ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

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ABSTRACT

BACKGROUND

Orforglipron is a small-molecule, nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist in clinical development for type 2 diabetes and weight management. Additional data on the efficacy and safety of orforglipron are needed.

METHODS

In this phase 3, double-blind, placebo-controlled trial, we randomly assigned participants in a 1:1:1:1 ratio to receive orforglipron at one of three doses (3 mg, 12 mg, or 36 mg) or placebo once daily for 40 weeks. Participants had type 2 diabetes treated only with diet and exercise, a glycated hemoglobin level of at least 7.0% but no more than 9.5%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 23.0. The primary end point was the change from baseline to week 40 in the glycated hemoglobin level. A key secondary end point was the percent change in body weight from baseline to week 40.

RESULTS

A total of 559 participants underwent randomization. The mean glycated hemoglobin level at baseline was 8.0%. At week 40, the estimated mean change from baseline in the glycated hemoglobin level was –1.24 percentage points with the 3-mg dose, –1.47 percentage points with the 12-mg dose, –1.48 percentage points with the 36-mg dose, and –0.41 percentage points with placebo. All three doses of orforglipron were superior to placebo with respect to the primary end point; the estimated mean difference from placebo was –0.83 percentage points (95% confidence interval [CI], –1.10 to –0.56) with the 3-mg dose, –1.06 percentage points (95% CI, –1.33 to –0.79) with the 12-mg dose, and –1.07 percentage points (95% CI, –1.33 to –0.81) with the 36-mg dose (P<0.001 for all comparisons). The mean glycated hemoglobin level at week 40 was 6.5 to 6.7% with orforglipron. The percent change in body weight from baseline to week 40 was –4.5% with the 3-mg dose, –5.8% with the 12-mg dose, –7.6% with the 36-mg dose, and –1.7% with placebo. The most common adverse events were mild-to-moderate gastrointestinal events, most of which occurred during dose escalation. No episodes of severe hypoglycemia were reported. Permanent discontinuation of orforglipron or placebo due to adverse events occurred in 4.4 to 7.8% of participants receiving orforglipron and 1.4% of participants receiving placebo.

CONCLUSIONS

In adults with early type 2 diabetes, orforglipron significantly reduced the glycated hemoglobin level over a period of 40 weeks. (Supported by Eli Lilly; ACHIEVE-1 ClinicalTrials.gov number, NCT05971940.)

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*A list of the principal ACHIEVE-1 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Glucagon-like peptide-1 (GLP-1) receptor agonists are well-established glucose-lowering medications for the pharmacologic treatment of type 2 diabetes. The use of these medications provides multiple beneficial effects beyond reduction in glucose levels, including reduction in body weight and protection against cardiovascular disease.[1] The use of GLP-1 receptor agonists has increased in recent years. Owing to considerations with regard to absorption and the large molecular weight and peptide structure of these medications, most GLP-1 receptor agonists are administered subcutaneously[2]; however, many patients prefer oral formulations over injectables.[3] Currently, the only oral GLP-1 receptor agonist available (oral semaglutide) is a peptide coformulated with an absorption enhancer, and restrictions with regard to meal timing and the amount of water consumed when the drug is administered are required for the drug to reach therapeutic concentrations.[4] Nonpeptide, small-molecule GLP-1 receptor agonists have the potential to provide higher oral bioavailability with no dietary requirements and simpler administration.[5,6]

Orforglipron is a selective, high-affinity, partial agonist of the GLP-1 receptor that favors biased activation toward G protein over β-arrestin recruitment at the GLP-1 receptor.[7,8] Preclinical and early clinical studies showed that orforglipron had oral bioavailability of up to 40% and a dose-dependent pharmacokinetic profile with a half-life of 25 to 68 hours, features that support once-daily dose administration.[5] Orforglipron can be administered without restrictions on food or water intake, since the prandial state does not have a clinically meaningful effect on pharmacokinetics.[9] A 26-week phase 2 trial of orforglipron showed clinically meaningful reductions from baseline in the glycated hemoglobin level and body weight that were significantly greater than those with placebo or dulaglutide at a once-weekly dose of 1.5 mg in participants with type 2 diabetes, and the safety profile of orforglipron was consistent with those of the GLP-1 receptor agonist class.[10] In ACHIEVE-1 (A Study of Orforglipron in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Diet and Exercise Alone), we assessed the efficacy and safety of once-daily orforglipron at three doses (3 mg, 12 mg, and 36 mg) for use as monotherapy in persons with type 2 diabetes who had inadequate glycemic control with diet and exercise alone.

METHODS

TRIAL DESIGN AND PARTICIPANTS

This 40-week, phase 3, multicenter, double-blind, randomized, placebo-controlled trial was conducted in China, India, Japan, Mexico, and the United States. Participants were eligible for the trial if they were at least 18 years of age, had type 2 diabetes that was inadequately controlled with diet and exercise alone, and had received no other oral or injectable glucose-lowering medications within 3 months before enrollment in the trial. All the participants had never received insulin therapy, had a glycated hemoglobin level of at least 7.0% (53 mmol per mole) but no more than 9.5% (80 mmol per mole), had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 23.0, and had stable weight (within 5%) during the 3 months before screening. Key exclusion criteria were a history of pancreatitis; any liver disease (except metabolic dysfunction–associated steatotic liver disease) or an aspartate aminotransferase level of more than 5 times the upper limit of the normal range, an alanine aminotransferase level of more than 5 times the upper limit of the normal range, or both; and an estimated glomerular filtration rate of less than 15 ml per minute per 1.73 m^2 of body-surface area. A complete list of eligibility criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The sponsor (Eli Lilly) designed and oversaw the conduct of the trial. The investigators were responsible for data collection, and the sponsor performed site monitoring, data collation, and data analysis. The investigators worked under confidentiality agreements with the sponsor. All the authors had access to the data and analyses, critically reviewed the manuscript, approved the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first author and authors employed by the sponsor.

