ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

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ABSTRACT

BACKGROUND

Orforglipron, a small-molecule, nonpeptide oral glucagon-like peptide-1 (GLP-1) receptor agonist, is being investigated as a treatment for obesity.

METHODS

In this phase 3, multinational, randomized, double-blind trial, we examined the safety and efficacy of once-daily orforglipron at doses of 6 mg, 12 mg, or 36 mg, as compared with placebo (assigned in a 3:3:3:4 ratio) as an adjunct to healthy diet and physical activity for 72 weeks. All the patients had obesity without diabetes mellitus. The primary end point was the percent change in body weight from baseline to week 72, as assessed according to the treatment-regimen estimand in the intention-to-treat population.

RESULTS

A total of 3127 patients underwent randomization. The mean change in body weight from baseline to week 72 was −7.5% (95% confidence interval [CI], −8.2 to −6.8) with 6 mg of orforglipron, −8.4% (95% CI, −9.1 to −7.7) with 12 mg of orforglipron, and −11.2% (95% CI, −12.0 to −10.4) with 36 mg of orforglipron, as compared with −2.1% (95% CI, −2.8 to −1.4) with placebo (P<0.001 for all comparisons with placebo). Among the patients in the orforglipron 36-mg group, 54.6% had a reduction of 10% or more, 36.0% had a reduction of 15% or more, and 18.4% had a reduction of 20% or more, as compared with 12.9%, 5.9%, and 2.8% of the patients, respectively, in the placebo group. Waist circumference, systolic blood pressure, triglyceride levels, and non-HDL cholesterol levels significantly improved with orforglipron treatment as compared with placebo. Adverse events resulted in treatment discontinuation in 5.3 to 10.3% of the patients in the orforglipron groups and in 2.7% of those in the placebo group. The most common adverse events with orforglipron were gastrointestinal effects, which were mostly mild to moderate.

CONCLUSIONS

In adults with obesity, 72-week treatment with orforglipron led to significantly greater reductions in body weight than placebo; the adverse-event profile was consistent with that of other GLP-1 receptor agonists. (Funded by Eli Lilly; ATTAIN-1 ClinicalTrials.gov number, NCT05869903.)

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*The investigators in the ATTAIN-1 trial are listed in the Supplementary Appendix, available at NEJM.org.

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Overweight and obesity affect more than 2.5 billion persons worldwide and increase the risk of multiple health complications.[1] Long-term care for patients with obesity requires a multifaceted approach with safe, durable, and accessible treatment options.[2] Clinical guidelines recommend obesity-management medications for patients with obesity, as well as for those who are overweight with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 27 to less than 30 with coexisting complications.[3,4] The use of incretin-based therapies for obesity, such as glucagon-like peptide-1 (GLP-1) receptor agonists, are reported to result in mean weight reductions of approximately 15 to 20% and have shown additional health benefits, including decreased cardiovascular risk.[5-8] However, most available GLP-1–based medications are administered as a subcutaneous injection, which may limit treatment initiation and adherence.[9,10]

Oral small-molecule GLP-1 receptor agonists may mitigate the limitations of peptide GLP-1 therapies while retaining their biologic properties. These agents may be amenable to easier storage, distribution, and administration. In addition, many patients prefer oral to injectable medications. Such advantages theoretically may increase access to GLP-1–based therapies and to broader health benefits associated with their use and allow patients to select a formulation aligned with their needs.

Orforglipron is a small-molecule, nonpeptide GLP-1 receptor agonist that is designed for once-daily, oral administration without restrictions on food or liquid intake. This drug is in clinical development for obesity as well as for type 2 diabetes, hypertension, osteoarthritis, and obstructive sleep apnea.[11] We performed the ATTAIN-1 trial to evaluate the efficacy and safety of orforglipron at doses of 6 mg, 12 mg, and 36 mg in adults with obesity without diabetes mellitus.

METHODS

TRIAL DESIGN AND OVERSIGHT

We designed this phase 3, multinational, randomized, placebo-controlled trial to investigate once-daily, orally administered orforglipron, as compared with placebo, as an adjunct to healthy diet and physical activity in patients with obesity who did not have diabetes mellitus. The trial was performed at 137 sites in nine countries.

Local institutional review boards approved the protocol (available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. All the patients provided written informed consent.

The trial sponsor, Eli Lilly, designed the trial and oversaw its conduct. Trial investigators were responsible for data collection. The sponsor performed site monitoring, data collation, and data analysis. The investigators and authors worked under confidentiality agreements with the sponsor. The authors, with assistance from sponsor-funded medical writers, wrote the first draft of the manuscript. All the authors had access to the data and analyses, interpreted the data, critically reviewed the manuscript, approved the decision to submit it for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

PATIENTS

To be eligible to participate in the trial, adults (≥18 years of age) were required to have a BMI of at least 30 or to have a BMI between 27 and 30 and to have at least one obesity-related complication, including hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea, and a history of at least one patient-reported unsuccessful dietary effort to lose body weight. Key exclusion criteria were a diagnosis of diabetes mellitus and a change in body weight (either gain or loss) of more than 5 kg within 90 days before screening. An upper limit of 70% enrollment of women ensured a sufficient sample of men. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix (available at NEJM.org).

