ORIGINAL ARTICLE

Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity

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ABSTRACT

BACKGROUND

Oral semaglutide at a dose of 25 mg may provide an alternative treatment option to injectable semaglutide (2.4 mg) and higher-dose oral semaglutide (50 mg) for persons with overweight or obesity.

METHODS

In a 71-week, double-blind, randomized, placebo-controlled trial conducted at 22 sites in four countries, we enrolled persons without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication. The participants were randomly assigned in a 2:1 ratio to receive oral semaglutide (25 mg) or placebo once daily, plus lifestyle interventions. The coprimary end points at week 64 were the percent change in body weight and a reduction of 5% or more in body weight; confirmatory secondary end points included reductions in body weight of 10% or more, 15% or more, and 20% or more and the change in the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT) Physical Function score.

RESULTS

A total of 205 participants were randomly assigned to receive oral semaglutide, and 102 to receive placebo. The estimated mean change in body weight from baseline to week 64 was –13.6% in the oral semaglutide group and –2.2% in the placebo group (estimated difference, –11.4 percentage points; 95% confidence interval, –13.9 to –9.0; P<0.001). Participants in the oral semaglutide group were significantly more likely than those in the placebo group to have body-weight reductions of 5% or more, 10% or more, 15% or more, and 20% or more (P<0.001 for all comparisons) and to have an improved IWQOL-Lite-CT Physical Function score (P<0.001). Gastrointestinal adverse events were more common with oral semaglutide than with placebo (74.0% vs. 42.2%).

CONCLUSIONS

Oral semaglutide at a dose of 25 mg once daily resulted in a greater mean reduction in body weight than placebo in participants with overweight or obesity. (Funded by Novo Nordisk; OASIS 4 ClinicalTrials.gov number, NCT05564117.)

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*A list of the OASIS 4 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2025;393:1077-87.
DOI: 10.1056/NEJMoa2500969

A Quick Take is available at NEJM.org

The prevalence of obesity has continued to rise globally.[1,2] Persons with obesity have a risk of reduced life expectancy and an increased risk of the development of complications such as type 2 diabetes and cardiovascular disease.[3,4] Obesity medications are a useful adjunct to lifestyle interventions, because many people struggle to lose weight and maintain weight loss with diet and exercise alone.[3,4] Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that has been approved for weight management as a subcutaneous injection at a dose of 2.4 mg.[5]

Semaglutide also exists as an oral peptide, coformulated with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate to enable absorption in the stomach,[6] and may offer an alternative to subcutaneous semaglutide.[7,8] Oral semaglutide is approved for the treatment of type 2 diabetes (at doses up to 14 mg daily)[9] and has been shown to lead to both weight loss and reductions in blood glucose levels.[10] The phase 3 OASIS 1 (Oral Semaglutide Treatment Effect in People with Obesity) trial involving participants with overweight or obesity without type 2 diabetes showed that oral semaglutide at a dose of 50 mg once daily resulted in a mean body-weight reduction of 15.1%, as compared with 2.4% with placebo, and also ameliorated several cardiometabolic risk factors.[10]

A lower dose of oral semaglutide may provide an additional treatment option for persons with obesity. We now report the results of the OASIS 4 trial, which aimed to evaluate the efficacy and safety of oral semaglutide at a dose of 25 mg once daily as compared with placebo as an adjunct to lifestyle intervention for the reduction of body weight in participants with overweight or obesity.

Methods

Trial Design and Oversight

In a multicenter, double-blind, randomized trial conducted at 22 sites in four countries (Canada, Germany, Poland, and the United States), we compared oral semaglutide at a dose of 25 mg once daily with placebo. The trial was conducted in accordance with the principles of the International Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice.[11,12] The trial protocol and amendments, available with the full text of this article at NEJM.org, were approved by the relevant institutional review board or independent ethics committee at each site. A full list of investigators and sites is provided in the Supplementary Appendix, available at NEJM.org. Novo Nordisk, the sponsor, was responsible for designing the trial, preparing the protocol and the statistical analysis plan, and performing the statistical analyses. The investigators were responsible for trial-related medical decisions and data collection. The authors interpreted the aggregated data, participated in writing the first draft and subsequent drafts of the manuscript (with assistance from a medical writer, funded by the sponsor, who wrote the first draft under the direction of the authors), agreed to the submission of the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Adults 18 years of age or older without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease) and who reported at least one unsuccessful dietary effort to lose weight were eligible to participate. Full eligibility criteria are provided in the Supplementary Appendix. All the participants provided written informed consent.

