.5 mg/week, albeit at an increased incidence of gastrointestinal side effects.

The current data suggest that orforglipron should be initiated at a lower dose of 6–9 mg/day and then rapidly up-titrated to 12 mg/day. Depending on the clinical response and tolerance, the dosage can be further increased to a maximum of 45 mg/day. Weight loss data with lower doses of orforglipron, like 12 mg/day, was inferior to 24–45 mg/day doses. Interestingly, HbA1c reduction with orforglipron appears to be similar at doses ranging from 12 to 45 mg/day. The side effect profile of orforglipron is identical to other GLP1RAs and tends to be predominantly gastrointestinal and dose-dependent. The hazard ratio values for the different gastrointestinal side effects progressively increased with orforglipron doses from 12 to 45 mg/day, with no sign of plateau. Therefore, considering both efficacy and the side effect profile, orforglipron at 24 mg/day and 36 mg/day may be the two most optimal doses for weight loss and glycemic efficacy with manageable gastrointestinal side effects. There are many advantages of orforglipron compared to the currently available GLP1RAs for weight loss. Since it is a small non-peptide, the gut

peptidases do not break it down. Strict fasting for consumption, as seen with semaglutide, is not needed for orforglipron. Also, being a non-peptide, strictly maintaining a cold chain for storage and transport is not important for orforglipron.[11–13]

A lot of interesting advancements are happening in the field of oral GLP1RAs. A recently published paper showed that 68 weeks of use of a very high dose of oral semaglutide, 50 mg/day, was associated with 15.1% weight loss from the baseline, with 80% of patients reporting gastrointestinal side effects.[23] Danuglipron is another small molecule oral GLP1RA that has reached the stage of phase-3 clinical trials in diabetes and obesity.[24]

Although orforglipron has weight loss data that is less impressive than injectable tirzepatide and injectable retatrutide, it has a major advantage of being an oral and not injectable medication with less gastrointestinal side effects based on the hazard ratio values.

5 | CONCLUSION

In conclusion, orforglipron at 24 mg/day and 36 mg/day may be the best doses of this novel oral GLP1RA for managing diabetes and obesity. Orforglipron is a welcome addition to the basket of oral GLP1Ras, which until now only included oral semaglutide.

AUTHOR CONTRIBUTIONS

The meta-analysis was conceptualized by Deep Dutta and Lakshmi Nagendra. The literature search was done by A. B. M. Kamrul-Hasan, Meha Sharma, Beatrice Anne, and Manoj Kumar. Detailed reviews of articles were done by A. B. M. Kamrul-Hasan, Meha Sharma, and Manoj Kumar. Data entry was done by Deep Dutta, Lakshmi Nagendra, and A. B. M. Kamrul-Hasan. Statistical analysis was done by Deep Dutta, A. B. M. Kamrul-Hasan, and Lakshmi Nagendra. All authors contributed equally to the manuscript preparation and approval for submission. The manuscript has been read and approved by all the authors for submission to this journal for consideration for publication.

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