The protocol was approved by the local institutional review board at each participating center, and the trial was conducted in accordance with

the International Council for Harmonisation E6 guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All the participants provided written informed consent.

PROCEDURES

After a 4-week screening and lead-in period, participants were randomly assigned to receive oral orforglipron at one of three maintenance doses (3 mg, 12 mg, or 36 mg) or placebo once daily for 40 weeks, after which the participants underwent a 2-week safety follow-up period (Fig. S1 in the Supplementary Appendix). Participants who were assigned to receive orforglipron followed a dose-escalation regimen: the starting dose was 1 mg, and the dose increased every 4 weeks (to 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg, as applicable) until the assigned maintenance dose was reached.

Initiation of new glucose-lowering medications was allowed according to specific rescue criteria for severe persistent hyperglycemia, as described in the Supplementary Appendix. In the case of unacceptable gastrointestinal symptoms, participants were advised to adapt meals, use medications to control symptoms, and, if needed, temporarily pause orforglipron or placebo for up to two consecutive doses. De-escalation of the dose was not allowed.

END POINTS

The primary end point was the change in the glycated hemoglobin level from baseline to week 40. Key secondary end points controlled for type I error were a glycated hemoglobin level of less than 7.0% (53 mmol per mole) and of 6.5% (48 mmol per mole) or lower, the change from baseline in fasting serum glucose, and, for the 12-mg and 36-mg doses, the change and percent change from baseline in body weight, non–high-density lipoprotein (non-HDL) cholesterol, and triglycerides with orforglipron as compared with placebo at week 40. Additional end points (described in the protocol and in the Supplementary Appendix) included a glycated hemoglobin level of less than 5.7% (39 mmol per mole); reduction in body weight of at least 5%, at least 10%, and at least 15% from baseline; the change from baseline in mean seven-point participant-monitored blood glucose profiles, waist circumference, BMI, and blood pressure; and the percent change from baseline in other lipid measures at week 40.

Safety end points included serious adverse events, adverse events that emerged during the trial period, and discontinuation of orforglipron or placebo due to an adverse event. Adverse events of special interest included major adverse cardiovascular events, hypoglycemia (defined as a blood glucose level of <54 mg per deciliter [3.0 mmol per liter]), severe persistent hyperglycemia that led to rescue therapy, pancreatitis, C-cell thyroid tumors, hepatobiliary disorders, diabetic retinopathy complications, and hypersensitivity reactions.

STATISTICAL ANALYSIS

We estimated that a sample of 520 participants would provide the trial with more than 90% power to detect the superiority of orforglipron (at a dose of 3 mg, 12 mg, or 36 mg) to placebo with respect to the primary end point, assessed according to the intention-to-treat principle, under the assumption that the treatment effect (the mean change in the glycated hemoglobin level) from baseline to week 40 would be −0.6 percentage points with a common standard deviation of 1.2 percentage points. All participants who had undergone randomization were included in the efficacy analyses. Two estimands were prespecified to assess the primary and key secondary efficacy end points: the treatment-regimen estimand and the efficacy estimand. The treatment-regimen estimand was used to assess the estimated average treatment effect regardless of discontinuation of orforglipron or placebo or the initiation of additional glucose-lowering medications (intention-to-treat analysis). The efficacy estimand was used to assess the efficacy of orforglipron as compared with placebo under the assumption that all the participants who had undergone randomization continued to receive orforglipron or placebo as assigned for 40 weeks without the use of additional of glucose-lowering medications for more than 14 days. A graphical testing procedure was applied to strongly control the overall family-wise type I error rate at 0.05 within each estimand (Fig. S2). The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. All the results that are reported were obtained with the use of the treatment-regimen estimand, unless stated otherwise.

For the treatment-regimen estimand, data that were missing at week 40 were imputed with the use of the placebo washout method under the

assumption that data were missing at random for participants assigned to receive placebo and missing not at random for participants assigned to receive orforglipron.[11] The complete datasets for continuous efficacy end points were then assessed with the use of analysis of covariance, and binary end points were analyzed by logistic regression. Counts and percentages from logistic regression were calculated by combining percentages of participants across imputed datasets with the use of Rubin's rule. The unconditional trial-group effects, which were estimated by averaging the effects of the trial regimen over the baseline values from all participants who underwent randomization, are provided. R software, version 4.3.2 (R Foundation for Statistical Computing), and SAS software, version 8.2 (SAS Institute), were used for statistical calculations. Full details on statistical analysis methods are provided in the Supplementary Appendix.