Procedures

Participants were randomly assigned, in a 2:1 ratio, to receive oral semaglutide, administered as tablets, or matching placebo, in addition to lifestyle interventions. Screening was performed locally, and randomization was performed centrally with the use of an interactive online response system, with no stratification factors. Lifestyle interventions involved counseling on diet (500-kcal deficit per day) and physical activity (150 minutes of physical activity per week) that was provided by a dietician or a similarly qualified health care professional at each trial visit.

Oral semaglutide was initiated at a dose of 3 mg once daily and followed a fixed-dose escalation regimen, with dose increases every 4 weeks (increasing to 7 mg after 4 weeks and to 14 mg

after 8 weeks) to reach the maintenance dose of 25 mg at week 12. The maintenance period thereafter lasted 52 weeks (to week 64), followed by a 7-week follow-up period (Fig. S1 in the Supplementary Appendix). If the maintenance dose of 25 mg was associated with unacceptable adverse effects, the participants could continue to receive a lower dose at the investigator's discretion; at least one attempt to increase the dose again was recommended. Participants were instructed to swallow their assigned product whole with no more than 120 ml of water in the morning, after fasting overnight and 30 minutes before the intake of food, other liquids, and other oral medications. Participants who initiated any obesity medication during the trial that was not part of the trial procedures were instructed to stop such medication.

END POINTS AND ASSESSMENTS

All the end points were assessed from baseline to week 64. The coprimary end points were the percent change in body weight and a reduction in body weight of 5% or more. Confirmatory secondary end points were a reduction in body weight of 10% or more, 15% or more, and 20% or more, and a change in the five-item Physical Function score of the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT, in which scores range from 0 to 100, with higher scores indicating better level of function). Post hoc exploratory analyses included assessments of the interaction of treatment with subgroup for the percent change in body weight according to baseline BMI and for the change in glycated hemoglobin levels according to baseline glycemic status. Safety assessments included the number of adverse events and serious adverse events reported. A full list of end points is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated that a sample size of 300 would give the trial a power of more than 99% for the coprimary end points (on the basis of assumptions listed in the protocol). Efficacy end points were analyzed in the full analysis population (all the participants who underwent randomization). Safety end points were analyzed in the safety analysis population (all the participants who underwent randomization and received at least one dose of semaglutide or placebo).

Two observation periods were defined: the trial period, which comprised the uninterrupted time interval from the date of randomization to the date of the participant's last contact with the trial site, and the treatment period, which comprised the date of the first administration of semaglutide or placebo to the date of the last administration plus 3 days for efficacy analyses or 49 days for safety analyses, excluding any temporary interruptions.

Two estimands were used to assess treatment efficacy.[13] The treatment-policy estimand (traditional intention-to-treat analysis) assessed effects regardless of treatment discontinuation or rescue intervention (i.e., any other obesity medication or bariatric surgery). The trial-product estimand, synonymous with the "hypothetical estimand" as defined by the International Council for Harmonisation E9 guidelines,[13,14] represents the effects assuming that the drug or placebo was taken without discontinuation or use of rescue intervention. Observed values after intercurrent events were not used for this calculation. Instead, they were treated as missing, and treatment effect estimates were derived with a likelihood-based approach that estimated the means in each group and the treatment effects under the assumption that the intercurrent events did not occur. We acknowledge that in real-world scenarios, patients will discontinue treatment or initiate other therapies for a variety of reasons; the trial-product estimand represents a hypothetical efficacy in an idealized scenario in which treatment is not discontinued and other therapies are not initiated. All the results shown here are for the treatment-policy estimand, unless otherwise stated. Additional details of the estimands are shown in the Supplementary Appendix. Statistical analyses were performed with SAS, version 9.4.

Results are shown with two-sided 95% confidence intervals and corresponding two-sided P values. The type I error rate was controlled with a P-value threshold of less than 0.05 for each estimand sequentially within the testing hierarchy. The coprimary and confirmatory secondary end points were tested in a prespecified hierarchical order. Analyses of the end points for the trial-product estimand were not controlled for multiplicity and should not be used to infer definitive treatment effects. Missing data were imputed with

the use of a multiple imputation approach with available data in each treatment group according to timing, sex, value at the last available observation during receipt of semaglutide or placebo, and baseline values of the corresponding end point. Sensitivity analyses were performed for the imputation models. The Supplementary Appendix includes information on retrieved dropouts (participants who discontinued the randomly assigned regimen prematurely but returned to have an assessment at week 64) and further details on analysis methods.