PROCEDURES

Patients were randomly assigned in a 3:3:3:4 ratio to receive once-daily orforglipron at a dose of 6 mg, 12 mg, or 36 mg or placebo. Randomization was stratified according to country, sex, and the presence or absence of prediabetes. Prediabetes was diagnosed according to glycemic thresholds proposed by the American Diabetes Association (with details provided in the Supplementary Appendix). Orforglipron or matching placebo was administered daily by oral capsule. Orforglipron was started at a dose of 1 mg, which was esca-

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lated every 4 weeks until the assigned dose was reached (6 mg at 8 weeks, 12 mg at 12 weeks, and 36 mg at 20 weeks) (Fig. S1 in the Supplementary Appendix). Throughout the trial, all the patients received individualized lifestyle counseling focused on a healthy, balanced diet combined with physical activity.

The trial included a 3-week screening period followed by a 72-week treatment period. In patients with normoglycemia at randomization, the treatment period was followed by a 2-week off-drug safety follow-up period, whereas those with baseline prediabetes were scheduled to continue receiving the assigned regimen for 2 additional years. Here, we report the 72-week results for all the patients.

END POINTS

The primary end point was the percent change in body weight from baseline to week 72. Multiplicity-adjusted secondary end points were the percentage of patients who had a reduction in body weight of at least 5%, 10%, 15%, or 20% at week 72, along with the change from baseline to week 72 in waist circumference, systolic blood pressure, non–high-density-lipoprotein (HDL) cholesterol, and triglycerides. Additional secondary end points included changes in glycemic measures, diastolic blood pressure, and other lipid measures. Changes in body composition from baseline to week 72 were assessed for a subgroup of patients by means of dual-energy x-ray absorptiometry (DXA). All prespecified end points are described in the protocol.

STATISTICAL ANALYSIS

We determined that a sample size of 3042 patients would provide the trial with at least 90% power to show the superiority of individual doses of orforglipron over placebo for the primary end point at a familywise two-sided type I error rate of 0.05, assuming that the treatment effect in mean percent body-weight reduction from baseline to week 72, as compared with placebo, would be at least 5 percentage points with a common standard deviation of 10%.

The efficacy analysis included all the patients who had undergone randomization. Two estimands were predefined. The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation or the use of prohibited weight-management treatments (consistent with the intention-to-treat analysis). The efficacy estimand represents the treatment effect as if all the randomized patients adhered to the administration of either orforglipron or placebo as intended and did not initiate prohibited weight-management treatment. Thus, the efficacy estimand used a hypothetical strategy to account for intercurrent events; the corresponding potential outcome thus may not be realized. Therefore, the efficacy estimand is likely to lead to a larger treatment effect than the treatment-regimen estimand. All reported results were calculated with the treatment-regimen estimand, unless otherwise noted.

A graphical testing procedure for multiple comparisons was used for testing the primary and multiplicity-adjusted secondary end points[12,13] to control for the overall familywise type I error rate at 0.05 within each estimand. Model-based estimates and confidence intervals are reported. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. Safety analyses were conducted in all the patients who underwent randomization and received at least one dose of orforglipron or placebo. These analyses included data from the treatment and safety follow-up periods.

Statistical analyses for the treatment-regimen estimand were conducted by means of an analysis-of-covariance model for continuous efficacy outcomes and logistic regression for binary outcomes. Missing data at week 72 owing to early discontinuation of orforglipron or placebo were imputed within each trial group with the retrieved-dropouts method. Additional details regarding graphical testing, missing-data imputation, and statistical methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From June 5, 2023, to July 25, 2025, a total of 3127 patients underwent randomization in nine countries. At baseline, the demographic and clinical characteristics of the patients were similar in the trial groups (Table 1 and Table S1). The mean age of the patients was 45 years; 64.2% were women; and 56.5% were White, 28.6% were Asian, and 8.6% were Black. At randomization, the mean body weight was 103.2 kg and the mean BMI was 37.0. A total of 46.0% of the patients