Safety analyses were guided by an estimand that used data from the 40-week trial period and the 2-week safety follow-up period regardless of adherence to the trial regimen or the initiation of additional glucose-lowering medications. The safety population included all participants who had undergone randomization and received at least one dose of orforglipron or placebo. Analyses of hypoglycemia excluded events that occurred after the initiation of additional glucose-lowering medications.

RESULTS

PARTICIPANTS

Between August 9, 2023, and April 3, 2025, a total of 559 participants underwent randomization: 143 were assigned to receive orforglipron at a dose of 3 mg, 137 at a dose of 12 mg, and 141 at a dose of 36 mg, and 138 were assigned to receive placebo. A total of 526 participants (94.1%; 134 in the 3-mg group, 125 in the 12-mg group, 136 in the 36-mg group, and 131 in the placebo group) completed the trial, and 504 participants (90.2%; 129 in the 3-mg group, 120 in the 12-mg group, 127 in the 36-mg group, and 128 in the placebo group) continued to receive orforglipron or placebo throughout the 40-week trial period (Fig. S3). At baseline, participants had a mean duration of type 2 diabetes of 4.4 years, a mean glycated hemoglobin level of 8.0%, and a mean body weight of 90.2 kg; 48.1% of the participants were women, and 38.3% had previously received a glucose-lowering agent (most commonly metformin) (Table 1). The demographic and clinical characteristics of the participants at baseline were similar among trial groups. The participants in this trial were generally representative of the worldwide population of patients with type 2 diabetes (Table S1).

END POINTS

At week 40, the glycated hemoglobin level had decreased significantly from baseline in the orforglipron groups: the change was –1.24 percentage points (95% confidence interval [CI] –1.44 to –1.04) with the 3-mg dose, –1.47 percentage points (95% CI, –1.67 to –1.27) with the 12-mg dose, and –1.48 percentage points (95% CI, –1.66 to –1.29) with the 36-mg dose as compared with –0.41 percentage points (95% CI, –0.60 to –0.22) with placebo (Fig. 1A and Table S2). Orforglipron at any of the three doses was statistically superior to placebo with respect to the primary end point; the estimated mean difference from placebo was –0.83 percentage points (95% CI, –1.10 to –0.56) with the 3-mg dose, –1.06 percentage points (95% CI, –1.33 to –0.79) with the 12-mg dose, and –1.07 percentage points (95% CI, –1.33 to –0.81) with the 36-mg dose ($P<0.001$ for all comparisons) (Fig. 1A). The mean glycated hemoglobin level at week 40 was 6.5 to 6.7% with orforglipron.

The glycated hemoglobin target of less than 7.0% was reached in 68% of participants (98 of 143 in the 3-mg group) to 73% of participants (100 of 137 in the 12-mg group) with orforglipron as compared with 33% of participants (46 of 138) with placebo. A glycated hemoglobin level of 6.5% or lower was reached in 57% of participants (82 of 143 in the 3-mg group) to 62% of participants (86 of 141 in the 36-mg group) with orforglipron as compared with 15% of participants (21 of 138) with placebo, and a glycated hemoglobin level of less than 5.7% was reached in 17% of participants (26 of 143 in the 3-mg group) to 24% of participants (33 of 137 in the 12-mg group) with orforglipron as compared with 4% of participants (5 of 138) with placebo (Fig. 1C).

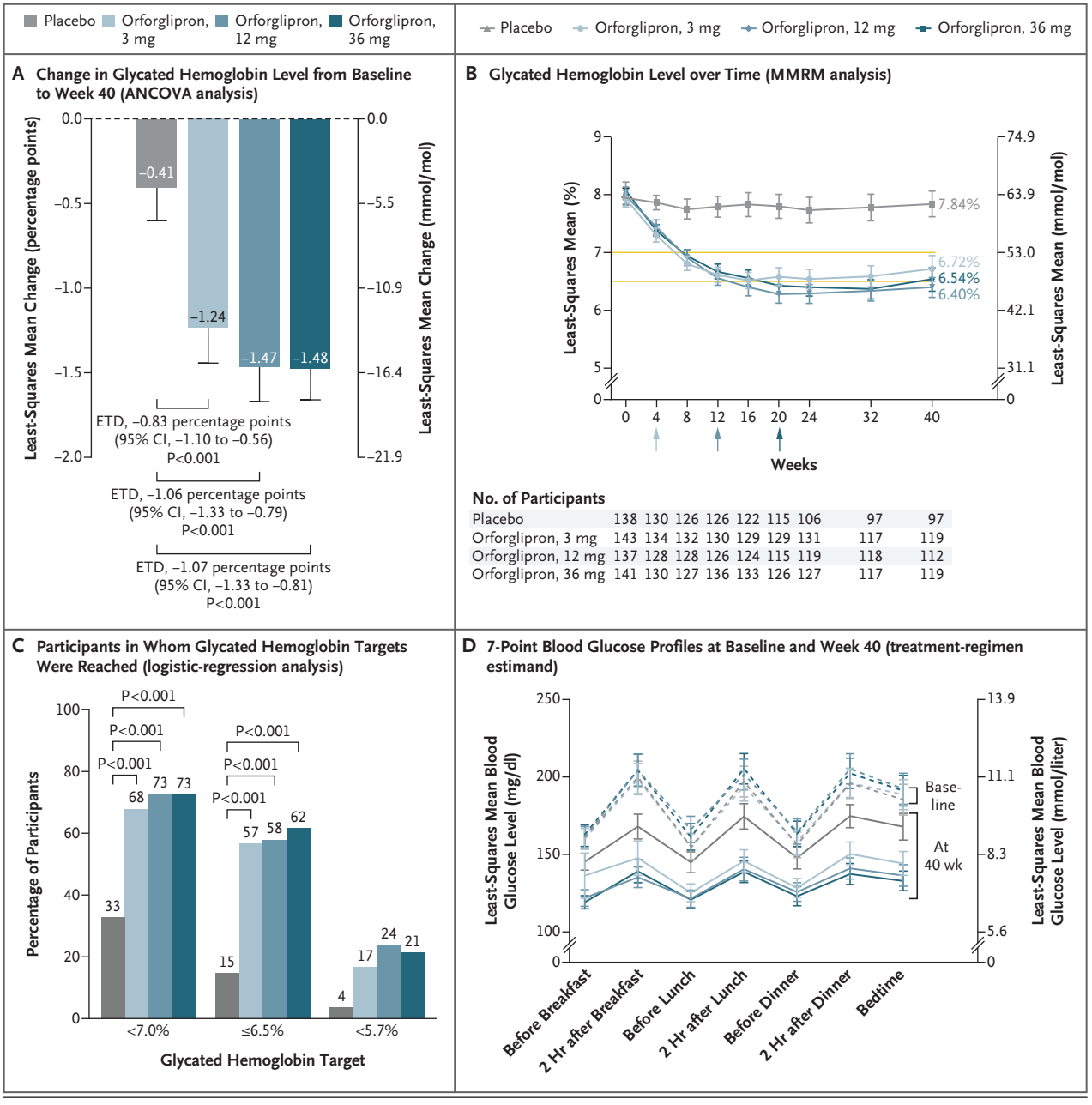
Significant reductions in fasting serum glucose from baseline were observed at week 40; the change was –31 mg per deciliter (–1.7 mmol per liter; 95% CI, –39 to –23) with the 3-mg dose,