RESULTS

PARTICIPANTS

From October 2022 through May 2024, a total of 307 participants underwent randomization — 205 participants were assigned to receive oral semaglutide, and 102 to receive placebo. Overall, 243 participants (79.2%) were receiving semaglutide or placebo at the end of the 64-week trial period — 167 (81.5%) in the oral semaglutide group and 76 (74.5%) in the placebo group; 290 participants (94.5%) completed the trial (i.e., attended the week 71 visit) — 95.6% of the participants in the oral semaglutide group and 92.2% of those in the placebo group (Fig. S2). Of those who completed treatment with oral semaglutide, 136 (81.4%) received a final dose of 25 mg, 14 (8.4%) received a final dose of 14 mg, and 16 (9.6%) received a final dose of less than 14 mg (Table S1). The baseline characteristics of the participants were balanced across the groups (Table 1 and Table S2). Most of the participants were women (78.8%) and White (91.5%); the mean body weight was 105.9 kg, the mean BMI was 37.6, the mean waist circumference was 113.9 cm, and the mean glycated hemoglobin level was 5.7%. Information on the representativeness of the trial participants is provided in the Supplementary Appendix.

EFFICACY

Body Weight

The estimated mean change in body weight from baseline to week 64 was significantly greater with oral semaglutide than with placebo (–13.6% vs. –2.2%; estimated difference, –11.4 percentage points; 95% confidence interval [CI], –13.9 to –9.0; P<0.001) (Table 2, Fig. 1A, Fig. S3A, and Table S4). For the hypothetical trial-product estimand, the estimated mean change in body weight was –16.6% with oral semaglutide and –2.7% with placebo (estimated difference, –13.9 percentage points; 95% CI, –16.5 to –11.2) (Fig. S4A and Table S3). We found no evidence that the treatment effect varied according to sex, race, or ethnic group (Table S5). The reduction in relative body weight from baseline to week 64 was similar across subgroups defined according to BMI at baseline (Table S6).

Participants in the oral semaglutide group were significantly more likely than those in the placebo group to have a reduction in body weight of 5% or more, 10% or more, 15% or more, and 20% or more at week 64 (P<0.001 for all comparisons) (Table 2). In the oral semaglutide group, 152 of 192 of the participants with an observation at week 64 (79.2%) had a reduction in body weight of 5% or more, 121 (63.0%) had a reduction of 10% or more, 96 (50.0%) had a reduction of 15% or more, and 57 (29.7%) had a reduction of 20% or more; in the placebo group, 28 of 90 of the participants (31.1%) had a reduction of 5% or more, 13 (14.4%) had a reduction of 10% or more, 5 (5.6%) had a reduction of 15% or more, and 3 (3.3%) had a reduction of 20% or more (Table 2 and Fig. 1B). Although the estimated effects based on the trial-product estimand were generally larger, the qualitative findings were similar (Fig. S4B). Figure S5 provides details on body-weight reduction in retrieved dropouts.

Physical Function

The estimated mean increase in the IWQOL-Lite-CT Physical Function score from baseline to week 64 was significantly greater with oral semaglutide than with placebo (16.2 points vs. 8.4 points; estimated difference, 7.7 points; 95% CI, 3.3 to 12.2; P<0.001) (Table 2 and Fig. S6A). The percentage of participants who had a clinically meaningful improvement (i.e., an increase of ≥14.6 points) in the IWQOL-Lite-CT Physical Function score was 55.3% (104 of 188 participants) with oral semaglutide and 34.8% (31 of 89 participants) with placebo (odds ratio, 2.4; 95% CI, 1.4 to 4.1) (Table 2 and Fig. S6C). As was the case with the body-weight end points, the trial-product effect estimates were similar to those of the treatment-policy estimand (Fig. S6B).

