Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

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- Obesity is a chronic condition that places a substantial burden on patients, health care systems, and the wider economy, affecting more than 1 billion people worldwide. Clinical guidelines now recommend treatment with weight-management medications for people with obesity and for those with overweight plus weight-related coexisting conditions. Glucagon-like peptide-1 (GLP-1) receptor agonists are being increasingly used as a component of obesity treatment.
- GLP-1 receptor agonists mimic the incretin hormone GLP-1, which promotes weight reduction by decreasing the appetite and delay ing gastric emptying, thereby leading to an improvement in energy balance.

Trials of injectable GLP-1 receptor agonists for weight management have shown long-term efficacy.

- Only two GLP-1 receptor agonists have been approved for weight management: liraglutide (3.0 mg once daily) and semaglutide (2.4 mg once weekly), both of which are peptides in injectable formulations. Although these treatments are effective, the injection has been associated with barriers to uptake and acceptability for patients. An oral formulation of semaglutide that uses an absorption enhancer to enable absorption in the stomach has been approved for the treatment of type 2 diabetes. This once-daily oral formulation is effective only when taken 30 minutes before breakfast, and the approved dose (14 mg) is less effective for weight reduction than the approved dose of injectable semaglutide.6 Higher doses of oral semaglutide (25 and 50 mg) are under development for the treatment of both obesity and type 2 diabetes.

Orforglipron is a once-daily oral nonpeptide GLP-1 receptor agonist that is in development for weight management and the treatment of type 2 diabetes. Orforglipron is a potent partial agonist of the GLP-1 receptor that has a greater effect on cyclic AMP (cAMP) signaling than on β-arrestin recruitment a pharmacologic profile that may offer lower receptor desensitization than full GLP-1 receptor agonists.The pharmacokinetic profile of orforglipron, with a half-life of 29 to 49 hours, supports oncedaily oral administration.In this trial, we evaluated the efficacy and safety of orforglipron in adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes.

Methods

We conducted a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallelgroup trial. The trial protocol (available with the full text of this article at NEJM.org) was approved by local institutional review boards. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. All the participants provided written informed consent.
The trial sponsor (Eli Lilly) designed and oversaw the conduct of the trial. Trial site investigators were responsible for data collection, and the sponsor undertook site monitoring, data collation, and data analysis. The authors participated in interpretation of the data and in critical review of the manuscript. The authors had full access to the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants were enrolled in Canada, the United States, and Hungary. Men and women 18 to 75 years of age were eligible for inclusion in the trial if they did not have diabetes (glycated hemoglobin level, <6.5% [48 mmol per mole]) and had obesity (body-mass index [BMI; the weight in kilograms divided by the square of the height in meters], ≥30) or had overweight (BMI, 27 to <30) plus at least one of the following weightrelated coexisting conditions: hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea. Participants were required to have a stable body weight (≤5% gain or loss) for the 3 months before randomization. Participants were randomly assigned to receive orforglipron at a dose of 12 mg, 24 mg, 36 mg or 45 mg or placebo once daily for 36 weeks. The 36-mg and 45-mg dose cohorts were each divided into two subcohorts that had different starting doses and dose-escalation schemes. With inclusion of these subcohorts, randomization was performed in a 5:5:3:3:3:3:5 ratio.

The trial period consisted of a 2-week screening and lead-in period, a 36-week treatment period, and a 2-week follow-up period (Fig. 1). During the treatment period, dose escalation was performed in all the orforglipron dose cohorts. The dose-escalation phase had a duration of up to 16 weeks, depending on the dose cohort. The starting dose was 2 mg or 3 mg, and additional dose-escalation steps were specific to the dose cohort (Fig. S1 in the Supplementary Appendix). Orforglipron or matching placebo was administered once daily by oral capsule in the morning without meal-timing restrictions. Throughout the trial, education regarding healthy eating and exercise was provided by trial personnel to all participants. The primary end point was the percentage change from baseline in body weight at week 26. Secondary end points included the percentage change from baseline in body weight at week 36; the absolute change from baseline in body weight, BMI, and waist circumference at week 26 and week 36; and weight reductions of at least 5% and at least 10% by week 26 and week 36. Exploratory end points included a weight reduction of at least 15% by week 26 and week 36.