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

Characteristic	Orforglipron, 3 mg (N=143)	Orforglipron, 12 mg (N=137)	Orforglipron, 36 mg (N=141)	Placebo (N=138)	Overall (N=559)
Age — yr	53.3±11.3	54.1±11.8	52.8±11.8	53.3±12.5	53.4±11.8
Female sex — no. (%)	63 (44.1)	71 (51.8)	72 (51.1)	63 (45.7)	269 (48.1)
Race or ethnic group — no. (%)†					
Asian	63 (44.1)	59 (43.1)	62 (44.0)	61 (44.2)	245 (43.8)
White	37 (25.9)	30 (21.9)	40 (28.4)	38 (27.5)	145 (25.9)
American Indian	35 (24.5)	38 (27.7)	35 (24.8)	35 (25.4)	143 (25.6)
Black	8 (5.6)	9 (6.6)	4 (2.8)	3 (2.2)	24 (4.3)
Hispanic or Latino	57 (39.9)	55 (40.1)	55 (39.0)	56 (40.6)	223 (39.9)
Country — no. (%)					
United States	42 (29.4)	40 (29.2)	42 (29.8)	41 (29.7)	165 (29.5)
Mexico	40 (28.0)	41 (29.9)	40 (28.4)	38 (27.5)	159 (28.4)
Japan	26 (18.2)	25 (18.2)	25 (17.7)	25 (18.1)	101 (18.1)
India	21 (14.7)	19 (13.9)	22 (15.6)	21 (15.2)	83 (14.8)
China	14 (9.8)	12 (8.8)	12 (8.5)	13 (9.4)	51 (9.1)
Glycated hemoglobin level — %‡	7.93±0.86	7.98±0.91	8.07±0.90	7.96±0.89	7.99±0.89
Glycated hemoglobin category — no. (%)					
≤8.0%	81 (56.6)	83 (60.6)	78 (55.3)	81 (58.7)	323 (57.8)
>8.0%	62 (43.4)	54 (39.4)	63 (44.7)	57 (41.3)	236 (42.2)
Fasting glucose level — mg/dl	142.9±38.7	155.3±55.1	148.8±40.0	143.3±42.2	147.5±44.5
Duration of diabetes — yr	4.0±4.8	5.1±6.0	4.2±5.1	4.4±5.6	4.4±5.4
Body weight — kg	90.3±25.7	90.6±23.1	90.1±22.9	90.0±20.7	90.2±23.1
BMI§	32.9±8.0	33.3±7.8	33.1±7.3	32.9±6.8	33.0±7.5
Waist circumference — cm	107.0±16.5	107.7±16.9	107.6±17.0	106.9±14.1	107.3±16.1
Triglycerides — mg/dl	170.4±104.0	168.9±103.2	192.9±187.1	170.7±155.1	175.8±142.2
Non-HDL cholesterol — mg/dl	140.3±40.6	141.6±40.3	140.6±41.3	141.2±42.1	140.9±41.0
Blood pressure — mm Hg					
Systolic	126.5±14.1	127.5±14.5	128.3±14.3	128.4±14.1	127.7±14.2
Diastolic	79.9±9.5	80.5±9.3	80.8±9.1	80.1±8.6	80.3±9.1
Pulse rate — beats/min	74.3±10.3	75.9±9.3	76.6±9.6	74.1±10.9	75.2±10.1
Previous use of any glucose-lowering medication — no. (%)	55 (38.5)	53 (38.7)	52 (36.9)	54 (39.1)	214 (38.3)