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

Characteristic	Oral Semaglutide (N=205)	Placebo (N=102)
Age — yr	48±13	47±13
Female sex — no. (%)	155 (75.6)	87 (85.3)
Body weight — kg	106.4±23.5	104.8±19.7
Race or ethnic group — no. (%)†		
White	190 (92.7)	91 (89.2)
Black or African American	13 (6.3)	9 (8.8)
Asian	1 (0.5)	1 (1.0)
Other	1 (0.5)	1 (1.0)
Hispanic or Latino ethnic group — no. (%)†		
No	188 (91.7)	95 (93.1)
Yes	17 (8.3)	7 (6.9)
BMI‡	37.5±6.7	37.8±6.1
BMI category — no. (%)		
<30	13 (6.3)	5 (4.9)
30 to <35	73 (35.6)	39 (38.2)
35 to <40	64 (31.2)	22 (21.6)
≥40	55 (26.8)	36 (35.3)
Waist circumference — cm	114.0±15.8	113.6±14.7
Glycated hemoglobin — %	5.7±0.4	5.7±0.3
Blood pressure — mm Hg		
Systolic	131.3±16	131.0±18
Diastolic	83.0±10	83.2±10
Glycemic status — no. (%)§		
Normoglycemia	105 (51.2)	53 (52.0)
Prediabetes	97 (47.3)	47 (46.1)
Diabetes	3 (1.5)	2 (2.0)

* Plus–minus values are means ±SD. Data shown include all participants in the full analysis population (all the participants who underwent randomization).
† Race and ethnic group were reported by the investigator (although reporting by the participant could be considered by the investigator). The category "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or not reported.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ Normoglycemia was defined by a glycated hemoglobin level of less than 5.7%, prediabetes by a glycated hemoglobin level of 5.7% to less than 6.5%, and diabetes by a glycated hemoglobin level of 6.5% or higher; although no participants had a glycated hemoglobin level of 6.5% or higher at screening, a glycated hemoglobin level of 6.5% or higher developed in five participants between screening and randomization.

Cardiometabolic Risk Factors

Changes favoring oral semaglutide were observed in absolute body weight, BMI, waist circumference, and levels of glycated hemoglobin, fasting plasma glucose, fasting serum insulin, very-low-density lipoprotein, triglycerides, and C-reactive protein (Table 2 and Figs. S7 through S14). Blood-pressure changes did not appear to differ between the groups (Table 2 and Figs. S15 and S16). In the oral semaglutide group, 71.1% of the participants with prediabetes at baseline had normoglycemia at week 64 (Table 2 and Fig. 2).

Table 2. Primary, Confirmatory Secondary, and Selected Exploratory End Points.*

End Point	Oral Semaglutide (N=205)	Placebo (N=102)	Difference (95% CI)†
Primary end points			
Percent change in body weight from baseline to week 64	–13.6	–2.2	–11.4 (–13.9 to –9.0)
Body-weight reduction of ≥5% at week 64 — no./total no. (%)‡	152/192 (79.2)	28/90 (31.1)	7.3 (4.2 to 12.8)
Confirmatory secondary end points			
Body-weight reduction of each target — no./total no. (%)‡			
≥10% at week 64	121/192 (63.0)	13/90 (14.4)	9.1 (4.7 to 17.3)
≥15% at week 64	96/192 (50.0)	5/90 (5.6)	15.7 (6.2 to 40.2)
≥20% at week 64	57/192 (29.7)	3/90 (3.3)	12.2 (3.7 to 40.3)
Change in IWQOL-Lite-CT Physical Function score from baseline to week 64 — points§	16.2	8.4	7.7 (3.3 to 12.2)
Supportive secondary end points¶			
Change in IWQOL-Lite-CT Physical Function score ≥14.6 at week 64 — no./total no. (%)‡	104/188 (55.3)	31/89 (34.8)	2.4 (1.4 to 4.1)
Change in cardiometabolic risk factors from baseline to week 64			
Body weight — kg	–14.2	–2.16	–12.0 (–14.6 to –9.5)
BMI	–5.1	–0.8	–4.3 (–5.2 to –3.4)
Waist circumference — cm	–12.2	–2.8	–9.5 (–12.4 to –6.6)
Systolic blood pressure — mm Hg	–6.8	–5.4	–1.4 (–4.6 to 1.8)
Diastolic blood pressure — mm Hg	–2.7	–2.1	–0.7 (–2.8 to 1.5)
Glycated hemoglobin — percentage points	–0.3	–0.1	–0.2 (–0.3 to –0.2)
Fasting plasma glucose — mg/dl	–6.6	0.4	–7.0 (–11.2 to –2.8)
Change in laboratory test results — ratio to baseline at week 64‖			
Total cholesterol	0.96	0.99	0.97 (0.93 to 1.02)
Triglycerides	0.82	0.92	0.88 (0.80 to 0.97)
Free fatty acids	0.86	0.93	0.93 (0.80 to 1.07)
HDL cholesterol	1.03	1.00	1.04 (0.99 to 1.08)
LDL cholesterol	0.96	1.00	0.95 (0.89 to 1.02)
VLDL cholesterol	0.82	0.92	0.89 (0.81 to 0.99)
Fasting serum insulin	0.76	0.99	0.77 (0.63 to 0.94)
C-reactive protein	0.54	0.96	0.56 (0.42 to 0.74)
Post hoc exploratory analyses			
Participants with prediabetes at baseline and normoglycemia at week 64 — no./total no. (%)‡	64/90 (71.1)	13/39 (33.3)	—
Participants with BMI ≥30 at baseline and <30 at week 64 — no./total no. (%)‡	77/179 (43.0)	9/86 (10.5)	11.6 (4.9 to 27.7)