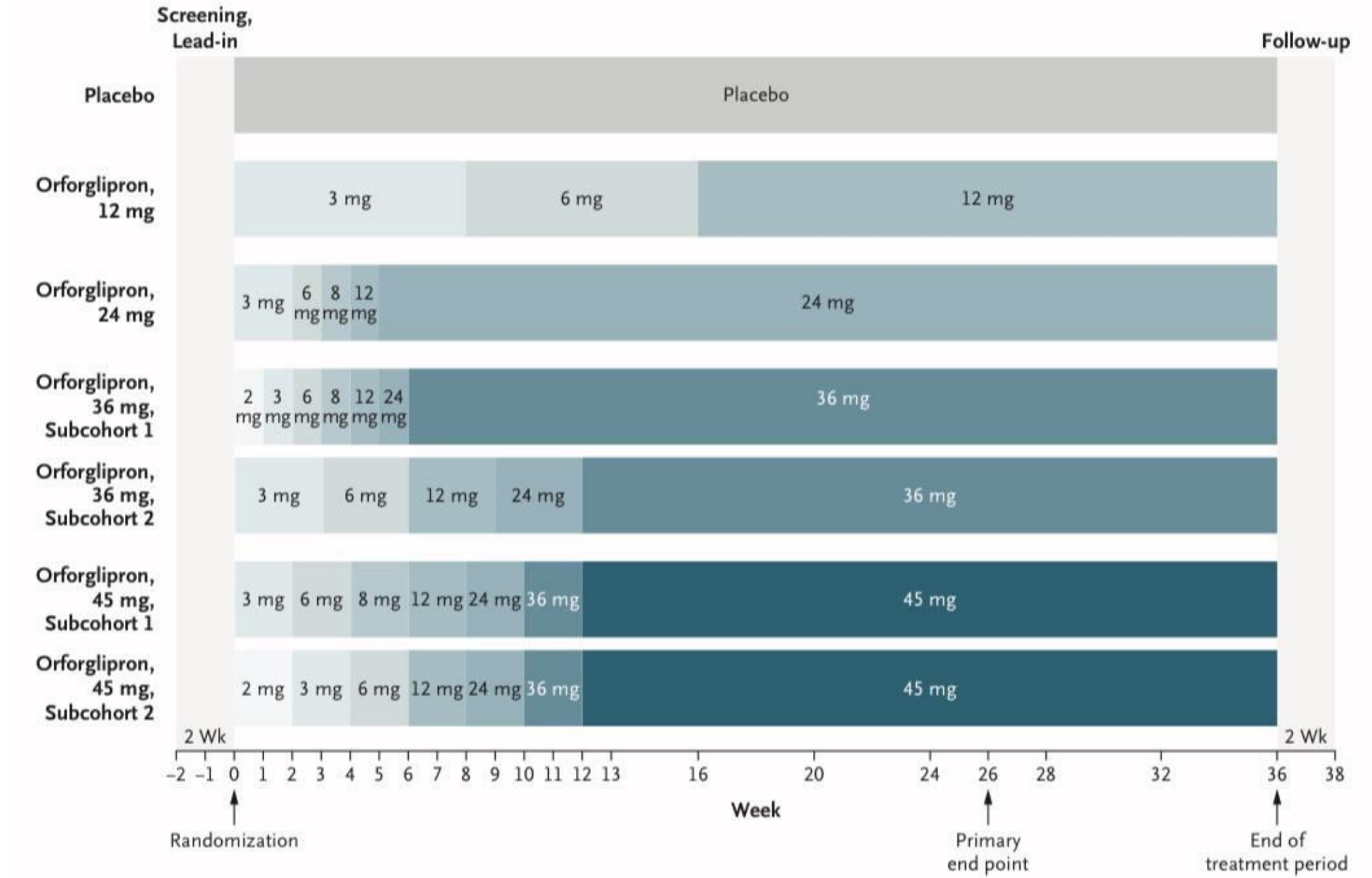

Figure 1. Trial Design.

