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

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Summary

Background Elecoglipron (AZD5004) is an oral small-molecule glucagon-like peptide-1 (GLP-1) receptor agonist administered once daily without food or fluid restriction, in development for weight management in people living with obesity or overweight and type 2 diabetes. We assessed the efficacy, safety, and tolerability of elecoglipron versus placebo in participants with obesity or overweight and at least one weight-related condition without diabetes.

Methods In this double-blind, randomised, controlled, phase 2 dose-ranging study with a total treatment duration of 36 weeks, adult participants were recruited from medical research centres and hospitals in Australia, Canada, Germany, Japan, Taiwan, the UK, and the USA. Participants were aged 18 years or older living with obesity (BMI ≥30 kg/m²) or with overweight (BMI ≥27 kg/m²) with at least one weight-related condition and without type 2 diabetes. Eligible participants were randomly assigned in a 2:3:3:3:3:5 ratio to receive 5 mg, 15 mg, 50 mg, 75 mg (weekly titration), or 75 mg (every 2-week titration) of elecoglipron or matching placebo. Elecoglipron was administered as oral once-daily tablets without titration (5 mg and 15 mg) and as three different dose-titration regimens. The daily dose of 50 mg was evaluated using an every-4-weeks dose-escalation schedule, while 75 mg was assessed with weekly or every 2-week dose-escalation schedules. Participants, treating physicians, and sponsor were masked to the treatment allocation. The dual primary endpoints were percent change in bodyweight from baseline and the proportion of patients reaching at least 5% weight loss at week 26. Safety and tolerability were assessed in all participants who received at least one dose of study treatment. This trial is registered at ClinicalTrials.gov (NCT06579092) and is completed.

Findings From Oct 8, 2024, to Feb 18, 2025, 472 individuals were screened for potential study inclusion, 162 did not meet the inclusion criteria, and 310 participants were randomly assigned to the varied elecoglipron groups or placebo. 288 participants (93%) completed the study and 231 (75%) completed the assigned treatment. The mean age of participants was 48·4 years (SD 13·7), 225 (73%) were female, 85 (27%) were male, their mean bodyweight was 106·9 kg (SD 24·1), and their mean BMI was 38·2 kg/m² (SD 7·2). At week 26, the estimated mean change from baseline in bodyweight was between –2·6% (5 mg elecoglipron), and –10·5% (75 mg with weekly titration steps) compared with –0·6% with placebo. The estimated proportion of participants reaching weight reductions of at least 5% at week 26 was 40·4–88·8% with elecoglipron versus 15·6% with placebo. Adverse events were reported by 84% (27 of 32) to 98% (48 of 49) of participants across elecoglipron doses compared with 84% (68 of 81) in the placebo group, the most common being nausea, constipation, diarrhoea, headache, and vomiting.

Interpretation Daily oral elecoglipron demonstrated clinically meaningful weight reductions and a safety and tolerability profile consistent with the GLP-1 receptor agonist class in this phase 2 dose-ranging study, supporting phase 3 investigation in people living with obesity or overweight.

Funding AstraZeneca.

Lancet 2026; 407: 2503–14

Published Online June 8, 2026 https://doi.org/10.1016/S0140-6736(26)00748-8

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Introduction

Weight loss can significantly reduce the risk of overweight-related or obesity-related conditions, such as hypertension and cardiometabolic disorders.[1,2] In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists have offered proven benefits for bodyweight and cardiovascular risk reduction as an adjunct to lifestyle modification.[3–6] First-generation GLP-1 receptor agonists were formulated as injectable peptides and are, for some users, associated with limitations such as lower adherence due to route of administration.[6,7] Furthermore, requirements for cold chain supply and refrigerated storage might restrict access.[8]

Oral formulations of small-molecule GLP-1 receptor agonists have the potential to offer similar clinical benefits to injectables and further improve acceptance

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Research in context

Evidence before this study

We searched PubMed for review articles published in English between June, 2021, and May, 2026, using the search term "oral GLP-1 receptor agonist". Glucagon-like peptide-1 (GLP-1) receptor agonists have transformed the management of obesity and type 2 diabetes, producing clinically meaningful weight loss and improvements in glucose control, as well as cardiometabolic risk. Injectable GLP-1 receptor agonists have showed substantial weight reductions in weight management trials as well as in clinical practice. However, injectable administration could negatively affect adherence in some patients. Furthermore, injectable GLP-1 receptor agonists require cold chain transport and storage which drives cost and could be perceived as impractical by many users. Semaglutide administered as an oral peptide GLP-1 receptor agonist has shown good efficacy in clinical trials, but requires fasting conditions for optimal bioavailability. In recent years, development of non-peptide oral small-molecule GLP-1 receptor agonists has accelerated. Phase 2 and 3 studies of agents including orforglipron have demonstrated that oral non-peptide GLP-1 receptor agonism can reach clinically relevant weight loss, but tolerability and discontinuation at higher doses remain key challenges. Additionally, uncertainty remains regarding the dose–response relationship, optimal titration strategies, and longer-term weight loss trajectories.

Added value of this study

The VISTA phase 2 trial evaluated elecoglipron, a novel oral non-peptide small-molecule GLP-1 receptor agonist, across a broad dose range (5–75 mg) in adults living with obesity or overweight without type 2 diabetes. At the highest dose (75 mg), mean weight loss reached 10·5% at 26 weeks and increased further to 11·8% at 36 weeks, demonstrating sustained weight reduction without evidence of a plateau yet being reached. Similarly, the estimated proportion of participants reaching weight reductions of at least 5% at 26 weeks was up to 89%, among participants receiving elecoglipron 75 mg. The trial provides important insights into tolerability and dose escalation. The safety profile of elecoglipron was consistent with findings from other trials within the GLP-1 receptor agonist class in phase 2 with nausea, constipation, diarrhoea, and vomiting being among the most common adverse events reported.

Implications of all the available evidence

Elecoglipron resulted in notable weight loss in adults living with obesity or overweight without type 2 diabetes. The sustained reduction in bodyweight up to 36 weeks without evidence of a plateau suggests that maximal weight loss might not have been reached by 6 months; longer-term evaluation in phase 3 trials is needed to confirm the extent of longer-term weight loss. Elecoglipron does not have food or fluid dosing restrictions and might offer a convenient, effective, and safe oral therapy for people living with obesity or overweight. Phase 3 studies will be required to confirm long-term efficacy and safety.

and adherence, and practical handling aspects.[6,7,9] The first approved oral GLP-1 receptor agonist preparation, semaglutide, is also a peptide which limits oral bioavailability. Fasting for 8 h before intake of oral semaglutide is recommended, followed by another 30 min before eating or drinking.[10] Currently, several oral, non-peptide, small-molecule GLP-1 receptor agonists, which could further improve convenience and thereby adherence, are at different stages of clinical development. There remains a need for next-generation GLP-1 receptor agonist treatment options that deliver clinically meaningful efficacy and a favourable safety and tolerability profile, in a practical formulation. Notably, these small molecules also open the possibility for fixed-dose combinations with other small molecules, such as SGLT2 inhibitors, to enhance efficacy and cardiorenal protection in patients living with obesity or overweight.[5,11]

Elecoglipron (AZD5004/ECC5004) is an oral, small-molecule GLP-1 receptor agonist in development for weight management in patients living with obesity or overweight, and for glycaemic control in those with type 2 diabetes. Elecoglipron has demonstrated an encouraging safety, tolerability, and pharmacokinetic profile compatible with once-daily dosing in a phase 1, first-in-human study.[12] The phase 2 VISTA trial aimed to evaluate the efficacy, safety, and tolerability of elecoglipron in adults living with obesity or overweight and at least one weight-related condition.