* All data are estimated mean changes for the trial period unless otherwise stated, and comparisons are for the treatment-policy estimand. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.
† Shown is the estimated difference between the groups unless otherwise stated. P<0.001 for the primary and confirmatory secondary end points.
‡ The data shown are the observed (i.e., as measured) number and percentage of participants from the trial period, and the difference is the estimated odds ratio for the treatment-policy estimand (odds ratios were not estimated for the change in glycemic status). The percentages were based on the number of participants with an observation at week 64.
§ The Physical Function score is a five-item subscore of the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT), in which scores range from 0 to 100, with higher scores indicating better level of function.
¶ Analyses for estimated differences for the supportive secondary end points have not been adjusted for multiplicity.
‖ The ratio to baseline and the corresponding baseline values were log-transformed before analysis. The comparison is the ratio of values for semaglutide to those for placebo.

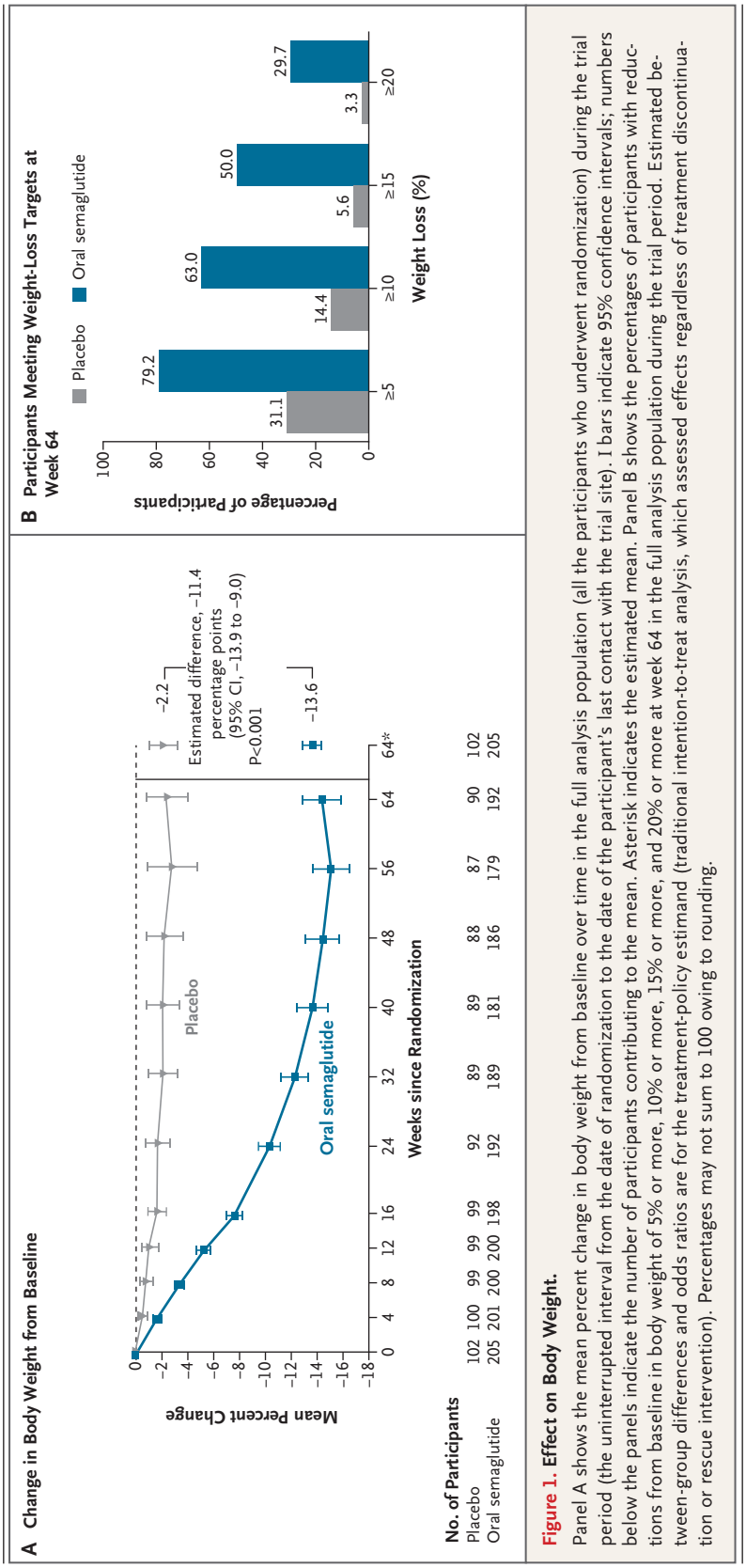

Figure 1. Effect on Body Weight.

Panel A shows the mean percent change in body weight from baseline over time in the full analysis population (all the participants who underwent randomization) during the trial period (the uninterrupted interval from the date of randomization to the date of the participant's last contact with the trial site). I bars indicate 95% confidence intervals; numbers below the panels indicate the number of participants contributing to the mean. Asterisk indicates the estimated mean. Panel B shows the percentages of participants with reductions from baseline in body weight of 5% or more, 10% or more, 15% or more, and 20% or more at week 64 in the full analysis population during the trial period. Estimated between-group differences and odds ratios are for the treatment-policy estimand (traditional intention-to-treat analysis, which assessed effects regardless of treatment discontinuation or rescue intervention). Percentages may not sum to 100 owing to rounding.