* Plus–minus values are means ±SD. 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.
† Race and ethnic group were reported by participants. One participant in the 36-mg group did not report race or ethnic group and is not included in the numbers shown.
‡ The glycated hemoglobin level was 63.2±9.4 mmol per mole in the 3-mg group, 63.8±9.9 mmol per mole in the 12-mg group, 64.7±9.8 mmol per mole in the 36-mg group, and 63.8±9.7 mmol per mole in the placebo group.
§ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

–37 mg per deciliter (–2.0 mmol per liter; 95% CI, –42 to –31) with the 12-mg dose, and –35 mg per deciliter (–1.9 mmol per liter; 95% CI, –42 to –27) with the 36-mg dose as compared with –11 mg per deciliter (–0.6 mmol per liter; 95% CI, –17 to –4) with placebo (P<0.001 for all comparisons). The seven-point participant-monitored blood glucose profiles appeared to show greater reductions in the mean daily, premeal, and 2-hour postmeal glucose values and in glucose excursions between



the premeal and 2-hour postmeal measurements with orforglipron than with placebo at week 40 (Fig. 1D and Fig. S4). During the trial, rescue therapy for persistent hyperglycemia was initiated in 4.4 to 6.3% of participants in the orforglipron groups as compared with 23.2% in the placebo group.

At week 40, the mean percent change from baseline in body weight was −4.5% (95% CI, −5.4 to −3.6) with the 3-mg dose, −5.8% (95% CI, −6.8 to −4.7) with the 12-mg dose, and −7.6% (95% CI, −8.8 to −6.4) with the 36-mg dose as compared with −1.7% (95% CI, −2.6 to −0.8) with placebo (Fig. 2A). This percent change corresponds to a mean weight change from baseline of −4.2 kg (95% CI, −5.1 to −3.4), −5.2 kg (95% CI, −6.2 to −4.3), −7.2 kg (95% −8.4 to −5.9), and −1.5 kg (95% CI, −2.3 to −0.8), respectively. Orforglipron at a dose of 12 mg or 36 mg was superior to placebo: the estimated differ-

Figure 1 (facing page). Glycated Hemoglobin Levels and Participant-Monitored Blood Glucose Profiles.

The least-squares mean change from baseline in the glycated hemoglobin level at week 40 was assessed with the use of analysis of covariance (ANCOVA) according to the treatment-regimen estimand (an intention-to-treat approach) (Panel A). Estimated treatment differences (ETDs) are least-squares means and 95% confidence intervals for orforglipron as compared with placebo. I bars indicate 95% confidence intervals. The least-squares mean glycated hemoglobin level over time was assessed with a mixed-model repeated-measures (MMRM) analysis according to the efficacy estimand (Panel B). Arrows indicate when the maintenance dose was reached. Yellow lines indicate the prespecified thresholds of 7.0% (53 mmol per mole) and 6.5% (48 mmol per mole). I bars indicate 95% confidence intervals. The percentage of participants who had a glycated hemoglobin level of less than 7.0%, 6.5% or lower, or less than 5.7% (39 mmol per mole) was assessed with the use of logistic-regression analysis (treatment-regimen estimand) (Panel C). The percentages were calculated by combining percentages of participants across imputed datasets with the use of Rubin's rule. The least-squares mean seven-point participant-monitored blood glucose profiles at baseline (dashed lines) and week 40 (solid lines) are shown (treatment-regimen estimand) (Panel D). I bars indicate 95% confidence intervals. For all end points, the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. P values shown indicate the superiority of orforglipron to placebo, with adjustment for multiplicity at week 40. For end points that were not controlled for type I error, P values are not reported.

ence from placebo in the percent change in body weight was −4.1 percentage points (95% CI, −5.4 to −2.7) with the 12-mg dose and −5.9 percentage points (95% CI, −7.4 to −4.4) with the 36-mg dose (P<0.001 for both comparisons) (Fig. 2A). The percentages of participants in the orforglipron groups who had a body-weight reduction of at least 5% (43 to 61%), at least 10% (15 to 30%), and at least 15% (4 to 10%) appeared to be greater than those in the placebo group (17%, 6%, and 1%, respectively) (Fig. 2C). Similarly, mean reductions from baseline in BMI and waist circumference appeared to be greater with orforglipron than with placebo (Fig. S5).

At week 40, triglyceride levels had decreased significantly from baseline with orforglipron at a dose of 12 mg or 36 mg and non-HDL cholesterol levels had decreased significantly from baseline with orforglipron at a dose of 36 mg (Fig. 2D and Table S3). Results from the efficacy estimand for the change in the glycated hemoglobin level, the percentage of participants who had a glycated hemoglobin level that reached prespecified targets, changes in fasting serum glucose and body weight, the percentage of participants who had body-weight reduction that reached prespecified thresholds (at least 5%, 10%, and 15%), and changes in lipid levels are provided in Table S4.