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

Characteristic	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=725)	Orforglipron, 36 mg (N=730)	Placebo (N=949)	Total (N=3127)
Age — yr	44.9±12.1	45.4±12.6	44.9±11.9	45.1±11.9	45.1±12.1
Female sex — no. (%)	469 (64.9)	467 (64.4)	465 (63.7)	608 (64.1)	2009 (64.2)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	2 (0.3)	3 (0.4)	2 (0.3)	4 (0.4)	11 (0.4)
Asian	202 (28.3)	201 (28.1)	214 (29.6)	267 (28.5)	884 (28.6)
Black	68 (9.5)	60 (8.4)	67 (9.3)	72 (7.7)	267 (8.6)
White	408 (57.1)	405 (56.6)	394 (54.4)	539 (57.5)	1746 (56.5)
Native Hawaiian or other Pacific Islander	0	1 (0.1)	0	2 (0.2)	3 (0.1)
Multiple	35 (4.9)	45 (6.3)	47 (6.5)	54 (5.8)	181 (5.9)
Hispanic or Latino	273 (37.8)	275 (37.9)	258 (35.3)	369 (38.9)	1175 (37.6)
Body weight — kg	103.2±21.7	102.2±21.6	103.1±23.2	103.9±22.0	103.2±22.1
Body-mass index‡					
Mean	37.0±6.5	36.7±6.5	36.9±6.7	37.1±6.3	37.0±6.5
Distribution — no. (%)					
<30	62 (8.6)	72 (9.9)	68 (9.3)	86 (9.1)	288 (9.2)
30 to <35	263 (36.4)	272 (37.5)	285 (39.0)	331 (34.9)	1151 (36.8)
35 to <40	202 (27.9)	198 (27.3)	183 (25.1)	266 (28.0)	849 (27.2)
≥40	196 (27.1)	183 (25.2)	194 (26.6)	266 (28.0)	839 (26.8)
Waist circumference — cm	112.2±14.1	112.0±14.2	112.4±15.3	112.8±14.5	112.4±14.5
Blood pressure — mm Hg					
Systolic	125.4±14.1	125.1±13.7	125.8±15.9	125.8±14.5	125.5±14.6
Diastolic	81.0±9.3	81.2±9.4	80.9±10.1	81.8±9.9	81.3±9.7
Lipid measure — mg/dl					
Total cholesterol	196.2±37.6	195.0±39.0	196.3±39.5	196.5±39.5	196.0±38.9
HDL cholesterol	49.6±12.5	50.1±12.4	48.5±12.6	49.3±12.4	49.4±12.5
LDL cholesterol	119.6±32.2	118.3±34.1	119.4±33.6	119.0±33.6	119.1±33.4
Non-HDL cholesterol	146.4±36.1	144.6±38.0	147.5±38.7	147.0±38.1	146.4±37.7
VLDL cholesterol	26.1±11.8	25.9±11.7	27.3±13.2	27.3±12.9	26.7±12.5
Triglycerides	135.4±72.5	133.5±75.8	142.8±89.1	142.4±91.9	138.8±83.5

* Plus–minus values are means ±SD. 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.

† Race and ethnic group were reported by the patients. The percentages were calculated according to the total number of patients indicating their race or ethnic group. Thus, the denominators in this category were 715 in the 6-mg orforglipron group, 715 in the 12-mg orforglipron group, 724 in the 36-mg orforglipron group, and 938 in the placebo group, for a total of 3092 patients.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

had a BMI of less than 35, and 36.0% of the patients had prediabetes.

The trial was completed by 2662 patients (85.1%), including 625 patients (86.4%) in the orforglipron 6-mg group, 630 patients (86.9%) in the orforglipron 12-mg group, 639 patients (87.5%) in the orforglipron 36-mg group, and 768 patients (80.9%) in the placebo group. Administration of orforglipron or placebo was continued throughout the 72-week trial period in 2344 patients (75.0%), including 565 patients (78.1%) in the orforglipron 6-mg group, 562 patients (77.5%)

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in the orforglipron 12-mg group, 552 patients (75.6%) in the orforglipron 36-mg group, and 665 patients (70.1%) in the placebo group (Fig. S2).

Overall, the percentage of patients who discontinued treatment for any reason was 25.0% (21.9 to 24.4% in the orforglipron groups and 29.9% in the placebo group). The most common reasons were the patient's decision to withdraw from treatment (8.5 to 8.9% of the patients in the orforglipron groups and 13.8% of those in the placebo group), followed by adverse events (in 5.1 to 10.3% of the patients in the orforglipron groups and in 2.6% of those in the placebo group).

WEIGHT-RELATED END POINTS

The mean change in weight from baseline to week 72 was –7.5% (95% confidence interval [CI], –8.2 to –6.8) in the orforglipron 6-mg group, –8.4% (95% CI, –9.1 to –7.7) in the orforglipron 12-mg group, and –11.2% (95% CI, –12.0 to –10.4) in the orforglipron 36-mg group, as compared with –2.1% (95% CI, –2.8 to –1.4) in the placebo group (Table 2 and Fig. 1A). All orforglipron doses were superior to placebo, with a treatment difference of –5.5 percentage points (95% CI, –6.5 to –4.5) with orforglipron 6 mg, –6.3 percentage points (95% CI, –7.3 to –5.4) with orforglipron 12 mg, and –9.1 percentage points (95% CI, –10.1 to –8.1) with orforglipron 36 mg (P<0.001 for all doses).

At 72 weeks, significantly more patients in all the orforglipron groups met weight-reduction thresholds of at least 5%, 10%, 15%, and 20% than in the placebo group. Specifically, a body-weight reduction of 10% or more was met in 33.3% of the patients in the orforglipron 6-mg group, in 40.0% of those in the orforglipron 12-mg group, and in 54.6% of those in the orforglipron 36-mg group, as compared with 12.9% of those in the placebo group (P<0.001 for all comparisons with placebo) (Table 2 and Fig. 1C).