Methods

Study design

VISTA is a global, randomised, parallel-group, double-blind, placebo-controlled, multicentre phase 2 study which assessed the efficacy, safety, and tolerability of elecoglipron compared with placebo in adults living with obesity or overweight and at least one weight-related condition. The trial was conducted across seven countries: Australia, Canada, Germany, Japan, Taiwan, the UK, and the USA. Investigative research sites in multiple countries, including hospital-based centres, specialist outpatient research clinics, and primary care sites were included. Participants were recruited through the participating sites in accordance with local clinical practice; referral pathways (eg, from general practice) were not standardised or mandated across countries. Sites were selected based on their ability to meet standard clinical trial requirements, including appropriate infrastructure, trained personnel, regulatory and ethics approvals, capability to perform protocol-defined

assessments and investigational product administration, and access to an appropriate target patient population.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards or independent ethics committees at all sites approved the protocol before study initiation, and all participants provided written informed consent (appendix 1 p 4). A separate clinical events adjudication committee, masked to treatment, was set up to adjudicate prespecified adverse events. The statistical analysis plan is presented as appendix 2. This trial is registered with ClinicalTrials.gov (NCT06579092) and euclinicaltrials.eu (2024-513691-18-00).

The target top dose was adjusted during the trial based on phase 1 tolerability and pharmacokinetic data, aggregated after trial start. During protocol development, the study team met with people living with obesity. A total of 24 people from five countries participated in interviews. The team discussed the study visit schedule, study drug administration, visit procedures, and tools to support participation and retention. Additionally, the patients provided feedback about the informed consent form and diet and exercise advice provided to all study participants. Based on the input, the number of fasting visits and the visit frequency were reduced.

Participants

Adults 18 years and older were eligible for participation if they were living with obesity (a BMI ≥30 kg/m²) or with overweight (BMI ≥27 kg/m²) and at least one treated or untreated weight-related condition (hypertension, dyslipidaemia or hyperlipidaemia, cardiovascular disease, or obstructive sleep apnoea. Stable bodyweight (±5% bodyweight change) in the 3 months before screening was also required.

Individuals were excluded if they had obesity induced by endocrine disorders, such as Cushing's syndrome or monogenic or syndromic obesity such as Prader–Willi syndrome, had received prescription or non-prescription medication for weight loss within the 3 months before screening, or previous or planned (within study period) bariatric surgery or fitting of a weight loss device (eg, a gastric balloon or duodenal barrier). Other key exclusion criteria included a history of type 1 or type 2 diabetes, glycated haemoglobin A_{1c} of 6·5% or more (48 mmol/mol) at screening, or treatment with diabetes medication in the 3 months before screening. A full list of inclusion and exclusion criteria is provided in appendix 1 (p 5). Self-reported data on sex (male, female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, not reported, other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported) were collected.

Randomisation and masking

Study site staff and investigators working in the trial enrolled eligible participants who met full inclusion and exclusion criteria. All participants were randomly assigned centrally to treatment using central interactive response technology with randomisation and trial supply management. Eligible participants were randomly assigned in a 2:3:3:3:3:5 ratio to receive 5 mg (no titration), 15 mg (no titration), 50 mg (every 4-week titration), 75 mg (weekly titration), or 75 mg (every 2-week titration) of elecoglipron for each of the five active groups, or matching placebo. Participants, investigators, and sponsor personnel were masked to elecoglipron and placebo assignment. All doses of trial treatment were administered orally once daily. Elecoglipron and matching placebo tablets were identical in appearance at each dose level.

See Online for appendix 1

See Online for appendix 2

Procedures

The overall study duration was up to 42 weeks, including a screening period of up to 4 weeks and a treatment duration of up to 36 weeks. Visit frequency was weekly for the first 4 weeks of treatment, then approximately every 2 weeks until the final two on-treatment visits, which were 4 weeks apart. A final follow-up visit was scheduled approximately 14 days after the last on-treatment visit.

Elecoglipron was tested across a dose range from 5 mg to 75 mg, and was self-administered in two oral once-daily tablet schedules without titration (5 mg or 15 mg) and as three different dose-titration regimens, in which the 50 mg daily dose was evaluated using dose-escalation once every 4 weeks, and the 75 mg daily dose was evaluated using weekly or every 2-week dose-escalation schedules (appendix 1 p 18). All participants received advice and support to develop or continue diet and physical activity behaviours to support weight loss and healthy lifestyle. The study protocol recommended dietary advice aiming for a 500–750 kcal daily deficit. Bodyweight, vital signs (pulse rate, systolic and diastolic blood pressure), 12-lead ECG, blood and urine samples, adverse events, concomitant medications, Columbia-Suicide Severity Rating Scale, and Patient Health Questionnaire-9 (PHQ-9; only in the USA) were assessed at all visits.

Outcomes

The dual primary endpoints were percent change in bodyweight from baseline at week 26 and the proportion of patients reaching at least 5% weight loss at week 26.

Secondary endpoints were percent change in bodyweight from baseline at week 36, reaching at least 5% weight loss at week 36, absolute change in bodyweight from baseline at weeks 26 and 36, and reaching at least 10% and 15% weight loss at weeks 26 and 36.

Safety and tolerability were assessed, including the occurrence and time to first occurrence of an adverse event, serious adverse event, serious adverse event with an outcome of death, adverse event leading to treatment

discontinuation or dose reduction, and those possibly related to elecoglipron as assessed by the investigator. Key vital signs, electrocardiograms, and centrally assessed laboratory parameters were also evaluated.

Statistical analysis

The dual primary endpoints each provided about 80% or more power for at least 160 evaluable participants at week 26 when comparing each elecoglipron group with the pooled placebo group. The efficacy estimand (used in the main analysis of primary, secondary, and exploratory endpoints) included only data collected before any intercurrent event (either permanent discontinuation of study intervention, bariatric surgery, or death), thereby estimating the treatment effect as if any intercurrent event did not happen.

The percent change in bodyweight from baseline at week 26 was analysed using a mixed model for repeated measures comprising the fixed effects of baseline weight (kg), sex, baseline BMI (<30 kg/m², ≥30 kg/m²), treatment, and interaction of visit and treatment-by-visit. Missing data and data after the occurrence of any intercurrent event was implicitly imputed under the missing-at-random assumption. A similar analysis was performed for all continuous efficacy endpoints. For patients reaching weight loss of 5% or more from baseline at week 26, effects were analysed using logistic regression, stratified by baseline weight (kg), sex, and baseline BMI (<30 kg/m², ≥30 kg/m²). Missing data and data after the occurrence of any intercurrent event were explicitly imputed under the missing-at-random assumption and the resulting estimates were combined using Rubin's rules. A similar analysis was performed for all binary efficacy endpoints.

A supplementary subgroup analysis was conducted. For each subgroup variable and its categories, the same model used in the main analysis was fitted separately within each category; for example, for male and female. The significance of the subgroup-by-treatment interaction was obtained by fitting the same model as the main analysis with the addition of the fixed effects for subgroup, subgroup-by-treatment, and subgroup, subgroup-by-treatment-by-visit.