Statistical Analysis

We calculated that a sample of 270 participants would provide the trial with at least 90% power for testing the superiority of orforglipron as compared with placebo with respect to the primary end point.

data were analyzed with the use of a mixed model for repeated measures; potential data that would have been collected after the occurrence of intercurrent events, if participants had not had intercurrent events, were imputed implicitly. For binary efficacy outcomes, data wereanalyzed with the use of logistic regression; missing values were imputed according to the multiple-imputation approach, and values were combined according to Rubin’s rule.

Results

From September 2021 through late November 2022, a total of 272 participants underwent randomization; the distribution across the trial groups reflected the planned randomization ratio. Demographic and disease-related characteristics of the participants appeared to be well balanced across the trial groups (Table 1). The mean age of the participants was 54.2 years; most participants were female (59%) and White (91%). The mean body weight was 108.7 kg, and the mean BMI was 37.9. The percentage of participants who completed the trial was similar in the orforglipron dose cohorts and the placebo group. Overall, 235 participants (86%) completed the trial, and 207 participants (76%) completed the assigned orforglipron or placebo.

A total of 37 participants prematurely discontinued the trial: 10 because of adverse events, and 27 for reasons unrelated to adverse events . A total of 65 participants discontinued orforglipron or placebo: 36 because of adverse events, and 29 for reasons unrelated to adverse events.

Gastrointestinal events were the most common adverse events that led to trial discontinuation (8 out of 10 cases) and to discontinuation of orforglipron or placebo (31 out of 36 cases), and most gastrointestinal events occurred during dose escalation. At week 26, the estimated mean change from baseline in body weight was −8.6% with the 12-mg dose of orforglipron, −11.2% with the 24-mg dose, −12.3% with the 36-mg dose, −12.6% with the 45-mg dose, and −2.0% with placebo. At week 36, the estimated mean change from base line in body weight was −9.4% with the 12-mg dose of orforglipron, −12.5% with the 24-mg dose, −13.5% with the 36-mg dose, −14.7% with the 45-mg dose, and −2.3% with placebo.

Orforglipron was associated with dose-dependent weight reduction at week 26 (Table 2 and Fig. 2A), with the placebo-corrected percentage change from baseline in body weight ranging from −6.5% to −10.6% across dose cohorts. Weight reduction continued through week 36, with the placebo-corrected percentage change from baseline in body weight ranging from −7.1% to −12.3% in the efficacy estimand. Weight reduction did not appear to have plateaued by week 36.

The use of orforglipron resulted in a dosedependent, continuous absolute decrease in body weight (Fig. 2B). Across dose cohorts, the placebocorrected absolute change from baseline in body weight ranged from −6.9 kg to −11.2 kg at week 26 and ranged from −7.4 kg to −13.0 kg at week 36. Weight reductions of at least 5%, at least 10%, and at least 15% were more likely to occur with orforglipron than with placebo. The weight reduction observed at week 36 (end of the treatment period) was greater than that observed at week 26 (primary end point).