Table 3. Adverse Events.*

Event	Oral Semaglutide (N=204)			Placebo (N=102)		
	no. of participants (%)	*no. of events*	*events per 100 participant-yr of exposure*	*no. of participants (%)*	*no. of events*	*events per 100 participant-yr of exposure*
Any adverse event	190 (93.1)	1239	493.5	87 (85.3)	432	355.9
Serious adverse events	8 (3.9)	17	6.8	9 (8.8)	13	10.7
Adverse events leading to discontinuation of semaglutide or placebo	14 (6.9)	14	5.6	6 (5.9)	6	4.9
Gastrointestinal disorders	7 (3.4)	7	2.8	2 (2.0)	2	1.6
Fatal events	0	0	0	0	0	0
Adverse events reported in ≥10% of participants						
Nausea	95 (46.6)	157	62.5	19 (18.6)	27	22.2
Vomiting	63 (30.9)	105	41.8	6 (5.9)	6	4.9
Nasopharyngitis	43 (21.1)	59	23.5	27 (26.5)	40	33.0
Coronavirus disease 2019	42 (20.6)	46	18.3	18 (17.6)	19	15.7
Constipation	41 (20.1)	59	23.5	10 (9.8)	11	9.1
Dyspepsia	37 (18.1)	50	19.9	9 (8.8)	11	9.1
Diarrhea	36 (17.6)	61	24.3	9 (8.8)	10	8.2
Headache	24 (11.8)	35	13.9	9 (8.8)	10	8.2
Eructation	21 (10.3)	23	9.2	2 (2.0)	2	1.6

* Included are all adverse events that occurred in the safety analysis population (all the participants who underwent randomization and were exposed to at least one dose of semaglutide or placebo) during the treatment period. Adverse events were classified by severity as mild (causing minimal discomfort and not interfering with everyday activities), moderate (causing sufficient discomfort to interfere with normal everyday activities), or severe (preventing normal everyday activities).

The estimated difference between the semaglutide group and the placebo group in glycated hemoglobin levels among participants with baseline levels of less than 5.7% was −0.22 percentage points (95% CI, −0.34 to −0.10), and the difference among those with baseline levels of 5.7% or greater was −0.24 percentage points (95% CI, −0.36 to −0.12) (Table S7). Results for supportive secondary end points that were based on the trial-product estimand were similar.