Safety outcomes were assessed on the full analysis set, including all randomly assigned participants who received at least one dose of study intervention, and according to the treatment group to which participants were randomly assigned.

All hypothesis tests were performed two-sided at $\alpha=0\cdot05$ and 95% CIs were unadjusted for multiplicity. Analyses were done with SAS 9·4. The full statistical analyses are described in appendix 2.

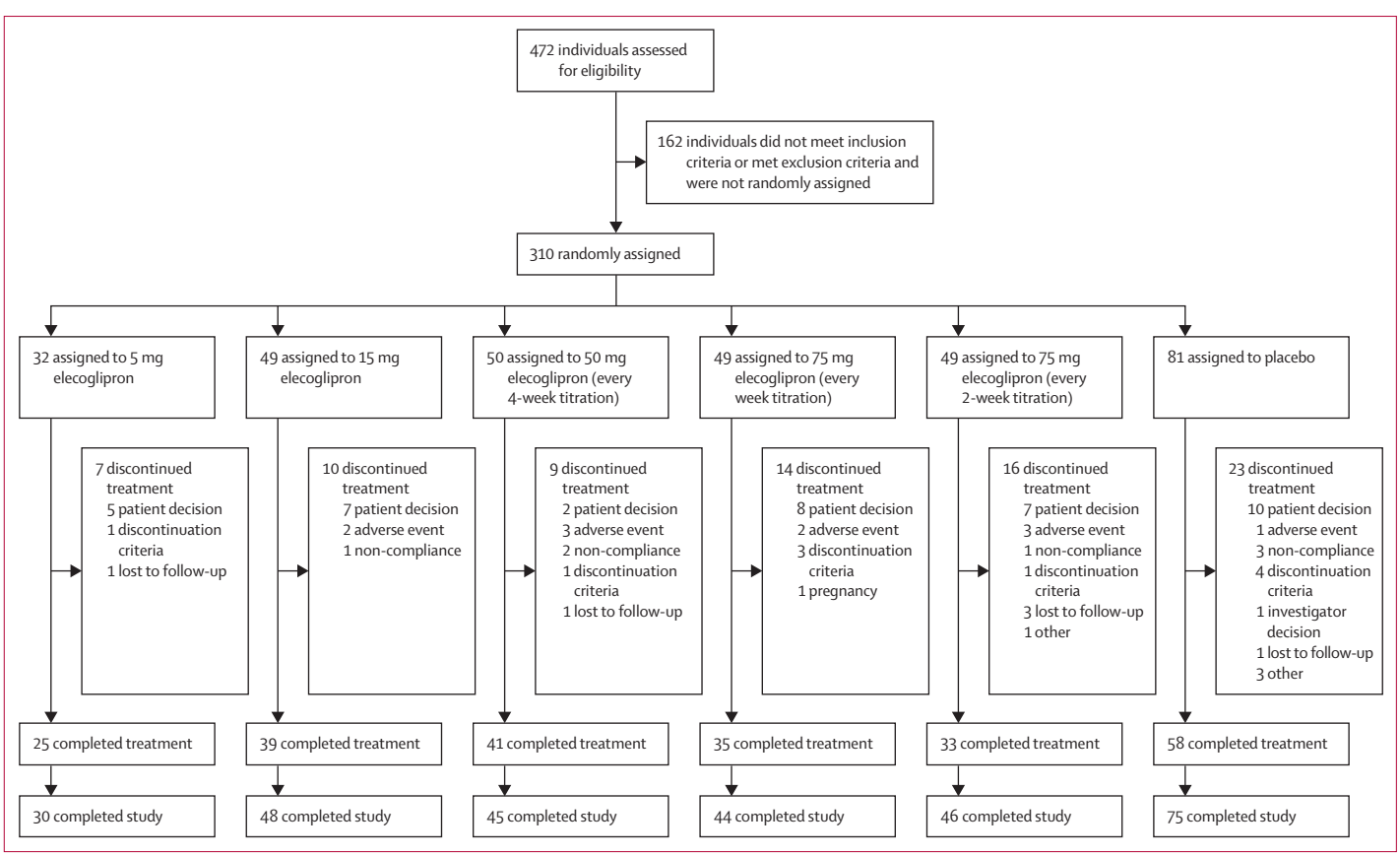


Figure 1: **Trial profile**

	Elecoglipron					Pooled placebo (n=81)	Total (N=310)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)		
Age, years	50·7 (12·2)	46·7 (13·3)	51·0 (12·7)	48·0 (11·9)	48·9 (15·7)	46·9 (14·7)	48·4 (13·7)
Females	26 (81%)	33 (67%)	40 (80%)	28 (57%)	41 (84%)	57 (70%)	225 (73%)
Males	6 (19%)	16 (33%)	10 (20%)	21 (43%)	8 (16%)	24 (30%)	85 (27%)
Race							
American Indian or Alaska Native	0	0	0	0	0	1 (1%)	1 (<1%)
Asian	4 (13%)	9 (18%)	5 (10%)	9 (18%)	7 (14%)	10 (12%)	44 (14%)
Black or African American	5 (16%)	4 (8%)	10 (20%)	3 (6%)	4 (8%)	11 (14%)	37 (12%)
Native Hawaiian or other Pacific Islander	0	0	0	1 (2%)	0	0	1 (<1%)
Multiple	0	0	1 (2·0%)	0	1 (2%)	0	2 (1%)
White	23 (72%)	35 (71%)	33 (66%)	36 (73%)	37 (76%)	59 (73%)	223 (72%)
Not reported	0	1 (2%)	1 (2%)	0	0	0	2 (1%)
Bodyweight, kg	107·5 (20·7)	109·7 (21·6)	104·4 (20·8)	106·7 (27·5)	103·5 (28·1)	108·7 (24·2)	106·9 (24·1)
BMI, kg/m²	38·7 (5·8)	39·0 (6·8)	37·8 (5·9)	37·4 (8·4)	37·3 (8·3)	38·8 (7·2)	38·2 (7·2)
BMI range							
<30 kg/m²	0	2 (4%)	1 (2%)	4 (8%)	3 (6%)	4 (5%)	14 (5%)
30 to <35 kg/m²	11 (34%)	15 (31%)	17 (34%)	18 (37%)	22 (45%)	21 (26%)	104 (34%)
35 to <40 kg/m²	8 (25%)	10 (20%)	14 (28%)	13 (27%)	9 (18%)	27 (33%)	81 (26%)
≥40 kg/m²	13 (41%)	22 (45%)	18 (36%)	14 (29%)	15 (31%)	29 (36%)	111 (36%)
Obesity-related comorbidities							
Hypertension	8 (25%)	16 (33%)	17 (34%)	17 (35%)	13 (27%)	27 (33%)	98 (32%)
Dyslipidaemia	7 (22%)	10 (20%)	7 (14%)	16 (33%)	8 (16%)	14 (17%)	62 (20%)
Cardiovascular disease	1 (3%)	2 (4%)	0	1 (2%)	1 (2%)	3 (4%)	8 (3%)
Obstructive sleep apnoea	6 (19%)	9 (18%)	8 (16%)	6 (12%)	5 (10%)	8 (10%)	42 (14%)
Waist circumference, cm							
Males	128·5 (10·9)	123·4 (15·5)	119·4 (15·5)	122·6 (17·6)	129·7 (26·9)	122·9 (17·4)	123·5 (17·3)
Females	109·2 (10·8)	112·6 (17·0)	114·2 (18·7)	106·3 (15·8)	108·7 (12·7)	110·4 (15·1)	110·4 (15·4)
Glycated haemoglobin group							
≥5·7%	8 (25%)	17 (35%)	15 (30%)	16 (33%)	16 (33%)	35 (43%)	107 (35%)
Blood pressure, mm Hg							
Systolic	125·3 (14·2)	121·4 (14·7)	127·4 (14·0)	124·1 (12·3)	124·6 (14·7)	125·7 (12·3)	124·9 (13·6)
Diastolic	81·0 (8·4)	78·5 (10·5)	83·6 (9·9)	80·9 (6·9)	80·3 (8·2)	80·7 (8·0)	80·8 (8·7)
Pulse, beats per min	75·6 (10·4)	73·9 (10·0)	71·7 (10·2)	72·3 (10·1)	69·6 (10·0)	70·7 (9·8)	72·0 (10·1)
eGFR, mL/min per 1·73m²	97·2 (15·2)	100·0 (18·7)	97·1 (18·1)	100·4 (15·4)	96·0 (19·4)	102·1 (17·4)	99·2 (17·6)