Table 1. **Demographic and Clinical Characteristics of the Participants at Baseline.***

Characteristic	Orforglipron						Placebo (N=50)
	12 mg (N=50)	24 mg (N=53)	36 mg, Subcohort 1 (N=29)†	36 mg, Subcohort 2 (N=29)†	45 mg, Subcohort 1 (N=31)†	45 mg, Subcohort 2 (N=30)†	
Age — yr	49.8±10.5	57.0±9.1	56.3±11.8	55.4±10.9	56.5±10.7	50.9±12.6	54.0±8.8
Female sex — no. (%)	31 (62)	30 (57)	18 (62)	18 (62)	19 (61)	16 (53)	29 (58)
Race or ethnic group — no. (%)‡							
American Indian or Alaska Native	0	1 (2)	0	0	0	0	0
Asian	0	0	0	0	0	0	2 (4)
Black	3 (6)	6 (11)	4 (14)	4 (14)	1 (3)	0	1 (2)
Multiple	0	0	0	0	0	0	2 (4)
White	47 (94)	46 (87)	25 (86)	25 (86)	29 (94)	30 (100)	45 (90)
Missing data	0	0	0	0	1 (3)	0	0
Body weight — kg	107.5±25.3	112.1±30.2	107.8±22.5	108.8±28.5	105.2±20.4	110.9±28.1	107.6±25.2
BMI§	37.7±7.7	38.1±7.7	38.0±6.4	38.0±6.3	36.8±5.5	38.7±7.6	37.8±6.5
BMI range — no. (%)§							
<30	4 (8)	2 (4)	3 (10)	0	2 (6)	1 (3)	4 (8)
30 to <35	16 (32)	21 (40)	7 (24)	11 (38)	11 (35)	9 (30)	13 (26)
35 to <40	18 (36)	14 (26)	9 (31)	8 (28)	10 (32)	10 (33)	19 (38)
≥40	12 (24)	16 (30)	10 (34)	10 (34)	8 (26)	10 (33)	14 (28)
Waist circumference — cm	114.4±16.5	120.1±19.1	116.2±16.2	118.4±14.7	116.1±12.8	117.7±14.8	115.5±15.4
Glycated hemoglobin level — %	5.5±0.4	5.7±0.3	5.7±0.4	5.6±0.4	5.7±0.3	5.6±0.4	5.6±0.4
Fasting glucose level — mg/dl	94.4±9.8	97.5±12.0	95.7±13.2	98.0±13.5	98.0±8.5	92.3±10.1	97.2±10.2
Blood pressure — mm Hg							
Systolic	129.4±12.1	129.7±10.8	131.1±11.4	131.7±12.6	128.9±11.0	126.4±11.6	128.5±9.5
Diastolic	82.9±6.8	82.1±7.4	81.5±7.6	81.2±8.1	80.6±8.5	78.0±8.5	81.5±7.2
Pulse — beats/min	73.9±9.1	71.9±12.1	69.7±9.3	69.0±9.3	71.2±9.6	68.4±10.4	69.6±10.6
eGFR — ml/min/1.73 m^2¶	86.4±18.3	81.8±13.9	82.3±14.6	83.7±10.7	80.2±14.3	85.8±16.4	85.0±14.5

Lipid level — mg/dl							
Cholesterol							
Total	187.0±6.0	198.9±5.9	193.3±7.7	184.7±7.6	189.0±7.5	190.9±7.5	197.0±6.0
HDL	49.3±2.0	51.3±1.9	51.9±2.6	48.4±2.5	51.5±2.6	50.7±2.5	46.9±1.8
LDL	112.3±5.4	118.1±5.3	111.4±6.6	104.6±6.5	109.2±6.5	110.1±6.5	120.9±5.5
VLDL	21.2±1.4	23.8±1.5	23.7±2.0	24.6±2.1	22.5±1.9	25.7±2.1	26.3±1.7
Triglycerides	106.1±7.2	119.1±7.5	118.6±10.0	122.5±10.7	112.6±9.5	128.9±10.7	132.3±8.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.
† The 36-mg and 45-mg dose cohorts were each divided into two subcohorts that had different starting doses and dose-escalation schemes.
‡ Race or ethnic group was reported by the participant.
§ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
¶ The estimated glomerular filtration rate (eGFR) was measured according to the method of the Chronic Kidney Disease Epidemiology Collaboration.

