ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Obesity is a major risk factor for many leading causes of illness and death worldwide. Data are needed regarding the efficacy and safety of the nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist orforglipron as a once-daily oral therapy for weight reduction in adults with obesity.

METHODS

In this phase 2, randomized, double-blind trial, we enrolled adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks. The percentage change from baseline in body weight was assessed at week 26 (primary end point) and at week 36 (secondary end point).

RESULTS

A total of 272 participants underwent randomization. At baseline, the mean body weight was 108.7 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body weight ranged from –8.6% to –12.6% across the orforglipron dose cohorts and was –2.0% in the placebo group. At week 36, the mean change ranged from –9.4% to –14.7% with orforglipron and was –2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified weight-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.

CONCLUSIONS

Daily oral orforglipron, a nonpeptide GLP-1 receptor agonist, was associated with weight reduction. Adverse events reported with orforglipron were similar to those with injectable GLP-1 receptor agonists. (Funded by Eli Lilly; GZGI ClinicalTrials.gov number, NCT05051579.)

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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.[1] 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.[2] GLP-1 receptor agonists mimic the incretin hormone GLP-1, which promotes weight reduction by decreasing the appetite and delaying gastric emptying, thereby leading to an improvement in energy balance.[3] Trials of injectable GLP-1 receptor agonists for weight management have shown long-term efficacy.[4,5]

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.[4,5] 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. There is a need for oral treatment options that are easy to use and have weight-reduction efficacy similar to that of the approved and currently available injectable GLP-1 receptor agonists.

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.[7,8] 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.[7] The pharmacokinetic profile of orforglipron, with a half-life of 29 to 49 hours, supports once-daily oral administration.[7] 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

Trial Design and Oversight

We conducted a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group 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

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 weight-related 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. Details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix (available at NEJM.org).

Procedures

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.

END POINTS

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. Key safety end points included adverse events, the blood pressure, the pulse, safety-related laboratory measures, pharmacokinetic measures, and participant-reported outcomes. A complete list of end points is provided in the protocol.