Data are reported as mean (SD) or n (%). Percentages might not total 100 because of rounding. eGFR=estimated glomerular filtration rate.

Table 1: **Baseline characteristics**

Role of the funding source

The funder of the study contributed to study design, study conduct, data collection, data analyses, data interpretation, and writing of this report.

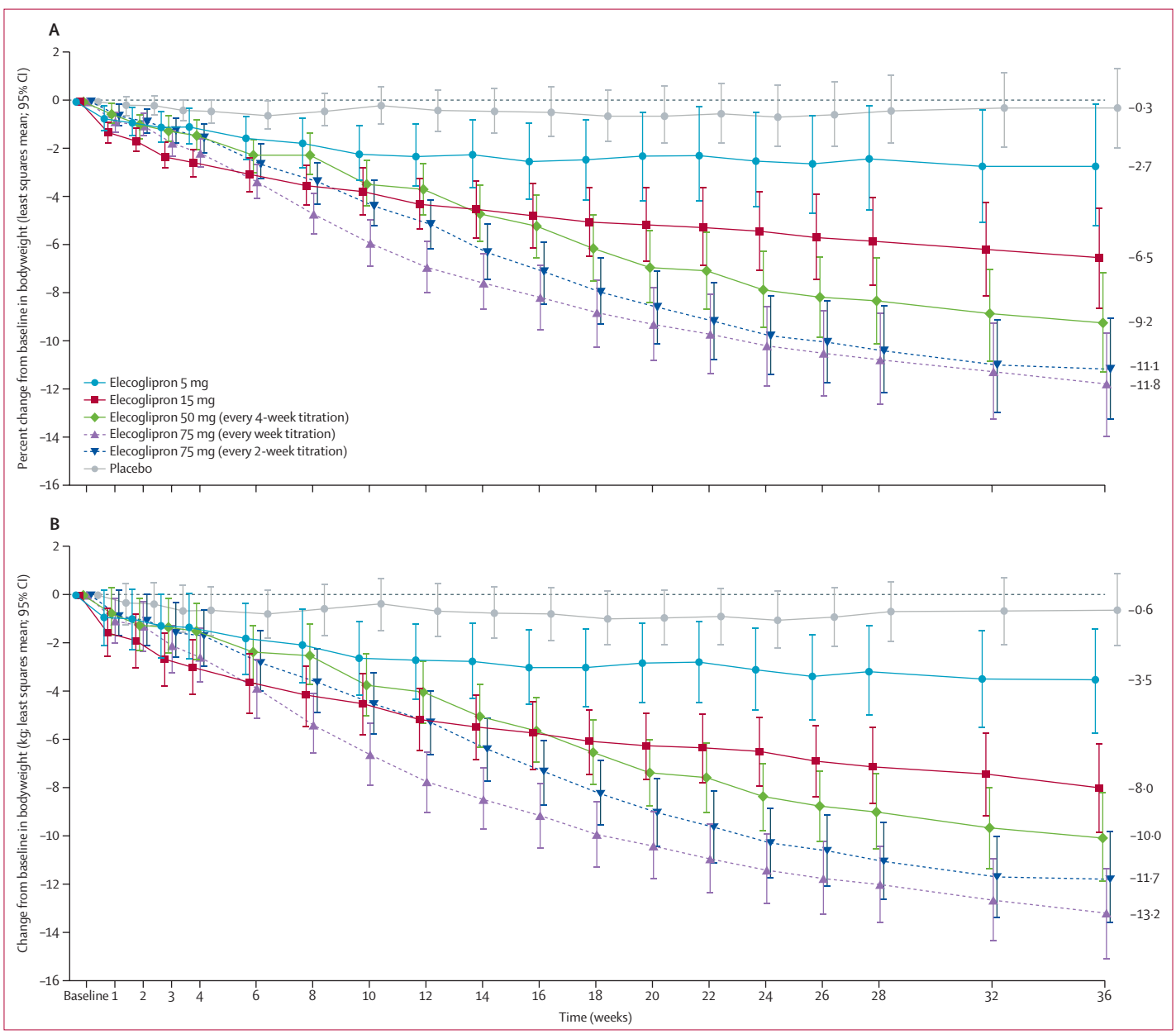
Results

From Oct 8, 2024, to Feb 18, 2025, 472 individuals were screened for eligibility and 162 did not meet the inclusion criteria, resulting in 310 participants being randomly assigned to an intervention, according to the planned allocation ratio. Completion rates were comparable between the elecoglipron dose groups and the placebo group. Overall, 288 participants (93%) completed the study, and 231 (75%) completed the assigned treatment (figure 1). In total, 79 participants discontinued study treatment, 24% (56 of 229) in the elecoglipron groups and 28% (23 of 81) in the placebo group. The primary reason for discontinuations as reported by the investigators were: 11 (4%) due to adverse events, and 39 (13%) due to participant decision.

The summary of participant baseline demographics and clinical characteristics is presented in table 1. The mean age was 48·4 years (SD 13·7), most participants were female (225 [73%] of 310; 85 [27%] were male) and White (223 [72%] of 310). Mean bodyweight was 106·9 kg (SD 24·1), and mean BMI was 38·2 kg/m² (SD 7·2).

Treatment with elecoglipron induced a dose-dependent weight reduction in study participants (figure 2; table 2). At week 26, the estimated mean change from baseline in bodyweight was –2·6% with the 5 mg dose of elecoglipron, –5·6% with the 15 mg dose, –8·1% with the 50 mg dose, –10·5% with the 75 mg dose (weekly titration), –10·0% with the 75 mg dose (every 2-week titration), and –0·6% with placebo, as assessed by the efficacy estimand. Placebo-corrected percent change from baseline in bodyweight ranged from –2·1% to –9·9% across dose groups. The estimated proportion of participants reaching weight reductions of at least 5% was greater with elecoglipron (40·4–88·8%) than with placebo (15·6%; figure 2C; table 2).