Table 2. Primary and Secondary End Points (Efficacy Estimand).*

End Point	Orforglipron				Placebo
	12 mg	24 mg	36 mg	45 mg	
Primary end point					
Percentage change from baseline in body weight at week 26 — % (95% CI)	−8.6 (−10.2 to −6.9)	−11.2 (−12.8 to −9.6)	−12.3 (−13.8 to −10.7)	−12.6 (−14.1 to −11.1)	−2.0 (−3.6 to −0.4)
Secondary end points					
Percentage change from baseline in body weight at week 36 — % (95% CI)	−9.4 (−11.5 to −7.4)	−12.5 (−14.5 to −10.5)	−13.5 (−15.3 to −11.6)	−14.7 (−16.5 to −12.8)	−2.3 (−4.3 to −0.4)
Absolute change from baseline in body weight — kg (95% CI)					
Week 26	−9.0 (−10.7 to −7.2)	−12.3 (−14.0 to −10.6)	−12.9 (−14.5 to −11.3)	−13.3 (−14.9 to −11.7)	−2.1 (−3.8 to −0.4)
Week 36	−9.8 (−11.9 to −7.6)	−13.6 (−15.7 to −11.6)	−14.2 (−16.2 to −12.3)	−15.4 (−17.4 to −13.5)	−2.4 (−4.5 to −0.4)
Weight reduction of ≥5% — % of participants (95% CI)					
Week 26	74 (62 to 87)	89 (80 to 98)	90 (81 to 98)	87 (79 to 96)	23 (11 to 35)
Week 36	72 (59 to 85)	90 (81 to 98)	92 (85 to 99)	90 (83 to 98)	24 (12 to 36)
Weight reduction of ≥10% — % of participants (95% CI)					
Week 26	39 (25 to 54)	57 (43 to 70)	71 (60 to 83)	70 (58 to 82)	2 (0 to 6)
Week 36	46 (32 to 61)	62 (49 to 75)	75 (63 to 86)	69 (57 to 81)	9 (1 to 17)
Weight reduction of ≥15% — % of participants (95% CI)†					
Week 26	21 (9 to 33)	26 (14 to 38)	34 (22 to 47)	34 (22 to 46)	0
Week 36	22 (10 to 35)	33 (20 to 46)	43 (30 to 56)	48 (35 to 61)	1 (0 to 3)
Change from baseline in BMI — value (95% CI)					
Week 26	−3.2 (−3.8 to −2.6)	−4.2 (−4.8 to −3.6)	−4.6 (−5.1 to −4.0)	−4.7 (−5.2 to -4.2)	−0.8 (−1.3 to −0.2)
Week 36	−3.4 (−4.2 to −2.7)	−4.7 (−5.4 to −4.0)	−5.0 (−5.7 to −4.4)	−5.5 (−6.1 to −4.8)	−0.9 (−1.6 to −0.2)
Change from baseline in waist circumference — cm (95% CI)					
Week 26	−8.0 (−10.0 to −6.0)	−8.8 (−10.8 to −6.8)	−10.1 (−12.0 to −8.3)	−12.2 (−14.1 to −10.4)	−3.6 (−5.5 to −1.7)
Week 36	−9.6 (−11.9 to −7.3)	−11.2 (−13.4 to −8.9)	−10.6 (−12.7 to −8.5)	−13.6 (−15.7 to −11.5)	−4.0 (−6.2 to −1.8)

* For the end points regarding change from baseline, least-squares means are presented. For the end points regarding weight reduction at a specified target, the results were calculated according to Rubin's rule, with combining of the percentages of participants who met the target in imputed data sets. For the 36-mg and 45-mg dose cohorts, data were pooled across subcohorts for each dose.

† A weight reduction of at least 15% was an exploratory end point.