SAFETY

The percentages of participants who reported at least one adverse event and who discontinued orforglipron or placebo due to adverse events are listed in Table 2. The most frequently reported adverse events were gastrointestinal (diarrhea, dyspepsia, nausea, constipation, and vomiting), were mostly mild to moderate in severity, and occurred primarily during the dose-escalation period; the prevalence of gastrointestinal side effects generally decreased over time (Table 2, Table S5, and Fig. S6). Discontinuation due to gastrointestinal adverse events occurred in 2.2 to 5.7% of participants in the orforglipron groups and no participants in the placebo group. Antidiarrheal medications were used by 7.3 to 9.9% of participants in the orforglipron groups and 4.3% in the placebo group, antiemetic medications were used by 6.3 to 15.3% and 2.9%, respectively, and medications to treat constipation were used by 7.7 to 15.3% and 2.2%, respectively.

Serious adverse events occurred in 24 participants (4.3%): 8 (5.6%) in the 3-mg group, 7 (5.1%) in the 12-mg group, 4 (2.8%) in the 36-mg group, and 5 (3.6%) in the placebo group (Table 2). A total of four deaths occurred during the trial: two in the 3-mg group, one in the 12-mg group, and one in the placebo group (Table 2 and Table S6). None of the deaths were considered by the investigators to be related to orforglipron or placebo.

No episodes of severe hypoglycemia (defined as a hypoglycemic event characterized by altered mental status, altered physical status, or both that the participant was unable to resolve without assistance) occurred (Table 2). At week 40, changes from baseline in mean systolic blood pressure ranging from −3.3 to −5.7 mm Hg with orforglipron as compared with −1.2 mm Hg with placebo were observed, with no effect on dia-

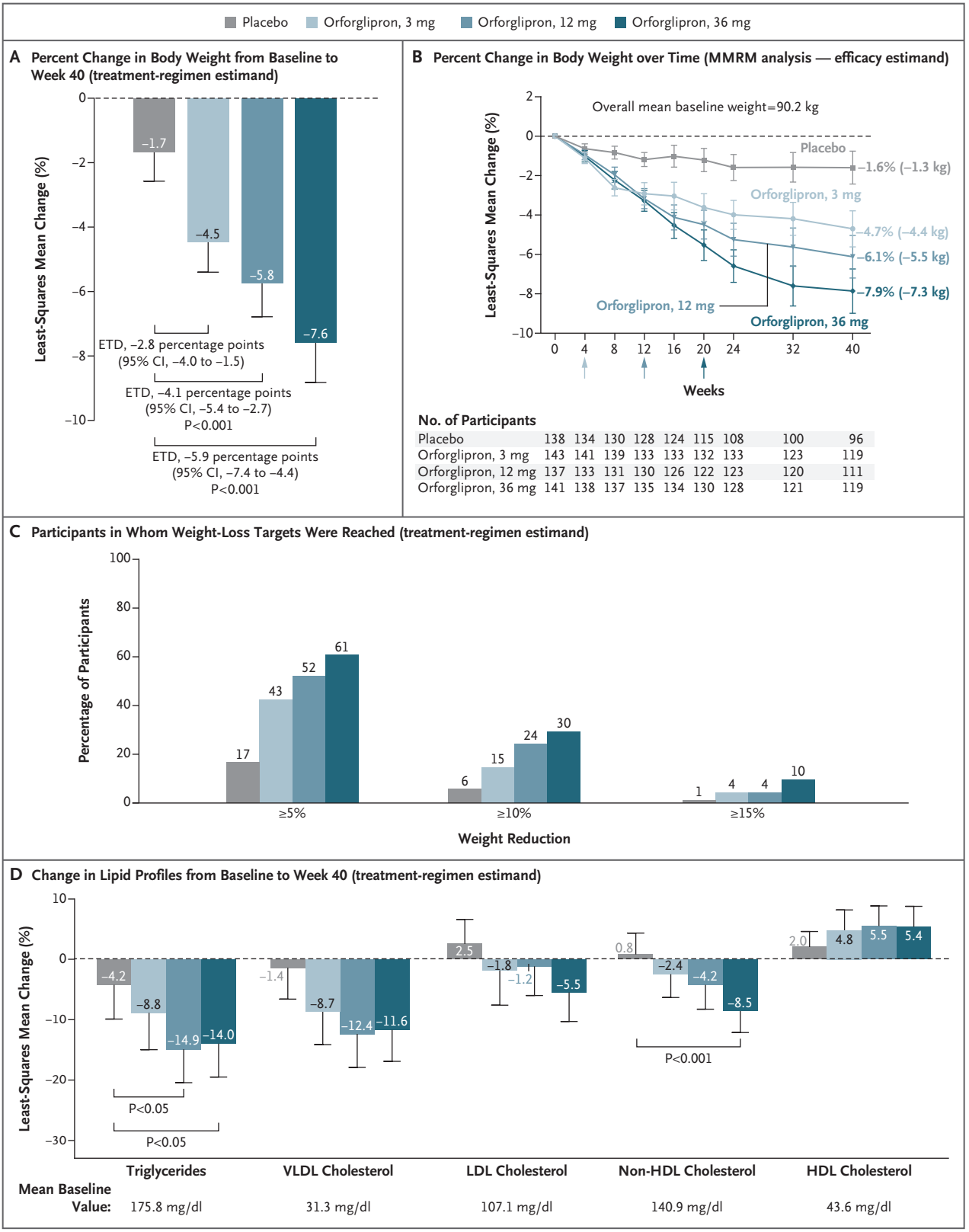


Figure 2 (facing page). Body Weight, Body-Weight Reduction Thresholds, and Lipid Profiles.