Bodyweight decreased progressively up to week 36 (figure 2; table 2). At week 36, the estimated mean change from baseline in bodyweight was –2·7% with the 5 mg dose of elecoglipron, –6·5% with the 15 mg dose, –9·2% with the 50 mg dose, –11·8% with the 75 mg dose (weekly titration), –11·1% with the 75 mg dose (every 2-week titration), and –0·3% with placebo (figure 2A). The placebo-corrected percent change from baseline in bodyweight ranged from –2·4% to –11·5% across dose groups at week 36 (table 2). The absolute change in bodyweight from baseline ranged from –3·5 kg to



(Figure 2 continues on next page)

–13·2 kg at week 36 with elecoglipron treatment (figure 2B). At week 36, across elecoglipron dose groups, the estimated proportion reaching at least 10% weight loss ranged from 8·8% to 62·5% versus 4·5% with placebo; the estimated proportion reaching at least 15% weight loss ranged from 4·9% to 39·8% versus 2·7% with placebo (figure 2D; table 2).

A supplementary analysis on percent weight change at week 36, including data after permanent discontinuation of study intervention, showed similar weight changes from baseline and somewhat smaller placebo-corrected changes than observed in the main analysis using the efficacy estimand (appendix 1 p 9) .

Furthermore, supplementary analyses were conducted to assess the consistency of the treatment effect across subgroups. The subgroup analyses of percent change from baseline in bodyweight at week 36 generally showed consistent results across dose groups and major subgroups; however, the small sizes of several subgroups limited interpretation.

Elecoglipron led to decreases in BMI and waist circumference from baseline through week 36 (appendix 1 p 24). Across dose groups, the placebo-corrected change in BMI ranged from –0·9 to –4·4 kg/m², and in waist circumference from –2·0 to –9·9 cm at week 36.

A dose-dependent reduction in systolic blood pressure was observed with elecoglipron. The mean change from baseline at week 36 in the elecoglipron groups ranged from 0·9 mm Hg to –9·3 mm Hg, compared with –0·5 mm Hg with placebo (appendix 1 p 10). Both systolic and diastolic blood pressure showed reductions in the elecoglipron 50 mg and 75 mg dose groups compared with placebo at the end of the trial, with 95% CI separated from unity. High-sensitivity C-reactive protein also showed reductions ranging from –25·4% to –44·4% compared with placebo at the end of the trial (appendix 1 p 11).

Overall, adverse events were reported by 84% (27 of 32) to 98% (48 of 49) of participants across the elecoglipron dose groups, compared with 84% (68 of 81) in the placebo group. Nausea, constipation, diarrhoea, headache, and vomiting were the most common adverse events with elecoglipron, occurring more frequently than with placebo (table 3). Across elecoglipron dose groups, nausea occurred in 9% (3 of 32) to 56% (28 of 50) of participants versus 20% (16 of 81) with placebo, and vomiting occurred in 6% (two of 32) to 29% (14 of 49) versus 5% (four of 81) with placebo. The highest incidences of nausea and vomiting were observed with the 50 mg and 75 mg (every 2-week titration group), respectively. Most gastrointestinal events were mild to moderate, emerged during dose titration period, and were transient, resolving mostly without permanent discontinuation of study intervention (appendix 1 p 25). In overtime analyses, the prevalence of constipation and nausea tended to decline over time, whereas diarrhoea and vomiting occurred at low

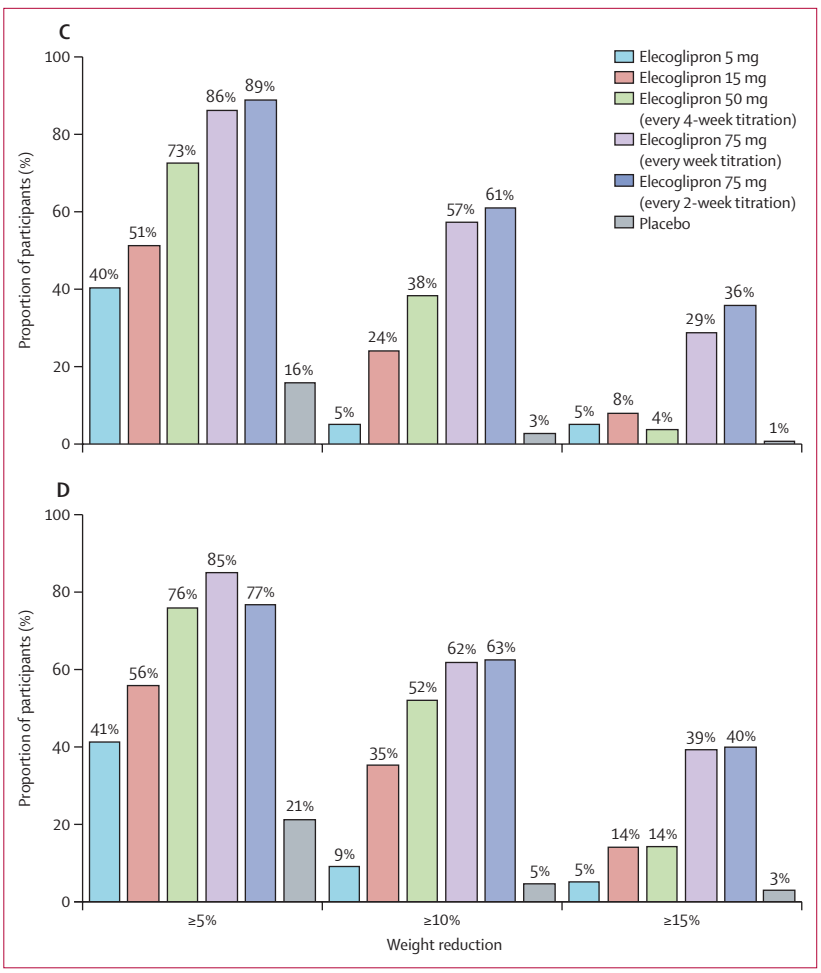


Figure 2: **Efficacy outcomes**
The percentage change (A) and the absolute change (B) from baseline in bodyweight by week in the efficacy estimand are shown. Least-square means are presented, and bars indicate 95% CI. Proportion of participants who had weight reductions of at least 5%, at least 10%, and at least 15% by week 26 (C) and week 36 (D). The results were calculated according to Rubin's rule.

frequencies and remained relatively stable across dose levels. In general, the overall temporal burden decreased after achievement of target dose concentrations in the respective dose groups.

Liver enzymes were reduced in participants receiving elecoglipron compared with those receiving placebo (appendix 1 p 16). Asymptomatic laboratory-derived events of increased serum bilirubin, without any associated increases in transaminases, were reported in the 50 mg and 75 mg dose groups (table 3). In total, two patients (2·0%) in the 75 mg dose groups had confirmed asymptomatic bilirubin increases above three times the upper limit of normal, one of whom had a history of Gilbert's syndrome. One of the patients continued the study on the 75 mg dose and one received a reduced dose of 50 mg.