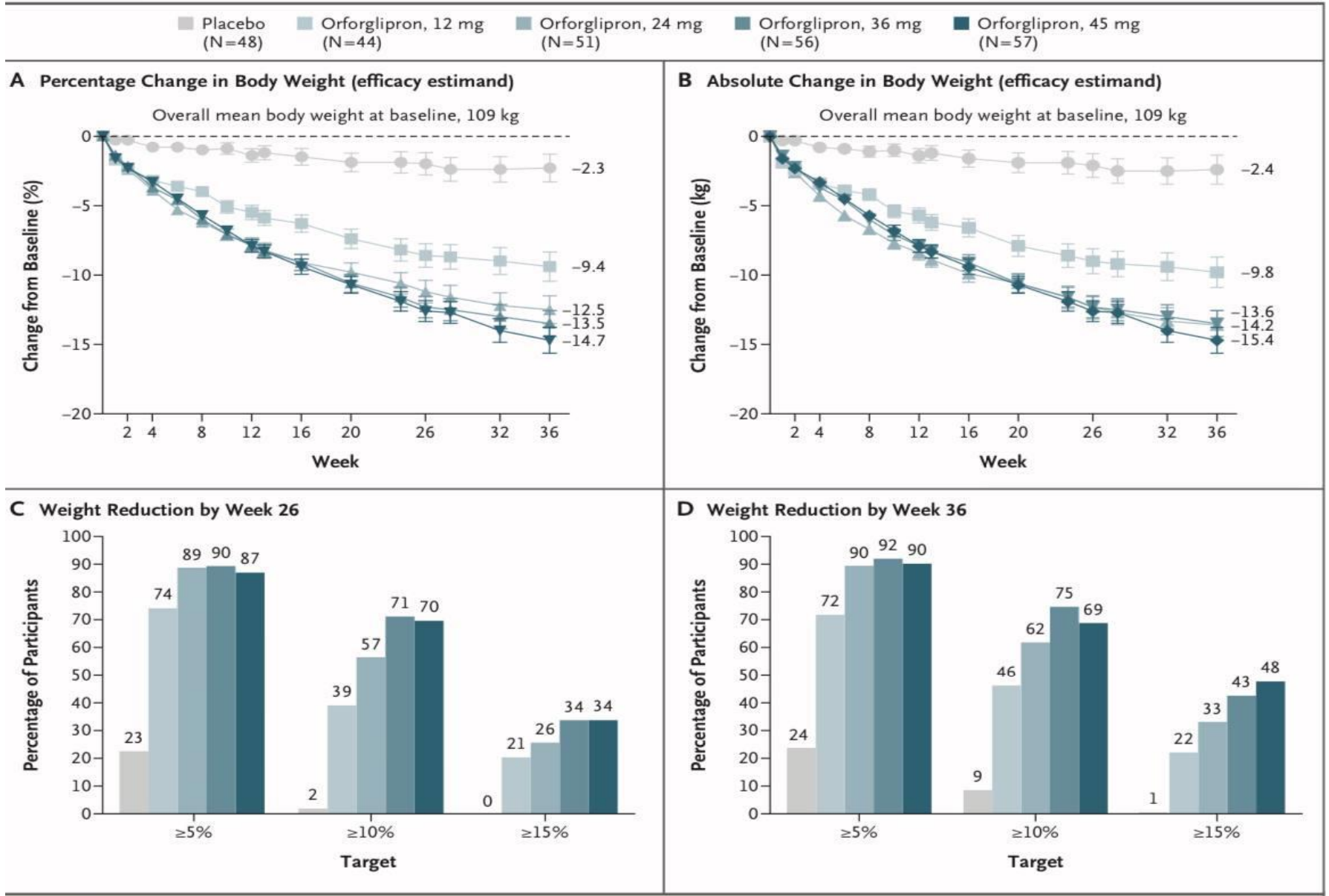

Figure 2. Change in Body Weight with Daily Oral Orforglipron versus Placebo.