Treatment with all orforglipron doses was associated with a greater reduction in absolute body weight and in BMI than with placebo (Figs. S3 and S4). Of the patients in the orforglipron 36-mg group, at week 72, 11.1% had a BMI of less than 25, 18.6% had a BMI of less than 27, and 37.3% had a BMI of less than 30, as compared with 0.9%, 3.5%, and 15.7%, respectively, in the placebo group (Fig. S5). Table S3 shows subgroup analyses assessing treatment interac-

Table 2. Primary and Key Secondary End Points.*

End Point	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=725)	Orforglipron, 36 mg (N=730)	Placebo (N=949)
Primary end point				
Percent change in body weight (95% CI)†	–7.5 (–8.2 to –6.8)	–8.4 (–9.1 to –7.7)	–11.2 (–12.0 to –10.4)	–2.1 (–2.8 to –1.4)
Difference vs. placebo (95% CI) — percentage points	–5.5 (–6.5 to –4.5)	–6.3 (–7.3 to –5.4)	–9.1 (–10.1 to –8.1)	—
Key secondary end points				
Category of weight reduction — % of patients (95% CI)‡				
≥5%	60.6 (56.5 to 64.6)	63.5 (59.8 to 67.2)	71.8 (68.1 to 75.4)	26.8 (23.3 to 30.2)
≥10%	33.3 (29.7 to 36.9)	40.0 (36.4 to 43.7)	54.6 (50.7 to 58.4)	12.9 (10.3 to 15.6)
≥15%	15.1 (12.4 to 17.8)	20.3 (17.3 to 23.3)	36.0 (32.4 to 39.5)	5.9 (4.0 to 7.8)
≥20%	6.4 (4.6 to 8.3)§	9.0 (6.9 to 11.1)	18.4 (15.5 to 21.3)	2.8 (1.6 to 4.0)
Change in waist circumference (95% CI) — cm†	–7.1 (–7.7 to –6.5)	–8.2 (–8.9 to –7.5)	–10.0 (–10.7 to –9.3)	–3.1 (–3.7 to –2.4)

* The primary and key secondary end points were tested under a multiplicity-control procedure. P<0.001 for all comparisons with placebo.
† In this category, data are model-based estimates and 95% confidence intervals assessed with the use of analysis of covariance according to the treatment-regimen estimand. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All changes are from baseline to week 72.
‡ Data are presented as model-based estimates and 95% confidence intervals as calculated by logistic regression according to the treatment-regimen estimand. The percentage was calculated by combining the percentages of patients who met the target in imputed datasets with the use of Rubin's rule.
§ This data point was not controlled for multiplicity.

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tion with important factors that could potentially affect changes in body weight, including baseline BMI, age, and sex. Observed values over time as well as the efficacy estimand for the percent change in body weight are shown in Figure 1B. Additional end points for both estimands are shown in Tables S4 through S6.

ADDITIONAL TREATMENT OUTCOMES

Orforglipron significantly improved cardiometabolic risk factors, which were assessed as key secondary end points controlled for multiplicity, including waist circumference, systolic blood pressure, non-HDL cholesterol, and triglycerides (Table 3, Table S4, and Figs. S4 and S6). Orforglipron was associated with improvements in diastolic blood pressure, other lipid fractions, high-sensitivity C-reactive protein, and waist-to-height ratio (Table S4 and Figs. S6 and S7), as well as levels of glycated hemoglobin, fasting glucose, and fasting insulin (Table S4). In the orforglipron groups, 74.6 to 83.7% of the patients with prediabetes at randomization had normoglycemic levels at week 72, as compared with 44.6% of those in the placebo group.

CHANGES IN BODY COMPOSITION

In the subgroup of 171 patients who underwent DXA, patients in the pooled orforglipron groups had a mean percent change of −13.8% in total body fat mass, −4.5% in lean mass, and −19.0% in visceral fat mass at week 72, as compared with changes of −1.7%, 0.3%, and 7.4%, respectively, with placebo (Fig. S8). In the pooled orforglipron groups, 73.1% of the body-weight reduction was due to a loss in fat mass and 26.9% was due to a loss in lean mass.

SAFETY

The most frequent adverse events with orforglipron were nausea, constipation, diarrhea, vomiting, and dyspepsia (Table S7 and Fig. S9). Gastrointestinal events in the orforglipron groups were mostly mild to moderate in severity and first occurred mainly during dose escalation. Treatment discontinuation because of gastrointestinal adverse events occurred in 3.5 to 7.0% of the patients in the orforglipron groups and in 0.4% of those in the placebo group.