Adverse events leading to elecoglipron discontinuation occurred in 12 (5%) of 229 participants: of these, five discontinued because of gastrointestinal adverse

	Elecoglipron						Pooled placebo (n=81)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)	75 mg total (n=98)	
Bodyweight change from baseline, %							
Week 26 (dual primary endpoint)							
Number of participants	27	38	44	35	36	71	61
Least squares mean (95% CI)	−2·6 (−4·7 to −0·6)	−5·6 (−7·4 to −3·9)	−8·1 (−9·8 to −6·5)	−10·5 (−12·3 to −8·7)	−10·0 (−11·7 to −8·3)	−10·3 (−11·5 to −9·0)	−0·6 (−1·9 to 0·8)
Least squares mean difference *vs* placebo (95% CI)	−2·1 (−4·5 to 0·4)	−5·1 (−7·2 to −2·9)	−7·6 (−9·7 to −5·5)	−9·9 (−12·1 to −7·8)	−9·4 (−11·6 to −7·3)	−9·7 (−11·5 to −7·9)	..
Week 36 (secondary endpoint)							
Number of participants	24	38	39	35	29	64	54
Least squares mean (95% CI)	−2·7 (−5·2 to −0·2)	−6·5 (−8·6 to −4·4)	−9·2 (−11·3 to −7·2)	−11·8 (−13·9 to −9·6)	−11·1 (−13·2 to −9·0)	−11·5 (−13·0 to −9·9)	−0·3 (−2·0 to 1·3)
Least squares mean difference *vs* placebo (95% CI)	−2·4 (−5·4 to 0·6)	−6·2 (−8·8 to −3·6)	−8·9 (−11·5 to −6·3)	−11·5 (−14·1 to −8·8)	−10·8 (−13·5 to −8·2)	−11·1 (−13·3 to −8·9)	..
Participants reaching at least 5% weight loss							
Week 26 (dual primary endpoint)							
Probability of event, % (95% CI)	40·4 (24·2 to 59·0)	51·3 (36·2 to 66·2)	72·5 (58·0 to 83·5)	86·1 (71·4 to 93·9)	88·8 (74·7 to 95·5)	87·5 (78·1 to 93·2)	15·6 (8·7 to 26·5)
OR (95% CI) *vs* placebo	3·7 (1·4 to 9·9)	5·7 (2·3 to 14·1)	14·3 (5·6 to 36·5)	33·5 (10·8 to 103·6)	42·9 (13·1 to 140·9)	37·9 (14·7 to 97·8)	..
Week 36 (secondary endpoint)							
Probability of event, % (95% CI)	41·3 (24·2 to 60·8)	55·7 (40·3 to 70·1)	76·1 (60·8 to 86·7)	85·1 (70·1 to 93·3)	76·8 (60·2 to 87·8)	81·4 (71·0 to 88·6)	21·4 (12·8 to 33·4)
OR (95% CI) *vs* placebo	2·6 (0·9 to 7·1)	4·6 (1·9 to 11·1)	11·7 (4·6 to 30·0)	21·1 (7·1 to 62·4)	12·2 (4·5 to 32·6)	16·1 (6·9 to 37·2)	..
Participants reaching at least 10% weight loss							
Week 26 (secondary endpoint)							
Probability of event, % (95% CI)	4·9 (1·0 to 21·4)	24·1 (13·5 to 39·1)	38·1 (25·2 to 53·0)	57·2 (40·9 to 72·0)	60·8 (44·4 to 75·0)	59·0 (47·5 to 69·6)	2·7 (0·6 to 11·4)
OR (95% CI) *vs* placebo	1·9 (0·2 to 17·7)	11·4 (2·1 to 61·4)	22·1 (4·3 to 114·0)	48·0 (8·9 to 257·8)	55·6 (10·7 to 290·6)	51·6 (10·4 to 255·7)	..
Week 36 (secondary endpoint)							
Probability of event, % (95% CI)	8·8 (2·5 to 26·5)	35·1 (22·0 to 51·0)	52·0 (37·0 to 66·6)	61·9 (45·4 to 76·0)	62·5 (45·7 to 76·7)	62·2 (50·6 to 72·5)	4·5 (1·4 to 13·3)
OR (95% CI) *vs* placebo	2·1 (0·4 to 12·1)	11·5 (3·0 to 44·5)	23·0 (6·1 to 86·5)	34·5 (9·0 to 131·2)	35·4 (9·1 to 136·8)	34·9 (9·9 to 122·6)	..
Participants reaching at least 15% weight loss							
Week 26 (secondary endpoint)							
Probability of event, % (95% CI)	5·0 (1·0 to 21·7)	8·0 (2·8 to 20·5)	3·5 (0·7 to 15·5)	28·7 (16·2 to 45·6)	35·8 (22·1 to 52·2)	32·1 (22·3 to 43·7)	0·7 (0·0 to 9·2)
OR (95% CI) *vs* placebo	7·9 (0·3 to 192·0)	12·9 (0·7 to 241·4)	5·5 (0·2 to 127·6)	60·2 (3·7 to 994·0)	83·2 (5·1 to 1368·2)	70·7 (4·5 to 1113·2)	..
Week 36 (secondary endpoint)							
Probability of event, % (95% CI)	4·9 (1·0 to 21·4)	14·0 (6·5 to 27·7)	14·1 (6·3 to 28·7)	39·3 (24·4 to 56·4)	39·8 (24·8 to 57·0)	39·5 (28·6 to 51·6)	2·7 (0·6 to 11·5)
OR (95% CI) *vs* placebo	1·8 (0·2 to 17·6)	5·8 (1·0 to 33·8)	5·9 (1·0 to 34·6)	23·1 (4·3 to 125·3)	23·6 (4·3 to 129·0)	23·4 (4·6 to 118·2)	–

Table 2: **Primary and secondary endpoints**

events (table 3). Serious adverse events were reported in eight (8%) of 98 participants who received elecoglipron in the 75 mg dose groups and in two (2%) of 81 participants who received placebo. Distribution of serious adverse event types with elecoglipron did not differ in a meaningful manner from that observed with placebo. No serious adverse event with outcome of death was reported during the study period.

By week 36, mean pulse changes ranged from −2·8 to 4·8 beats per minute across elecoglipron groups, compared

with 0·2 beats per minute in the placebo group (appendix 1 pp 10–11). Changes in pulse were comparable between participants in 50 mg and 75 mg dose groups. Five events of cholecystitis or cholelithiasis were reported in four participants receiving elecoglipron and none in the placebo group. No cases of clinical diagnosed pancreatitis were reported during the study period. Based on the Columbia-Suicide Severity Rating Scale and PHQ-9 assessments performed during the study, no suicidal ideation or behaviour was identified.

Discussion

In this phase 2 dose-ranging trial in adults living with obesity or overweight without type 2 diabetes, treatment with elecoglipron, an oral small-molecule GLP-1 receptor agonist, produced dose-dependent clinically meaningful and progressive weight loss, with the greatest efficacy observed at the highest dose. Mean weight loss at the 75 mg dose (weekly titration) was 10·5% at 26 weeks, increasing further to 11·8% at 36 weeks, confirming that a weight-reduction plateau was not reached at week 26, and providing insight to durability beyond the traditional 6-month phase 2 evaluation. Safety and tolerability results were consistent with the GLP-1 receptor agonist class, with no unanticipated safety signals. The study population (mean age 48 years, baseline BMI 38·2 kg/m², and 73% female) was representative of contemporary weight management pharmacotherapy trials, supporting generalisability to real-world clinical populations likely