The percentage change (Panel A) and the absolute change (Panel B) from baseline in body weight by week in the efficacy estimand are shown. Least-square means are presented, and I bars indicate standard errors. The percentages of participants who had weight reductions of at least 5%, at least 10%, and at least 15% by week 26 (Panel C) and by week 36 (Panel D) are also shown. The results were calculated according to Rubin's rule, with combining of the percentages of participants who met the target in imputed data sets. For the 36-mg and 45-mg dose cohorts, data were pooled across subcohorts for each dose.

The use of orforglipron resulted in a continuous decrease in the BMI and in the waist circumference from baseline through week 26 and week 36. Across dose cohorts, the placebo-corrected change from baseline in BMI ranged from –2.4 to –3.9 at week 26 and ranged from –2.5 to –4.6 at week 36, and the placebo-corrected change from baseline in waist circumference ranged from –4.4 cm to –8.7 cm at week 26 and ranged from –5.6 cm to –9.6 cm at week 36 . There was a clinically meaningful change in the systolic blood pressure among participants who received orforglipron. The mean change from baseline in the systolic blood pressure was up to −10.5 mm Hg at week 26 and was up to −10.5 mm Hg at week 36 with orforglipron, as compared with −3.6 mm Hg and −1.8 mm Hg, respectively, with placebo. The systolic blood pressure tended to be lower in all orforglipron dose cohorts than in the placebo group during the trial. There was no clinically meaningful change in the diastolic blood pressure among participants who received orforglipron. The use of orforglipron was beneficial with respect to the changes in the levels of fasting lip ids, including triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, non HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and very-LDL cholesterol

Table 3. Adverse Events during the Trial Period (Safety Analysis Set).*

Event	Orforglipron								Placebo (N=50)
	12 mg (N=50)	24 mg (N=53)	36 mg, Subcohort 1 (N=29)	36 mg, Subcohort 2 (N=29)	36 mg, Pooled (N=58)	45 mg, Subcohort 1 (N=31)	45 mg, Subcohort 2 (N=30)	45 mg, Pooled (N=61)	
	number of participants (percent)								
Any adverse event	43 (86)	46 (87)	24 (83)	28 (97)	—	28 (90)	27 (90)	—	38 (76)
Any serious adverse event	0	2 (4)	0	3 (10)	—	2 (6)	0	—	0
Adverse event that led to discontinuation of orforglipron or placebo	7 (14)	10 (19)	3 (10)	6 (21)	—	5 (16)	4 (13)	—	1 (2)
Adverse event that occurred in ≥5% of participants in any trial group									
Nausea	25 (50)	31 (58)	12 (41)	14 (48)	—	13 (42)	11 (37)	—	5 (10)
Vomiting	13 (26)	17 (32)	8 (28)	4 (14)	—	9 (29)	8 (27)	—	3 (6)
Constipation	12 (24)	17 (32)	8 (28)	7 (24)	—	6 (19)	4 (13)	—	3 (6)
Diarrhea	12 (24)	19 (36)	1 (3)	4 (14)	—	5 (16)	10 (33)	—	5 (10)
Coronavirus disease 2019	9 (18)	9 (17)	4 (14)	7 (24)	—	5 (16)	5 (17)	—	9 (18)
Eructation	9 (18)	11 (21)	5 (17)	2 (7)	—	2 (6)	6 (20)	—	0
Headache	4 (8)	8 (15)	3 (10)	2 (7)	—	4 (13)	2 (7)	—	5 (10)
Fatigue	2 (4)	7 (13)	4 (14)	2 (7)	—	4 (13)	4 (13)	—	1 (2)
Gastroesophageal reflux disease	4 (8)	5 (9)	3 (10)	4 (14)	—	4 (13)	2 (7)	—	1 (2)
Dyspepsia	8 (16)	4 (8)	1 (3)	1 (3)	—	3 (10)	2 (7)	—	3 (6)
Dizziness	5 (10)	2 (4)	1 (3)	1 (3)	—	2 (6)	4 (13)	—	1 (2)
Abdominal pain	4 (8)	4 (8)	0	2 (7)	—	2 (6)	1 (3)	—	2 (4)
Decreased appetite	4 (8)	4 (8)	0	1 (3)	—	3 (10)	2 (7)	—	1 (2)
Urinary tract infection	2 (4)	3 (6)	0	3 (10)	—	1 (3)	2 (7)	—	3 (6)
Cardiac disorders†	0	5 (9)	—	—	5 (9)	—	—	9 (15)	0