SAFETY

Adverse events were reported by 190 participants (93.1%) in the oral semaglutide group and by 87 participants (85.3%) in the placebo group (Table 3). Most of the events were mild or moderate in severity and were resolved without a need for permanent discontinuation of the regimen. The most frequently reported adverse events were gastrointestinal disorders, reported by 151 participants (74.0%) in the oral semaglutide group and by 43 participants (42.2%) in the placebo group. The most common gastrointestinal disorders associated with oral semaglutide were nausea (in 95 participants [46.6%], vs. 19 participants [18.6%] with placebo) and vomiting (in 63 participants [30.9%], vs. 6 participants [5.9%] with placebo) (Table 3); these events were typically transient, with nausea occurring for a median duration of 13 days with oral semaglutide and 12 days with placebo, and vomiting for a median duration of 2 days with oral semaglutide and 1 day with placebo. Dyspepsia was reported in 37 participants (18.1%) in the oral semaglutide group as compared with 9 (8.8%) in the placebo group, and gastroesophageal reflux disease in 16 participants (7.8%) in the oral semaglutide group as compared with 5 (4.9%) in the placebo group. In the oral semaglutide group, 17 serious adverse events in 8 participants (3.9%)

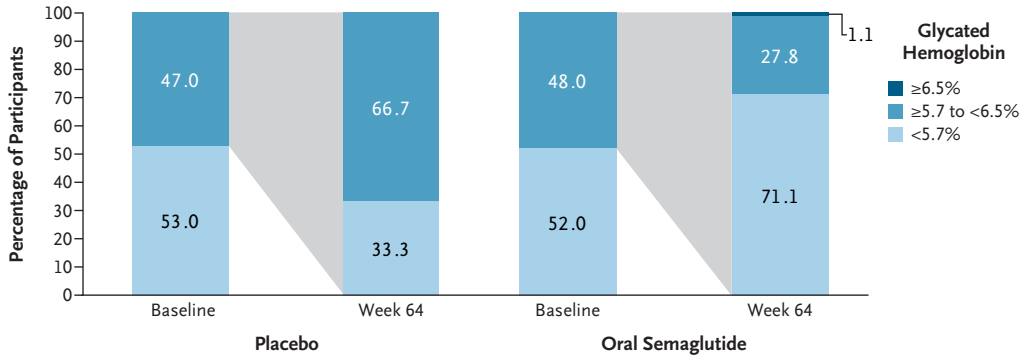

Figure 2. Change in Glycemic Status.

Shown is the change in glycemic status at week 64 according to glycemic status at baseline among participants in the full analysis population. Baseline glycemic status included all participants with normoglycemia (glycated hemoglobin <5.7%) or prediabetes (glycated hemoglobin ≥5.7 to <6.5%). The shading shows that the denominator for the percentages at week 64 are the participants who had prediabetes at baseline. The presence of type 2 diabetes at screening was an exclusion criterion. However, between screening and baseline, glycated hemoglobin levels in the range for diabetes diagnosis (≥6.5%) developed in five participants (three in the oral semaglutide group and two in the placebo group); data from these participants are not included here.

were reported, and in the placebo group, 13 serious adverse events in 9 participants (8.8%) were reported; adverse events leading to permanent discontinuation of semaglutide or placebo were reported by 14 participants (6.9%) and 6 participants (5.9%), respectively (Table 3). Gastrointestinal disorders were the most common type of adverse event leading to permanent discontinuation of the assigned regimen, reported by 7 participants (3.4%) in the oral semaglutide group and by 2 (2.0%) in the placebo group (Table 3). Data for prespecified safety focus areas are shown in Table S8. Dysesthesia, a grouped term describing altered skin sensation,[15] was reported by 10 participants (4.9%) in the oral semaglutide group (Table S9); all reported cases were nonserious and mild or moderate in severity. There were no reports of dysesthesia in the placebo group. No deaths occurred. The mean change from baseline in pulse was 1.9 beats per minute in the oral semaglutide group and 1.7 beats per minute in the placebo group (Table S10).

DISCUSSION

Currently available GLP-1 receptor agonists for the treatment of obesity are administered subcutaneously; oral formulations that do not compromise efficacy would offer patients greater choice. The reasons patients may prefer oral administration over the subcutaneous route are most often needle aversion and local skin reactions.[7,8] In addition, unlike injectable agents, oral agents may not require a refrigerated chain of delivery and could widen the reach of obesity care in many regions of the world where a lack of refrigeration represents a barrier to access.