	Elecoglipron					Pooled placebo (n=81)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)	
Overall adverse event information						
Adverse events	27 (84%)	43 (88%)	44 (88%)	48 (98%)	45 (92%)	68 (84%)
Serious adverse events	0	0	0	4 (8%)	4 (8%)	2 (2%)
Serious adverse events with an outcome of death	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	2 (4%)	3 (6%)	3 (6%)	4 (8%)	3 (4%)
Gastrointestinal adverse events leading to treatment discontinuation	0	1 (2%)	2 (4%)	1 (2%)	1 (2%)	0
Adverse events occurring in at least 5% of participants in any group (non-gastrointestinal)						
Headache	3 (9%)	6 (12%)	14 (28%)	15 (31%)	8 (16%)	11 (14%)
Fatigue	2 (6%)	5 (10%)	8 (16%)	4 (8%)	8 (16%)	6 (7%)
Nasopharyngitis	5 (16%)	8 (16%)	5 (10%)	3 (6%)	9 (18%)	9 (11%)
Upper respiratory tract infection	5 (16%)	7 (14%)	8 (16%)	6 (12%)	3 (6%)	10 (12%)
Arthralgia	4 (13%)	2 (4%)	5 (10%)	2 (4%)	4 (8%)	5 (6%)
Back pain	4 (13%)	7 (14%)	3 (6%)	2 (4%)	3 (6%)	7 (9%)
Dizziness	0	3 (6%)	3 (6%)	3 (6%)	3 (6%)	3 (4%)
Influenza	3 (9%)	2 (4%)	3 (6%)	1 (2%)	2 (4%)	3 (4%)
Amylase increased	0	2 (4%)	3 (6%)	1 (2%)	5 (10%)	1 (1%)
Insomnia	1 (3%)	0	5 (10%)	2 (4%)	1 (2%)	2 (2%)
Lipase increased	1 (3%)	1 (2%)	2 (4%)	1 (2%)	5 (10%)	1 (1%)
Blood bilirubin increased	0	0	2 (4%)	4 (8%)	4 (8%)	0
Lethargy	1 (3%)	1 (2%)	1 (2%)	3 (6%)	2 (4%)	0
Rash	2 (6%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)	2 (2%)
Viral upper respiratory tract infection	1 (3%)	3 (6%)	1 (2%)	4 (8%)	1 (2%)	1 (1%)
Gastroenteritis	0	0	4 (8%)	1 (2%)	1 (2%)	3 (4%)
Alopecia	0	1 (2%)	0	3 (6%)	3 (6%)	0
Bilirubin conjugate increased	0	0	0	2 (4%)	6 (12%)	0
Migraine	1 (3%)	1 (2%)	3 (6%)	1 (2%)	2 (4%)	1 (1%)
Cough	3 (9%)	2 (4%)	1 (2%)	0	3 (6%)	1 (1%)
Dysgeusia	0	1 (2%)	4 (8%)	0	2 (4%)	0
Oropharyngeal pain	1 (3%)	0	2 (4%)	3 (6%)	1 (2%)	2 (2%)
Sinusitis	2 (6%)	2 (4%)	0	1 (2%)	2 (4%)	2 (2%)
COVID-19	2 (6%)	0	3 (6%)	2 (4%)	1 (2%)	2 (2%)
Pain in extremity	2 (6%)	1 (2%)	2 (4%)	0	0	1 (1%)

(Table 3 continues on next page)

	Elecoglipron					Pooled placebo (n=81)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)	
(Continued from previous page)						
Gastrointestinal adverse events of special interest occurring in at least 5% of participants in any group						
Any	17 (53%)	38 (78%)	40 (80%)	41 (84%)	38 (78%)	42 (52%)
Nausea	3 (9%)	27 (55%)	28 (56%)	27 (55%)	22 (45%)	16 (20%)
Constipation	4 (13%)	13 (27%)	21 (42%)	20 (41%)	10 (20%)	5 (6%)
Diarrhoea	4 (13%)	13 (27%)	15 (30%)	17 (35%)	11 (22%)	20 (25%)
Vomiting	2 (6%)	6 (12%)	13 (26%)	13 (27%)	14 (29%)	4 (5%)
Dyspepsia	3 (9%)	10 (20%)	8 (16%)	7 (14%)	9 (18%)	2 (2%)
Abdominal pain (upper)	2 (6%)	5 (10%)	5 (10%)	10 (20%)	9 (18%)	4 (5%)
Gastro-oesophageal reflux disease	1 (3%)	5 (10%)	6 (12%)	5 (10%)	6 (12%)	2 (2%)
Abdominal distension	2 (6%)	3 (6%)	6 (12%)	6 (12%)	3 (6%)	6 (7%)
Eructation	0	4 (8%)	2 (4%)	5 (10%)	7 (14%)	0
Flatulence	1 (3%)	2 (4%)	2 (4%)	5 (10%)	4 (8%)	3 (4%)
Decreased appetite	2 (6%)	2 (4%)	3 (6%)	3 (6%)	2 (4%)	5 (6%)
Dry mouth	1 (3%)	2 (4%)	1 (2%)	3 (6%)	4 (8%)	0
Abdominal pain	1 (3%)	2 (4%)	5 (10%)	3 (6%)	1 (2%)	4 (5%)
Abdominal pain (lower)	1 (3%)	0	3 (6%)	2 (4%)	0	0

The table includes adverse events with an onset date on or after the day of the randomisation visit and participants are censored at the earliest of withdrawal of consent, death, or the date of the last clinical assessment. Only the first event per participant in each category is used in the analyses. Serious adverse events were as assessed by the investigator.

Table 3: **Summary of adverse events**

to be eligible for weight management therapy with GLP-1 receptor agonists.

A key feature of this study was the broad dose range (5 mg to 75 mg) of elecoglipron and the inclusion of differing titration approaches at higher doses. The 5 mg and 15 mg doses of elecoglipron were administered without titration, whereas the 75 mg dose was introduced through either weekly or every 2-week escalations, enabling achievement of the maximum dose by approximately 7 weeks or 12 weeks, respectively. By contrast, the 50 mg regimen incorporated a slower escalation approach, with dose increments every 4 weeks, resulting in a maximum-dose attainment time of approximately 16 weeks.

The dosing schedules provide insights into the relationship between exposure, tolerability, and clinical outcomes. The ability to reach substantial weight loss despite slower attainment of target dose in the 50–75 mg groups suggests that clinically meaningful efficacy does not require immediate exposure to the maximum dose, and that slower titration strategies could represent an approach to balancing efficacy with tolerability in later-phase development.

The magnitude of weight loss observed in this study with elecoglipron seems overall consistent with the data from other oral small-molecule GLP-1 receptor agonists.[13–15] In the current trial, up to 85% of participants treated with high elecoglipron doses reached at least a 5% weight loss, and 63% reached at least a 10% weight loss at 36 weeks. These results suggest that a sizeable proportion of people living with obesity or overweight can reach clinically meaningful weight-loss targets with elecoglipron. The weight reduction observed with elecoglipron is comparable to that reported for other oral small-molecule GLP-1 receptor agonists, albeit less than that seen with injectable incretin-based therapies.[16] Nevertheless, the weight loss reported in this trial is expected to translate into meaningful improvements in cardiometabolic risk profiles including cardiovascular and renal risk factors, thereby conferring important health benefits in at-risk populations.

The safety profile of elecoglipron in this phase 2 dose-ranging study was consistent with the GLP-1 receptor agonist class at this stage of development, with gastrointestinal adverse events being the most frequently reported. Subsequent phase 3 trials will be important to more fully define comparative tolerability and usability across GLP-1 receptor agonist modalities.