The least-squares mean percent change in body weight from baseline to week 40 was assessed according to the treatment-regimen estimand (Panel A). I bars indicate 95% confidence intervals. The least-squares mean percent change from baseline in body weight over time was assessed with the use of a mixed-model repeated-measures analysis according to the efficacy estimand (Panel B). I bars indicate 95% confidence intervals. Arrows indicate when the maintenance dose was reached. Percentages of participants who had a reduction in body weight of at least 5%, at least 10%, and at least 15% were calculated by combining percentages of participants who met specified targets across imputed datasets with the use of Rubin's rule (treatment-regimen estimand) (Panel C). The least-squares mean percent change from baseline in lipid levels at week 40 was assessed by log-transforming lipid levels before fitting the analysis of covariance and then back-transforming the results with the use of the delta method from the least-squares means and standard errors on the natural log scale (Panel D). I bars indicate 95% confidence intervals. For all end points, the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. P values shown indicate the superiority of orforglipron to placebo, with adjustment for multiplicity at week 40. For end points that were not controlled for type I error, P values are not reported. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

stolic blood pressure (Fig. S7). An increase in pulse rate of 2.2 to 4.8 beats per minute occurred in orforglipron-treated participants, whereas participants in the placebo group had a change of −0.9 beats per minute from baseline to week 40.

No adjudication-confirmed cases of pancreatitis occurred. Changes in lipase and pancreatic amylase levels are shown in Table S7. No clinically relevant changes in calcitonin occurred. Mean alanine aminotransferase and aspartate aminotransferase levels decreased during the trial. The percentage of participants with a post-baseline alanine aminotransferase or aspartate aminotransferase level of 3 times the upper limit of the normal range or higher was similar among trial groups, and levels returned to normal or near the baseline level in all orforglipron-treated participants while they were still receiving orforglipron (Table S8). No case met Hy's law criteria for hepatocellular drug-induced liver injury.

DISCUSSION

This trial of an oral, nonpeptide GLP-1 receptor agonist showed the efficacy and safety of once-daily orforglipron in adults with type 2 diabetes that was not controlled with diet and exercise alone. Significant and clinically meaningful reductions in the glycated hemoglobin level were observed with all three doses of orforglipron, and the changes were significantly greater than those with placebo. The glycated hemoglobin target of less than 7.0% was reached in 68 to 73% of participants assigned to receive orforglipron. In addition, a glycated hemoglobin level of less than 5.7% (near normoglycemia) was reached in up to 24% of participants with orforglipron.

To provide a clinical perspective, the magnitude of the reduction in the glycated hemoglobin level in our trial suggests consistency with results from two previous monotherapy trials, PIONEER 1 (Peptide Innovation for Early Diabetes Treatment 1) and SUSTAIN 1 (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes), which assessed oral and injectable GLP-1 receptor agonists, respectively, in patients with a relatively short duration of type 2 diabetes and baseline characteristics similar to those in our trial.[12,13] We hypothesized that the lowest glycated hemoglobin levels observed with orforglipron at week 40 and the lack of a clear glycemic dose–response relationship suggest a floor effect on the maximum achievable glycemic response, consistent with findings for other GLP-1 receptor agonists.[14] Our findings with respect to glycated hemoglobin levels were also consistent with the significant reductions in fasting serum glucose levels, which were observed as early as 4 weeks after the start of the trial period, along with improved pre- and postmeal blood glucose values, as shown by the participant-monitored blood glucose profiles. The ongoing ACHIEVE-3 randomized, controlled trial (ClincalTrials.gov number, NCT06045221) aims to provide further insights into the glycemic efficacy of orforglipron in comparison with oral semaglutide over 52 weeks in patients with type 2 diabetes.

Progressive and dose-related reductions in body weight of up to 7.6% from baseline were observed with orforglipron, and changes in body weight appear not to have reached a plateau at