Serious adverse events were reported in 3.8 to 5.5% of the patients in the orforglipron groups and in 4.9% of those in the placebo group (Table 4). During the 72-week trial period, three deaths were reported: one each in the orforglipron 6-mg and 12-mg groups and one in the placebo group (Table 4 and Table S8). Five cases of adjudication-confirmed mild pancreatitis occurred (all in the orforglipron groups), with no complications reported. In four of these patients, confirmation was based solely on symptoms and elevated enzyme levels, with cholelithiasis reported as a contributing factor in one patient. In the fifth patient, obstructive pancreatitis was confirmed on the basis of imaging (Table S9). No cases of medullary thyroid cancer were reported. Aminotransferase levels of at least 10 times the upper limit of the normal range (ULN) were reported in seven patients in the orforglipron groups and in one patient in the placebo group. For all seven patients in the orforglipron groups, alternative causes were identified (Table S10). In the orforglipron groups, two patients had both a total bilirubin level of more than two times the ULN and an alanine aminotransferase level of more than three times the ULN. Both cases had alternative causes and were not associated with drug-induced liver injury (Table S10). An increase in the mean pulse rate of 4.3 to 5.3 beats per minute occurred in the orforglipron groups, as compared with an increase of 0.8 beats per minute in the placebo group (Table S11). Additional safety information is provided in Table 4 and in Tables S7 and S11.

DISCUSSION

In this phase 3, multinational trial, we compared three once-daily doses of orforglipron (6 mg, 12 mg, and 36 mg) with placebo in 3127 patients who had obesity without diabetes. After 72 weeks of treatment, all the patients in the three orforglipron groups had a significant and clinically meaningful dose-dependent reduction in body weight. The patients who received the highest dose of orforglipron had an average 11.2% weight reduction; more than one third had a reduction of at least 15%, and nearly one fifth had a reduction of at least 20%. All measured cardiometabolic biomarkers improved with orforglipron treatment as compared with placebo.

Weekly injectable incretin-based obesity therapies, such as semaglutide and tirzepatide, have resulted in mean weight reductions of approximately 15% and more than 20%, respectively.[6,7] A weight reduction of 10% or more is a recognized therapeutic threshold, one that has been

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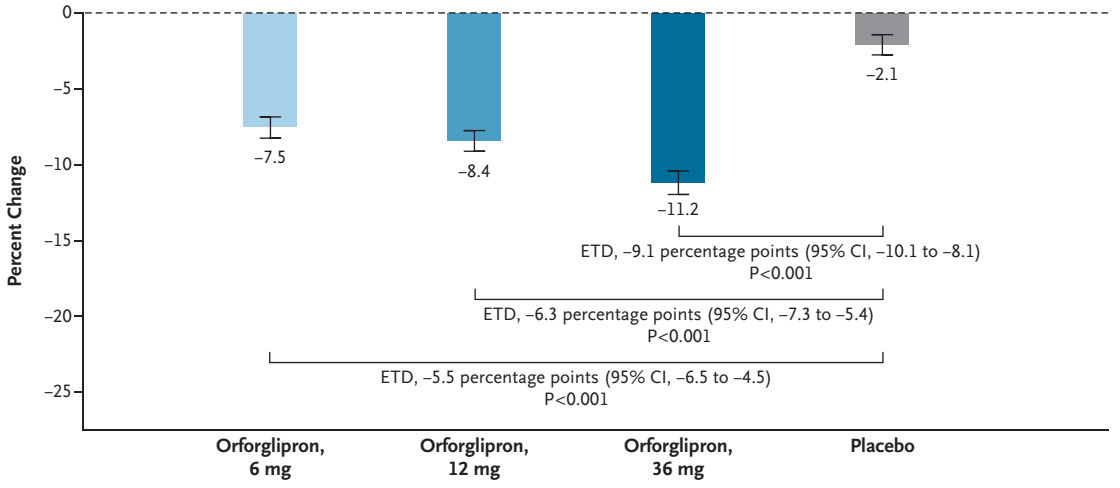
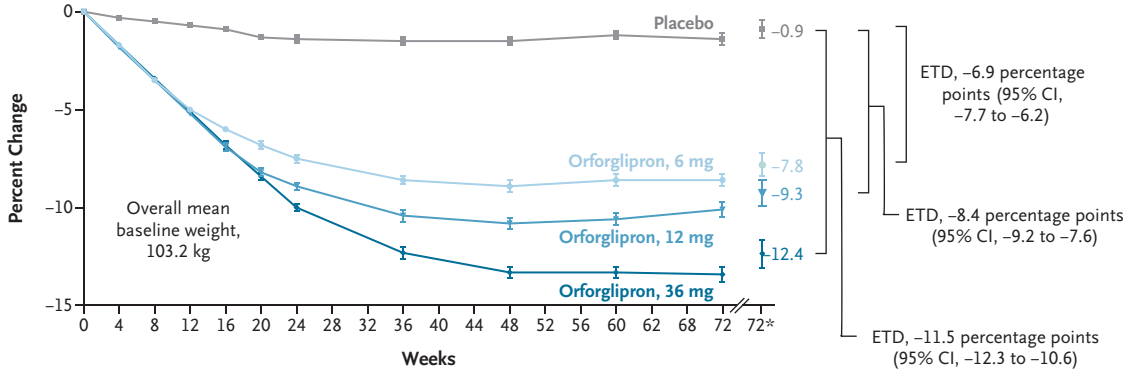
A Change in Body Weight from Baseline to Week 72 (treatment-regimen estimand)