Serious adverse events									
Retinal vein thrombosis	0	0	—	—	1 (2)	—	—	0	0
Vitreoretinal traction syndrome	0	0	—	—	0	—	—	1 (2)	0
Diverticulum intestinal	0	0	—	—	1 (2)	—	—	0	0
Gastrointestinal polyp hemorrhage	0	1 (2)	—	—	0	—	—	0	0
Coronary artery disease	0	0	—	—	0	—	—	1 (2)	0
Acute cholecystitis	0	1 (2)	—	—	0	—	—	0	0
Metastatic hepatic cancer	0	0	—	—	1 (2)	—	—	0	0

* The safety analysis set included all participants who underwent randomization and received at least one dose of the assigned orforglipron or placebo.
† Cardiac disorders are listed separately because they include multiple *Medical Dictionary for Regulatory Activities* terms: atrioventricular block first degree, palpitations, tachycardia, sinus tachycardia, supraventricular extrasystoles, ventricular extrasystoles, atrial tachycardia, atrioventricular block, coronary artery disease, early repolarization syndrome, left ventricular hypertrophy, sinus arrhythmia, and sinus bradycardia.

Discussion

In this phase 2, randomized, double-blind, placebo-controlled trial of orforglipron, participants in all dose cohorts (12, 24, 36, and 45 mg) had a greater decrease from baseline in body weight than those in the placebo group, both at 26 weeks (primary end point) and at 36 weeks (secondary end point). Decreases in BMI and waist circumference were also greater with orforglipron than with placebo. Orforglipron was associated with weight-reduction efficacy and with safety similar to those of injectable GLP-1 receptor agonists that have been approved for weight management. Given the currently available treatment options for weight management, there is an unmet need for an oral, incretin-based therapy with efficacy similar to that of injectable GLP-1 receptor agonists. Such therapy has the potential to increase acceptance of treatment, adherence to treatment, ease of use, and persistent use.

Liraglutide (3.0 mg once daily) and semaglutide (2.4 mg once weekly) are the only GLP-1 receptor agonists that have been approved for weight management; both are peptide-based injectables. Phase 3 trials of liraglutide (the SCALE trial4) and semaglutide (the STEP 1 trial5) showed significant weight reduction at 56 weeks and 68 weeks, respectively, with a mean reduction of 9.2% with liraglutide and 16.9% with semaglutide. This phase 2 trial of orforglipron showed weight reduction ranging from 8.6% to 12.6% at 26 weeks and ranging from 9.4% to 14.7% at 36 weeks. Semaglutide (3, 7, or 14 mg once daily) is the one available oral GLP-1 receptor agonist, and it has been approved for the treatment of type 2 diabetes but not for weight management. In this trial, orforglipron produced weight re duction at all evaluated doses. A weight reduction of at least 10% by 26 weeks occurred in up to 71% of participants who received orforglipron. Despite the relatively short trial period, the weight loss observed in this trial was similar to that observed with injectable GLP-1 receptor agonists that have been approved for weight management.

The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class in phase 2 studies. Similar to other GLP-1 receptor agonists, orforglipron produced improvements in the blood pressure and levels of circulating lipids. When abnormal, these levels are cardiovascular risk factors, so such improvements may lead to cardiovascular benefits, which have been observed with the GLP-1 receptor agonist class. Daily oral orforglipron was associated with weight reduction and related benefits that ap peared to be similar to the efficacy outcomes observed with injectable GLP-1 receptor agonists that have already been approved for weight management.

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با تشکر از توجه شما