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

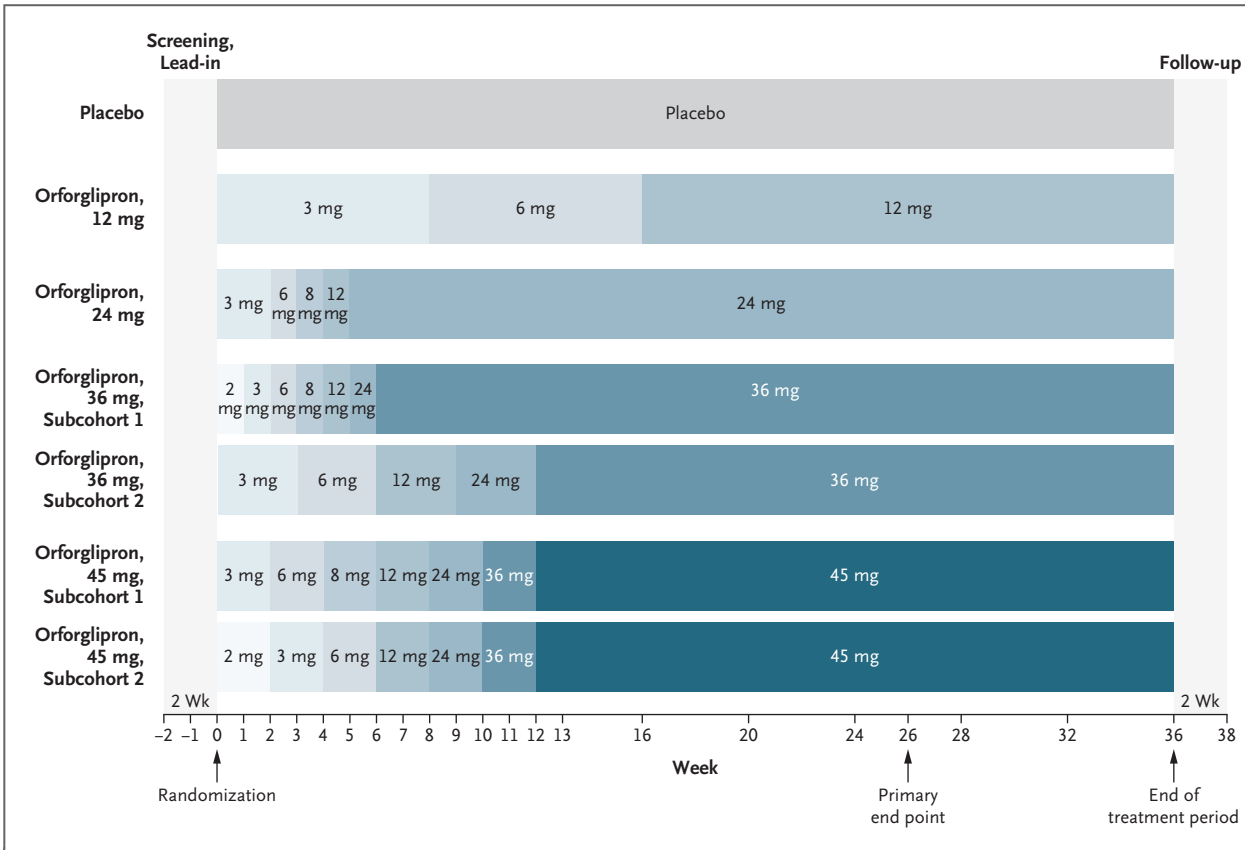


Figure 1. Trial Design.

end point. The estimand used for efficacy analyses (efficacy estimand) included only data that were collected before the occurrence of any intercurrent events (permanent discontinuation of orforglipron or placebo). For continuous efficacy outcomes, 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 were analyzed 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. No multiplicity adjustments were made for control of the type 1 error rate in this early-stage study of orforglipron. To test the efficacy of the 36-mg and 45-mg doses of orforglipron, data were pooled across subcohorts for each dose.

Safety analyses compared outcomes for orforglipron with those for placebo, regardless of adherence. These analyses were conducted in the safety analysis set, which included all participants who underwent randomization and received at least one dose of the assigned orforglipron or placebo. Details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PARTICIPANT CHARACTERISTICS

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. Data regarding the disposition and representativeness of the participants are provided in Fig. S1 and Table S1, respectively. A total of 37 participants prematurely discontinued the trial: 10 because of adverse events, and 27 for reasons unrelated to adverse events (Table S2). 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.

WEIGHT-RELATED OUTCOMES

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 baseline 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 dose-dependent, continuous absolute decrease in body weight (Fig. 2B). Across dose cohorts, the placebo-corrected 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 (Fig. 2C and 2D and Table S3). The weight reduction observed at week 36 (end of the treatment period) was greater than that observed at week 26 (primary end point). Results for additional, exploratory weight-related measures are shown in Table S4.

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 (Fig. S2).

CARDIOMETABOLIC OUTCOMES

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 (Table S5). 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 lipids, including triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and very-LDL cholesterol. Data regarding the changes in the use of antihypertensive and lipid-lowering medications are provided in Table S6.

SAFETY OUTCOMES

Nausea, constipation, vomiting, diarrhea, and eructation were the most common adverse events reported with orforglipron, and these gastrointestinal events occurred more frequently with orforglipron than with placebo (Table 3 and Fig. S3). The incidence of nausea ranged from 37% (11 of 30 participants) to 58% (31 of 53 participants) across the orforglipron dose cohorts and was 10% (5 of 50 participants) in the placebo group. The incidence of vomiting ranged from 14% (4 of 29 participants) to 32% (17 of 53 participants) with orforglipron and was 6% (3 of 50 participants) with placebo. Most gastrointestinal events were mild to moderate in severity, occurred during dose escalation, and were transient and resolved without permanent discontinuation of orforglipron or placebo. The incidence of nausea and of vomiting was highest among participants who received orforglipron at a dose of 24 mg. In the 24-mg dose cohort, a starting dose of 3 mg was administered for 2 weeks, and then the dose was increased weekly. This dose-escalation schedule was different from that of the other dose cohorts.

Overall, the percentage of participants who reported adverse events ranged from 86% (43 of 50 participants) to 90% (55 of 61 participants) across the orforglipron dose cohorts and was 76% (38 of 50 participants) in the placebo group. The most frequent gastrointestinal events did not increase in a dose-dependent manner with orforglipron doses higher than 3 mg. This trial was designed to inform the dose selection, starting dose, and dose-escalation scheme for phase 3 trials. The incidence of gastrointestinal events throughout the trial was higher with the 3-mg starting dose than with the 2-mg starting dose. The incidence of adverse events was higher with dose escalation every 1 or 2 weeks than with dose escalation every 3 weeks. Overall, after the dose-escalation phase, orforglipron was associated with few adverse events at all doses. Liver-function values were not more elevated among participants who received orforglipron than among participants who received placebo (Table S7).