B Change in Body Weight from Baseline to Week 72 (efficacy estimand)



No. of Patients

Placebo	949	937	923	910	875	847	817	766	716	688	654	949
Orforglipron, 6 mg	723	713	702	690	675	664	652	630	601	578	559	723
Orforglipron, 12 mg	725	719	695	687	672	652	648	624	602	582	559	725
Orforglipron, 36 mg	730	715	704	689	670	662	644	617	583	573	549	730

C Patients with Weight Reduction According to Logistic-Regression Analysis (treatment-regimen estimand)

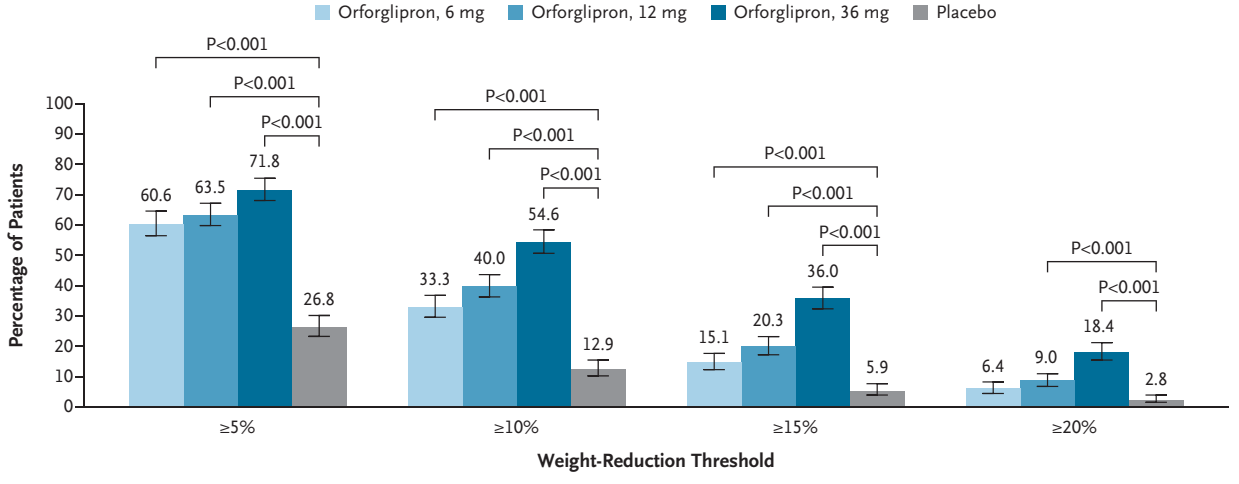


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Figure 1 (facing page). Body Weight and Body-Weight Reduction Thresholds.

Panel A shows the model-based estimate with 95% confidence intervals for the percent change in body weight from baseline to week 72 in the orforglipron groups and the placebo group, along with the estimated treatment difference (ETD) between groups, as calculated by means of analysis of covariance (ANCOVA), according to the treatment-regimen estimand. Panel B shows the results of two separate analyses combined into one panel. The curves at the left show changes from week 0 to week 72 based on observed on-treatment means with standard errors according to the efficacy estimand, including all data points obtained during the treatment period and up to the earliest date of discontinuation of orforglipron or placebo or the initiation of prohibited weight-management treatments. The data at the right of the curves at week 72 (marked with an asterisk) show the results of a model-based estimate, with 95% confidence intervals, according to the efficacy estimand — a prespecified analysis for the primary end point of the trial — along with the ETD between the orforglipron groups and the placebo group. Panel C shows the percentage of patients with a weight reduction of at least 5%, 10%, 15%, or 20%, as calculated by logistic-regression analysis (treatment-regimen estimand). The weight-reduction threshold of at least 20% was a key secondary end point for the orforglipron doses of 12 mg and 36 mg only. The percentages were calculated by combining percentages of patients who met targets across imputed datasets with the use of Rubin's rule. I bars indicate 95% confidence intervals. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. For end points that were not controlled for multiplicity, P values are not reported, regardless of statistical significance.

linked to meaningful cardiometabolic benefits.[14,15] In our current trial, patients who received orforglipron had a mean weight reduction of as much as 11.2%, and such reductions were associated with improvements in systolic and diastolic blood pressure, as well as lipid, glycemic, and high-sensitivity C-reactive protein levels. Although differences in design and population preclude direct cross-trial comparisons, these cardiometabolic improvements were similar to those reported with oral and injectable semaglutide in obesity trials, despite the modestly lower weight loss in the current trial, a finding that reinforces the clinical significance of a weight reduction of 10% or more.[8,16] In the Look AHEAD trial, which included patients with type 2 diabetes, patients who had a weight loss of 10% or more through a lifestyle intervention had a 21% reduction in cardiovascular events. Similarly, in the SELECT study, a cardiovascular outcomes trial involving patients with obesity without diabetes, a 9.4% weight loss with semaglutide over a period of 2 years was associated with a 20% reduction in major adverse cardiovascular events.[7,14] GLP-1 receptor agonists may improve cardiovascular outcomes both by inducing weight reduction and by their direct, weight-independent actions.[17] Whether orforglipron-induced weight reduction and biomarker changes will translate into a reduction in cardiovascular risk requires dedicated outcome trials.