Table 2. Adverse Events.*

Event	Orforglipron, 3 mg (N=143)	Orforglipron, 12 mg (N=137)	Orforglipron, 36 mg (N=141)	Placebo (N=138)	Overall (N=559)
	number of participants (percent)				
Any adverse event emerging during treatment	102 (71.3)	111 (81.0)	119 (84.4)	102 (73.9)	434 (77.6)
Any serious adverse event	8 (5.6)	7 (5.1)	4 (2.8)	5 (3.6)	24 (4.3)
Death†	2 (1.4)	1 (0.7)	0	1 (0.7)	4 (0.7)
Adverse event leading to discontinuation of orforglipron or placebo	8 (5.6)	6 (4.4)	11 (7.8)	2 (1.4)	27 (4.8)
Gastrointestinal adverse event leading to discontinuation of orforglipron or placebo	4 (2.8)	3 (2.2)	8 (5.7)	0	15 (2.7)
Adverse events that emerged during treatment and occurred in ≥5% of participants in any trial group					
Diarrhea	27 (18.9)	29 (21.2)	36 (25.5)	12 (8.7)	104 (18.6)
Dyspepsia	15 (10.5)	28 (20.4)	21 (14.9)	9 (6.5)	73 (13.1)
Nausea	18 (12.6)	25 (18.2)	23 (16.3)	3 (2.2)	69 (12.3)
Hyperglycemia	10 (7.0)	6 (4.4)	9 (6.4)	37 (26.8)	62 (11.1)
Constipation	12 (8.4)	23 (16.8)	19 (13.5)	5 (3.6)	59 (10.6)
Abdominal distention	6 (4.2)	7 (5.1)	16 (11.3)	11 (8.0)	40 (7.2)
Decreased appetite	5 (3.5)	14 (10.2)	16 (11.3)	3 (2.2)	38 (6.8)
Vomiting	7 (4.9)	9 (6.6)	20 (14.2)	2 (1.4)	38 (6.8)
Headache	8 (5.6)	5 (3.6)	10 (7.1)	6 (4.3)	29 (5.2)
Diabetic retinopathy	5 (3.5)	2 (1.5)	13 (9.2)	6 (4.3)	26 (4.7)
Eructation	5 (3.5)	6 (4.4)	10 (7.1)	0	21 (3.8)
Nasopharyngitis	2 (1.4)	9 (6.6)	3 (2.1)	6 (4.3)	20 (3.6)
Gastroesophageal reflux	3 (2.1)	7 (5.1)	5 (3.5)	2 (1.4)	17 (3.0)
Abdominal pain	1 (0.7)	4 (2.9)	7 (5.0)	2 (1.4)	14 (2.5)
Upper abdominal pain	0	8 (5.8)	4 (2.8)	1 (0.7)	13 (2.3)
Lipase increase	2 (1.4)	7 (5.1)	2 (1.4)	2 (1.4)	13 (2.3)
Other adverse events emerging during treatment					
Hypoglycemia‡	2 (1.4)	0	1 (0.7)	1 (0.7)	4 (0.7)
Severe hypoglycemia§	0	0	0	0	0
Initiation of rescue therapy for severe persistent hyperglycemia	9 (6.3)	6 (4.4)	8 (5.7)	32 (23.2)	55 (9.8)
Thyroid cancer	0	0	0	0	0
Pancreatitis as confirmed by adjudication	0	0	0	0	0
Cholelithiasis	0	2 (1.5)	0	0	2 (0.4)

* Participants may be included in more than one category.
† Deaths were also counted as serious adverse events and discontinuations due to adverse events.
‡ Hypoglycemia was defined as a blood glucose level of less than 54 mg per deciliter (3.0 mmol per liter).
§ Severe hypoglycemia was defined as a hypoglycemic event characterized by altered mental status, altered physical status, or both that the participant was unable to resolve without assistance.

40 weeks; these findings are particularly notable in the context of the diverse racial and ethnic groups represented in our trial. In addition, a high percentage (43 to 61%) of participants treated with orforglipron had at least 5% weight reduction, a magnitude of weight loss associated with improvements in glycemic control and reductions in cardiovascular risk factors,[15] and approximately one third of participants had at least 10% weight reduction at the highest dose. In the PIONEER 1 trial of oral semaglutide at a dose of 3 mg, 7 mg, or 14 mg, 21 to 44% of participants had a weight reduction of at least 5%, and in the SUSTAIN 1 trial, 37 to 45% of participants had at least 5% weight reduction with injectable semaglutide at a dose of 0.5 mg or 1.0 mg.[12,13] Beyond glycemic control and body-weight reduction, we observed reductions in cardiometabolic risk factors, including lipid levels, waist circumference, and systolic blood pressure, findings that indicate a favorable cardiovascular risk profile.

The dose-escalation plan in our trial was designed to reduce gastrointestinal side effects that were observed in phase 2 trials, with a lower starting dose of orforglipron and dose-escalation every 4 weeks.[10] Gastrointestinal adverse events were the most frequently reported adverse events, were mostly mild to moderate in severity, and most frequently occurred during the dose-escalation period, consistent with previous findings with agents from the GLP-1 receptor agonist drug class.[10,12,13] Only 2.2 to 5.7% of participants in the orforglipron groups discontinued treatment due to gastrointestinal adverse events, and these percentages are similar to those in previous trials of monotherapy with GLP-1 receptor agonists.[12,13] Hypoglycemia occurred in 0 to 1.4% of participants in the orforglipron groups, and no cases of severe hypoglycemia were reported, consistent with the glucose-dependent mechanism of action of incretin-based therapies. No hepatic safety signal was identified in this trial.

Our trial has certain limitations. First, we enrolled participants in whom type 2 diabetes was treated only with diet and exercise at the time of enrollment, and 61.7% of participants had not received any previous glucose-lowering medications, which limits the generalizability of our findings to the broader population of patients with type 2 diabetes who are receiving other background antihyperglycemic medications. Second, our trial was of relatively short duration. The ongoing ACHIEVE-4 trial (NCT05803421) comparing orforglipron with insulin glargine over at least 104 weeks may help to assess the long-term safety and efficacy of orforglipron, including the sustainability of glycemic control and body-weight reduction. Strengths of the trial include the relatively large sample size, the high level of participant retention, and the robust, double-blind, randomized, placebo-controlled design.

In participants with early type 2 diabetes treated with diet and exercise, the new small-molecule, nonpeptide oral GLP-1 receptor agonist orforglipron led to significant and clinically meaningful improvements in glycemic control.

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