Discontinuation of orforglipron because of an adverse event occurred in 35 participants, and 30 of these participants (10 to 17% of all participants across dose cohorts) reported a gastrointestinal event as the reason for discontinuation. Serious adverse events were reported by 7 participants who received orforglipron. There was no clinically relevant difference in the incidence of serious adverse events between the orforglipron dose cohorts and the placebo group. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.

The blood pressure and pulse were measured before the administration of orforglipron or placebo at each visit in all trial groups. For each measurement, two values were obtained 5 minutes apart and the mean value was recorded. The mean pulse was increased in all orforglipron dose cohorts, with the maximal change from baseline occurring at approximately week 12. At week 36, the change from baseline in the pulse ranged from 3.2 to 7.4 beats per minute across the orforglipron dose cohorts and was –1.8 beats per minute in the placebo group. The change in the pulse was similar in the 36-mg and 45-mg dose cohorts. There was no clinically relevant change in the calcitonin level among participants who received orforglipron. One participant in

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.

the 24-mg dose cohort had an investigator-reported pancreatic event. This potential case of pancreatitis was evaluated by an independent adjudication committee, and after diagnostic follow-up, it was determined that the participant did not have pancreatitis.

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 trial[4]) and semaglutide (the STEP 1 trial[5]) 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) with the permeation enhancer salcaprozate sodium (SNAC)[6] 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. For sufficient absorption, this drug must be taken at least 30 minutes before the first intake of food, beverages, or other oral medications of the day and taken with no more than 30 ml of plain water. In the PIONEER 1 trial, the use of the highest dose of oral semaglutide (14 mg)

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.

led to a weight reduction of 2.3 kg after 26 weeks among patients with type 2 diabetes.[6]

Higher doses of oral semaglutide (25 and 50 mg) are in phase 3 development for the treatment of type 2 diabetes and obesity. A recent press release[9] reported that the use of oral semaglutide led to weight loss similar to that observed with injectable semaglutide among patients with obesity (in the STEP 1 trial), with gastrointestinal adverse events similar to those observed with the injectable GLP-1 receptor agonist class; however, the higher doses still require strict food and water restrictions and an absorption enhancer. Danuglipron, an oral small-molecule GLP-1 re-