Clinically, weight-reduction targets are individualized. Treat-to-target approaches that are based on thresholds of BMI or waist-to-height ratio have recently been proposed, although a single defined target remains a matter of debate.[18,19] Results of exploratory analyses in the current trial suggested that patients who received orforglipron had a higher likelihood of having a normal BMI or a near-normal waist-to-height ratio (<0.53) than those who received placebo, particularly among patients who had class I obesity or a BMI of 27 to 30 and associated complications at baseline. As with other obesity-management medications, weight-reduction responses varied substantially; notably, nearly one fifth of patients who received the highest dose had a weight reduction of at least 20%. We speculate that these findings may hold particular clinical relevance for patients with lower BMI values (for example, <35), who constitute the majority of patients with excess adiposity. Furthermore, orforglipron could represent an effective option for many patients, such as those who prefer oral therapy or lack access to injectable peptide-based obesity-management medications, including those in low- and middle-income countries where access is limited owing to low cold-chain availability.

In a phase 2 trial involving patients with obesity, 36-week treatment with 12 mg or 36 mg of orforglipron per day led to a substantial reduction in body weight, a loss that did not appear to plateau.[21] Despite the longer duration of the current trial, weight reduction after 72 weeks was similar to the reduction at 36 weeks in the phase 2 trial. Reasons may include differences in trial design and population, including greater geographic diversity in the current trial than in the phase 2 trial. Also, in the current trial, we enrolled a higher percentage of men than in historical phase 3 obesity trials, a factor that lim-

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Table 3. Key Secondary and Additional Secondary End Points.*

End Point	Pooled Orforglipron† (N=2178)	Placebo (N=949)	Estimated Treatment Difference vs. Placebo (95% CI)
Key secondary end points‡			
Change in systolic brood pressure (95% CI) — mm Hg	−5.7 (−6.3 to −5.0)	−1.4 (−2.4 to −0.5)	−4.2 (−5.3 to −3.2)
Percent change (95% CI)§			
Triglycerides	−14.8 (−16.3 to −13.3)	−3.8 (−6.8 to −0.7)	−11.5 (−14.5 to −8.3)
Non-HDL cholesterol	−6.7 (−7.6 to −5.8)	−1.9 (−3.6 to −0.2)	−4.9 (−6.7 to −3.1)
Additional secondary end points			
Change in diastolic blood pressure (95% CI) — mm Hg	−2.4 (−2.9 to −2.0)	−1.4 (−2.1 to −0.7)	−1.0 (−1.8 to −0.2)
Percent change (95% CI)§			
Total cholesterol	−4.1 (−4.8 to −3.4)	−2.0 (−3.3 to −0.6)	−2.1 (−3.7 to −0.6)
LDL cholesterol	−4.8 (−5.8 to −3.7)	−1.3 (−3.0 to 0.4)	−3.5 (−5.5 to −1.5)
VLDL cholesterol	−14.6 (−16.1 to −13.1)	−3.5 (−6.3 to −0.6)	−11.5 (−14.5 to −8.5)

* Data are model-based estimates and 95% confidence intervals assessed with the use of analysis of covariance according to the treatment-regimen estimand. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All changes are from baseline to week 72.
† The pooled orforglipron group includes patients in the 6-mg, 12-mg, and 36-mg orforglipron groups.
‡ The key secondary end points were tested under a multiplicity-control procedure. P<0.001 for all comparisons with placebo.
§ Lipid measures were log-transformed before fitting the analysis-of-covariance model, and results were then back-transformed with the delta method from the model-based estimate and standard errors on the natural log scale.

its cross-trial comparisons, since men are reported to have less weight reduction than women in response to incretin-based treatment.[22] Variability in responses to obesity-management medications is well documented and not fully understood.[20] In this phase 3 study, a healthy, balanced diet, rather than a hypocaloric diet with a 500-kcal deficit, was implemented as part of the recommended lifestyle modifications in line with recent expert recommendations.[10] It remains uncertain whether this regimen influenced the trial results. Changes in body composition were consistent with what is expected after weight reduction with various interventions for weight management, including GLP-1–based therapies.[23]

Although the higher discontinuation rate in the placebo group in the current trial was consistent with earlier clinical trials of GLP-1 receptor agonists in patients with obesity, the increasing availability of efficacious obesity-management medications may have an adverse effect on trial retention.[6,8,24] In this trial, 6.2% of patients in the placebo group discontinued treatment because of a lack of efficacy, as compared with up to 1.0% in the orforglipron groups. Other weight-management interventions were initiated by 2.5% of the patients in the placebo group who continued in the trial.