In our trial, oral semaglutide at a dose of 25 mg once daily led to a clinically relevant mean reduction in body weight of 13.6% (11.4 percentage points more than that with placebo), with weight loss similar across baseline BMI subgroups. Almost a third of the participants in the oral semaglutide group had a reduction in body weight of 20% or more. The estimated difference in body-weight reduction between oral semaglutide at a dose of 25 mg and placebo in our trial is similar to that shown in the OASIS 1 trial of oral semaglutide at a dose of 50 mg once daily (12.7 percentage points more than that with placebo)[10] and the STEP 1 (Semaglutide Treatment Effect in People with Obesity) trial of weekly subcutaneous semaglutide at a dose of 2.4 mg (12.4 percentage points more than that with placebo),[16] although comparisons across trials should be interpreted with caution because of differences in populations and trial designs.

The safety profile and adverse events with oral semaglutide at a dose of 25 mg were as anticipated.[10,16] Gastrointestinal disorders were reported in 74.0% of the participants in the oral semaglutide group and were generally nonserious, mild to moderate in severity, and transient. The incidence of gastrointestinal disorders and the incidence of discontinuation of treatment due to gastrointestinal disorders were consistent with the results for the once-daily oral semaglutide group in the OASIS 1 trial[10] and for the once-weekly subcutaneous semaglutide group in the STEP 1 trial.[16] It is notable that the median duration of nausea events that were reported in the oral semaglutide group in our trial (13 days, vs. 12 days in the placebo group) was shorter than in the OASIS 1 trial (20 days, vs. 19 days in the placebo group).[10] In the OASIS 1 trial, an imbalance was shown in the incidence of dysesthesia between oral semaglutide at a dose of 50 mg and placebo (13% vs. 1%)[10]; a lower incidence was observed with oral semaglutide at a dose of 25 mg in the present trial (4.9%, vs. 0% with placebo). A possible mechanism linking GLP-1 signaling to dysesthesia is currently unknown.

Treatment with oral semaglutide was associated with improved physical function. In the oral semaglutide group, 55.3% of the participants reported a clinically meaningful improvement in the IWQOL-Lite-CT Physical Function score, which was in line with the percentage reported in the OASIS 1 trial (50.0%)[10] and in the STEP 1 trial (51.2%).[16] Treatment was also associated with substantial reductions in cardiometabolic risk factors including BMI, waist circumference, and levels of glycated hemoglobin, fasting plasma glucose, fasting serum insulin, lipids (very-low-density lipoprotein and triglycerides), and C-reactive protein. Similar findings were shown in the OASIS 1 and STEP 1 trials.[10,16] Of note, most participants with prediabetes at baseline had normoglycemia at the end of semaglutide treatment. The change in blood pressure with oral semaglutide was similar to that shown in the OASIS 1 and STEP 1 trials.[10,16]

Strengths of this trial include its multinational, double-blind, randomized, placebo-controlled design and high percentages of participants who adhered to the trial regimen and who completed the trial. Trial limitations include the predominance of female participants and the relatively low number of participants available for the assessment of effects according to subgroup. Approximately 20% of the trial population did not complete the trial, which led to a requirement of imputation for efficacy models. However, this is typical of findings in other obesity trials.[10,16] In addition, the lack of an active comparator (oral semaglutide at a dose of 50 mg or subcutaneous semaglutide at a dose of 2.4 mg) meant that it was not possible to compare adverse effects for a given dose or administration method.

Our data support oral semaglutide at a dose of 25 mg as an efficacious treatment option for obesity; the 25-mg dose resulted in substantial weight loss with a safety profile consistent with that of the GLP-1 class of medications. Oral semaglutide at a dose of 25 mg may enhance the flexibility of the treatment strategy for overweight and obesity by providing an alternative dose for the oral molecule as well as an alternative to subcutaneous semaglutide at a dose of 2.4 mg.

This trial showed that oral semaglutide at a dose of 25 mg once daily resulted in a greater reduction in mean body weight than placebo in participants with overweight or obesity.

Supported by Novo Nordisk.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial participants and the trial site staff who conducted the studies; and Rosina Pryor, Ph.D. (who wrote the first draft of the manuscript), and Ben McNeill, Ph.D., of Apollo, OPEN Health Communications, for medical writing support, funded by Novo Nordisk, in accordance with Good Publication Practice guidelines (ismpp.org/gpp-2022).

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