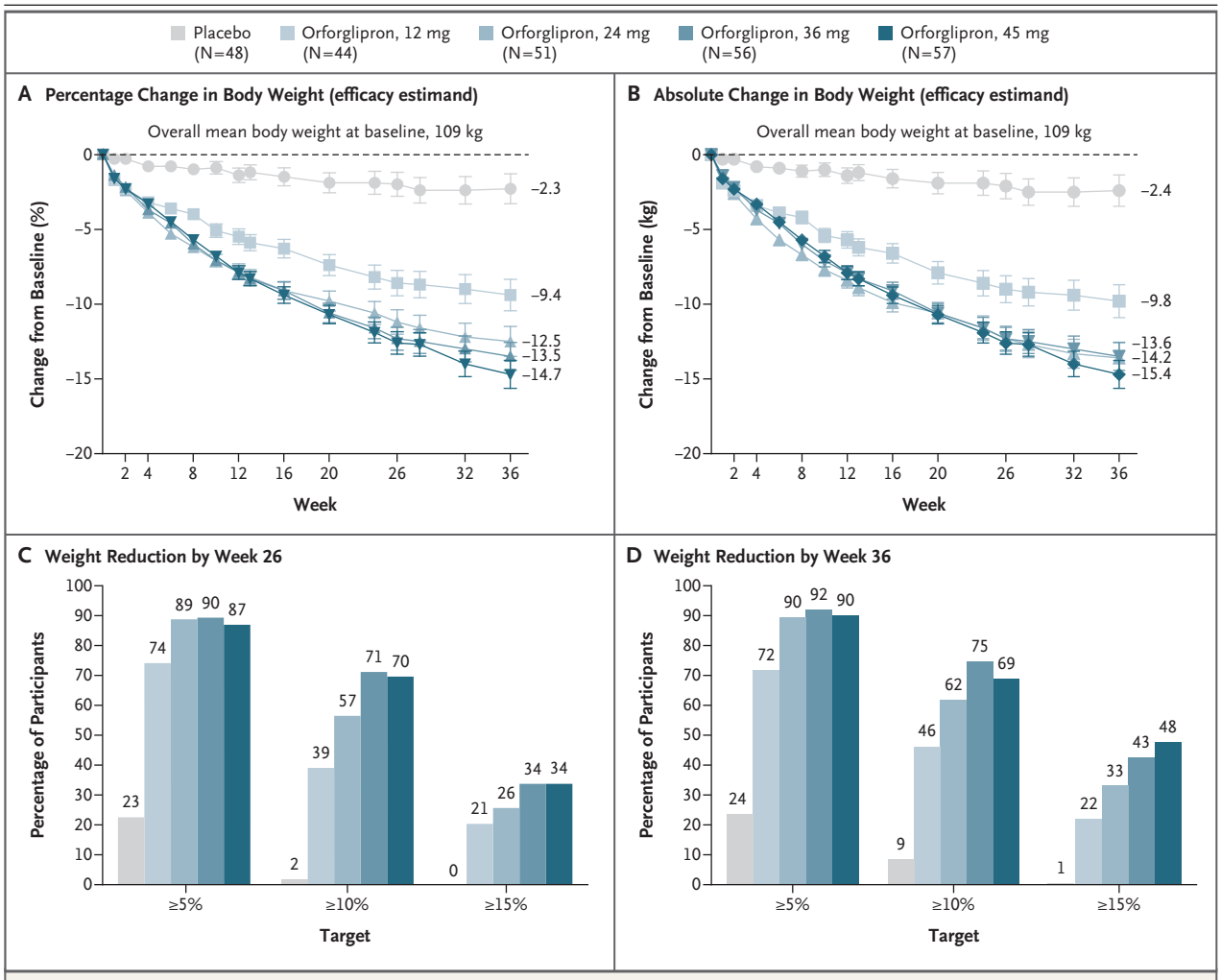


Figure 2. Change in Body Weight with Daily Oral Orforglipron versus Placebo.

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.

ceptor agonist, is also under development and was associated with few adverse events in phase 1 and phase 2 trials involving patients with type 2 diabetes.[10-12]

For orforglipron, the mechanism of activation of the GLP-1 receptor may contribute to the efficacy of the drug. Orforglipron action at the GLP-1 receptor produces cAMP signaling similar to that produced by native GLP-1, but it leads to low activation of the β-arrestin pathway, which regulates receptor internalization.[7] This biased signaling effect is also a feature of tirzepatide action at the GLP-1 receptor,[13] and tirzepatide has shown potent glucose-reduction and weight-reduction efficacy in the SURPASS and SURMOUNT trials.[14-19]

In this trial, orforglipron produced weight reduction 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. Furthermore, the weight loss had not yet plateaued at 36 weeks, which suggests the pos-

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.

sibility of additional weight loss with longer treatment. The magnitude of weight loss observed in this trial meets the currently recommended target for weight reduction that is expected to result in improvement in many obesity-associated coexisting conditions.[2] Further studies are needed to establish whether the health benefits seen with injectable GLP-1 receptor agonists are shared by orforglipron.

The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class in phase 2 studies. The most common adverse events reported with orforglipron were mild-to-moderate gastrointestinal events. The 24-mg dose cohort had the highest incidence of gastrointestinal events, possibly because of the higher starting dose (3 mg for 2 weeks) followed by the rapid dose escalation (weekly) until the maintenance dose was reached. In this dose cohort, the incidence of nausea and of vomiting was higher in the first 2 weeks and then decreased.

Although gastrointestinal events occurred at a higher incidence than desired, they allowed us to find the doses that were most efficacious. The pattern of gastrointestinal events was informative, as was the incidence (for nausea, 37 to 58% with orforglipron and 10% with placebo; for vomiting, 14 to 32% with orforglipron and 6% with placebo). These findings suggest that lower starting doses and slower dose escalation are indicated for reducing gastrointestinal events and reaching the target dose; this is the concept used for injectable GLP-1 receptor agonists. Nevertheless, even the lowest evaluated maintenance doses of orforglipron had clinically relevant benefits with respect to weight reduction. Adjustments to the starting dose and dose-escalation scheme in the phase 3 program are planned for the possible reduction of gastrointestinal events.

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. Whether these class effects are shared by orforglipron remains to be investigated. Orforglipron was associated with pulse increases that were consistent, in magnitude and time course, with those observed with other GLP-1 receptor agonists. Pulse increases have resulted in scrutiny of agents in

the class, but various trials of these agents that assessed cardiovascular outcomes showed an overall net benefit, which mitigates concerns regarding the long-term effects of these pulse increases.[20,21]

The limitations of this trial are related to the design features of a phase 2 trial, namely the relatively few people in each trial group and the homogeneous trial population, which was enrolled in only three countries and included a high percentage of women and White participants. These features may limit generalizability. Gastrointestinal events occurred at a higher incidence than desired because of the need for exploration of alternative dose-escalation regimens. The strengths of this trial include the randomized, double-blind, placebo-controlled design; the exploration of dose range; and the good levels of adherence and participant retention.

Daily oral orforglipron was associated with weight reduction and related benefits that appeared 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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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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