Small molecules may bind to off-target receptors, which raises the potential for additional adverse effects. No such effects have been detected in the orforglipron development program to date, and the orforglipron safety profile has been consistent with peptide GLP-1 receptor agonists in phase 3 clinical trials.[8,24] The most frequent adverse events were predominantly mild to moderate and gastrointestinal in nature, and the increase in pulse is consistent with findings observed with peptide GLP-1 receptor agonists.[8,24] In clinical practice, following best-practice recommendations for management of gastrointestinal symptoms on incretin-based therapies may further improve the side-effect profile. These practices can include the use of a slower dose-escalation schedule or dietary advice regarding eating schedules and food choices.[25] Liver safety has led to the discontinued clinical development of molecules such as lotiglipron and danuglipron and has been a potential concern with small-molecule oral GLP-1 receptor agonists.[26,27] Consequently, liver safety was thoroughly evaluated in the current trial, and no signal was detected.

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Table 4. Adverse Events.*

Adverse Event	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=724)	Orforglipron, 36 mg (N=728)	Placebo (N=948)	Total (N=3123)
	number of patients (percent)				
Any adverse event emerging during treatment period	603 (83.4)	627 (86.6)	620 (85.2)	763 (80.5)	2613 (83.7)
Serious adverse event	40 (5.5)	39 (5.4)	28 (3.8)	46 (4.9)	153 (4.9)
Death†	1 (0.1)	1 (0.1)	0	1 (0.1)	3 (0.1)
Event leading to discontinuation of orforglipron or placebo					
Any adverse event	38 (5.3)	57 (7.9)	75 (10.3)	26 (2.7)	196 (6.3)
Gastrointestinal disorder	25 (3.5)	38 (5.2)	51 (7.0)	4 (0.4)	118 (3.8)
Adverse event of special interest and other safety topics					
Hepatic event‡	1 (0.1)	0	2 (0.3)	2 (0.2)	5 (0.2)
Cancer	6 (0.8)	8 (1.1)	6 (0.8)	10 (1.1)	30 (1.0)
Adjudication-confirmed pancreatitis§	1 (0.1)	2 (0.3)	2 (0.3)	0	5 (0.2)
Hypotension or syncope‡	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Adjudication-confirmed MACE	7 (1.0)	0	4 (0.5)	4 (0.4)	15 (0.5)
Any cardiac disorder¶	1 (0.1)	1 (0.1)	0	2 (0.2)	4 (0.1)
Gastrointestinal event‡	10 (1.4)	19 (2.6)	25 (3.4)	6 (0.6)	60 (1.9)
Gallbladder disease‡	3 (0.4)	6 (0.8)	6 (0.8)	4 (0.4)	19 (0.6)
Acute renal event‡	0	0	0	1 (0.1)	1 (<0.1)
Major depressive disorder or suicidal ideation or behavior‡	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.1)	5 (0.2)
Hypersensitivity‡	0	0	0	1 (0.1)	1 (<0.1)
Dysesthesia‖	1 (0.1)	1 (0.1)	9 (1.2)	6 (0.6)	17 (0.5)
Other adverse event emerging during treatment period					
Cholelithiasis	6 (0.8)	11 (1.5)	11 (1.5)	8 (0.8)	36 (1.2)
Acute cholecystitis	1 (0.1)	2 (0.3)	4 (0.5)	1 (0.1)	8 (0.3)
Chronic cholecystitis	2 (0.3)	3 (0.4)	1 (0.1)	1 (0.1)	7 (0.2)

* MACE denotes major adverse cardiovascular event.
† Causes of death were reported as follows: undetermined for the patient in the 6-mg group, metastatic ovarian cancer in the patient in the 12-mg group, and pulmonary embolism for the patient in the placebo group. Deaths were also counted as serious adverse events and discontinuation of the trial regimen owing to adverse events.
‡ This category includes only events that were classified as severe or serious adverse events.
§ Additional information about adjudication-confirmed pancreatitis is provided in Table S10.
¶ Cardiac disorders included events that were classified as severe or serious arrhythmias and cardiac conduction disorders.
‖ Dysesthesia includes the *Medical Dictionary for Regulatory Activities* search terms of allodynia, dysesthesia, burning sensation, hyperesthesia, hyperpathia, pain of skin, paresthesia, sensitive skin, skin discomfort, and skin burning sensation.

Trial limitations include the lack of comparison with currently approved obesity-management medications, the use of cutoffs for BMI inclusion criteria that have been developed in White populations and that exclude patients with lower BMI values who may also have adiposity-related risks, and the increasing availability of obesity-management medications, which could have an effect on treatment adherence and efficacy results. The strengths of the trial include a highly diverse,

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large population from nine countries on four continents (Table S12), including more than 35% enrollment of men.

In patients with obesity, the use of orforglipron resulted in statistically and clinically significant weight reductions and an adverse-event profile that was consistent with that observed with other GLP-1 receptor agonists.

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