Notably, nausea was reported by approximately 45–56% of participants across the 15 mg to 75 mg dose groups of elecoglipron, with no clear difference across these dose levels. This plateauing of nausea rates at higher doses might reflect either early saturation of GLP-1 mediated nausea pathways or the effect of titration

strategies in moderating symptom escalation. Vomiting was less frequent but demonstrated a clearer dose relationship, reported by 12% of participants at 15 mg and 26–28% in the higher-dose groups. Despite this, no serious adverse events were attributed to gastrointestinal symptoms of nausea, vomiting, diarrhoea or constipation, and discontinuation due to gastrointestinal symptoms were rare (4% in 50 mg group and 2% in 15 and 75 mg groups). Overall, these findings suggest that while gastrointestinal adverse events remain a feature of GLP-1-based therapy, they might be manageable with appropriate starting doses, duration of titration, and supportive care, and might not preclude sustained dosing at levels required for clinically meaningful weight loss.

There were reductions in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase across all treatment groups. These findings align with evidence from other GLP-1 receptor agonist programmes demonstrating improvement in hepatic steatosis markers and liver biochemistry, potentially reflecting weight-loss-mediated improvements in metabolic dysfunction-associated steatotic liver disease. Asymptomatic events of increases in serum bilirubin concentrations, without increases in liver enzymes, were observed in a few participants in the higher dose groups of elecoglipron. The hepatic uptake transporters OATP1B1/3 and the enzyme UGT1A1 are involved in the disposition of bilirubin.[17] Based on in-vitro data, elecoglipron is predicted to inhibit OATP1B transporters and UGT1A1 at higher exposures. Hence, elevations of bilirubin concentrations were observed without any obvious association to liver injury.

In addition to weight loss, improvements were observed in cardiometabolic risk factors such as blood pressure and C-reactive protein, consistent with the established effects of GLP-1 receptor agonism and weight loss. Although phase 2 trials are not typically powered for definitive exploratory cardiometabolic outcomes, these findings support the expectation that weight loss of this magnitude, especially in conjunction with potential GLP-1 weight loss-independent pleotropic cardiovascular effects,[18,19] might translate into broader reductions in cardiovascular risk. Such improvements are consistent with those observed in other GLP-1 receptor agonist programmes and provide additional support for progression to phase 3 evaluation.

Several potential limitations should be acknowledged. As a phase 2 trial, the study was not designed to evaluate long-term durability, rare adverse events, or outcome events. The study size also limits the possibilities to fully evaluate the weight loss effects across a broad BMI range, including people living with overweight. Additionally, tolerability in routine practice might differ from that in a clinical trial setting with structured titration and monitoring. The high proportion of women, while consistent with weight management trial enrolment patterns, might limit generalisability to male populations, who tend to achieve less weight loss.

In summary, daily oral elecoglipron showed clinically meaningful weight reductions and a safety and tolerability profile consistent with the GLP-1 receptor agonist class in this phase 2 study. The phase 3 weight management clinical development programme (EMBOLD, EU CT Number 2025-524688-19) will further help elucidate the efficacy and safety of elecoglipron in participants living with overweight or obesity.

Contributors

The sponsor (AstraZeneca) conceived, designed, and supervised the trial which included site monitoring, data collation, and analysis. MJD, CDS, EM, EPR, SM, and AA were involved in conceptualisation of the study. MJD, CDS, DG, AA, PAJ, EPR, SM, and EM were involved in the methodology. DG, PAJ, EPR, SM, EM, and AA were involved in data curation and analysis. MJD, VRA, JR, MC, SDP, CDS, DG, AA, PAJ, EPR, SM, and EM were involved in data interpretation. MJD, CDS, EPR, DG, PAJ, AA, SM, and EM wrote the original draft of the manuscript. MJD, CDS, EPR, DG, PAJ, AA, SM, EM, JR, MC, and SDP reviewed and edited the original draft of the manuscript. MJD, JR, MC, and SDP were investigators in the trial. MJD and CDS verified the underlying data. All authors approved the final version of the manuscript and vouch for data accuracy and the fidelity of the trial to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MJD has acted as a consultant, advisor, and speaker for Eli Lilly, Novo Nordisk and Sanofi; as a consultant and advisor for Kailera; has attended advisory boards for AbbVie, Amgen, AstraZeneca, Biomea Fusion, Carmot Roche, Daewoong Pharmaceutical, Sanofi, Zealand Pharma, Regeneron, GSK, Innovent Bio, and EktaH; and as a speaker for AstraZeneca, Boehringer Ingelheim, and Zuellig Pharma. MJD has received grants from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. VRA has institutional contracts with Amgen, AstraZeneca, Applied Therapeutics, Biomea, Corcept, Eli Lilly, Fractyl, Kailera, Novo Nordisk, Pfizer, Recordati, Rhythm, and Servier and is a consultant for Baim, Mediflix, Roche, and Sanofi. JR reports clinical research grants from Amgen, Applied Therapeutics, AstraZeneca, Biomea Fusion, Boehringer Ingelheim, Corcept, Corxel, Eli Lilly, Hanmi, Merck, Novo Nordisk, Pfizer, Regeneron, Roche, Regor, Sanofi, Structure Therapeutics, and Terns; JR serves or has served on scientific advisory boards and received honoraria or consulting fees from Amgen, Applied Therapeutics, Arrowhead, Biomea Fusion, Boehringer Ingelheim, Corcept, Eccogene, Eli Lilly, Hanmi, i2O Therapeutics, Novo Nordisk, Regeneron, Roche, Sanofi, Structure Therapeutics, and Terns; and has received honoraria for lectures from Eli Lilly, Novo Nordisk, and Sanofi. MC has served as unpaid advisor to the National Institute of Health and Care Excellence on obesity and diabetes; is Medical Director for Lighterlife (commercial Very Low Calorie Diet provider); is Medical Advisor to McDonalds UK; has recieved research funding to perform clinical trials for AstraZeneca, Novo Nordisk, Lilly, Boehringer Ingelheim, and Amgen; honoraria for talks and advisory boards from Novo Nordisk, Lilly and Boehringer Ingelheim; and travel or subsistence costs to attend meetings or conferences from AstraZeneca, Novo Nordisk, Lilly, Boehringer Ingelheim, and Amgen. SDP has received grants for clinical trials from Novo Nordisk, AstraZeneca, Sanofi, Eli Lilly, Boehringer Ingelheim, Prometic, and Pfizer; and consulting fees from AstraZeneca, Bausch Health, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Sanofi, Merck, Abbott, Dexcom, HLS, Bayer, AbbVie, Roche, Amgen, and Pfizer. SDP has also received payment for medical education lectures and speakers bureaus from AstraZeneca, Bausch, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Sanofi, Merck, Abbott, Dexcom, HLS, Bayer, and Pfizer, and has received travel support from AstraZeneca, Bausch, Eli Lilly, Novo Nordisk, Beohringer Ingelheim, Abbott, and Dexcom. EM, SM, PAJ, DG, AA, EPR, and CDS are employees and stockholders of AstraZeneca.

Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy. Data for

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Acknowledgments
The VISTA trial was funded by AstraZeneca. We thank all investigators, study teams, and trial participants. The authors thank Meera Kodukulla for critical review of manuscript drafts. Editorial support was provided by David Floyd of Oxford Pharmagenesis, which was funded by AstraZeneca.

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