ORIGINAL ARTICLE

Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

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ABSTRACT

BACKGROUND

Cagrilintide and semaglutide have each been shown to induce weight loss as monotherapies. Data are needed on the coadministration of cagrilintide and semaglutide (called CagriSema) for weight management in adults with type 2 diabetes, including those in a subgroup who are undergoing continuous glucose monitoring.

METHODS

In this phase 3a, double-blind, randomized, placebo-controlled trial conducted in 12 countries, we assigned adults with a body-mass index of 27 or more, a glycated hemoglobin level of 7 to 10%, and type 2 diabetes in a 3:1 ratio to receive once-weekly cagrilintide–semaglutide (2.4 mg each) or placebo, along with lifestyle intervention, for 68 weeks. The two primary end points were the percent change in body weight and the percentage of patients with a weight reduction of at least 5%. Additional end points were changes in glycemic measures and safety assessments. Effect estimates were calculated with the use of the treatment-policy estimand (consistent with the intention-to-treat principle).

RESULTS

A total of 1206 patients underwent randomization to either the cagrilintide–semaglutide group (904 patients) or the placebo group (302 patients). The estimated mean change in body weight from baseline to week 68 was –13.7% in the cagrilintide–semaglutide group and –3.4% in the placebo group (estimated difference, –10.4 percentage points; 95% confidence interval, –11.2 to –9.5; P<0.001). More patients in the cagrilintide–semaglutide group than in the placebo group had a weight reduction of 5% or more (P<0.001); the same was true of reductions of at least 10%, 15%, and 20% (P<0.001 for the last comparison). The percentage of patients who had a glycated hemoglobin level of 6.5% or less was 73.5% in the cagrilintide–semaglutide group and 15.9% in the placebo group. Gastrointestinal adverse events were reported by 72.5% of the patients in the cagrilintide–semaglutide group and 34.4% in the placebo group, most of which were transient and mild or moderate in severity.

CONCLUSIONS

Once-weekly cagrilintide–semaglutide (at a dose of 2.4 mg each) resulted in a significantly lower body weight than placebo in adults with obesity and type 2 diabetes. (Funded by Novo Nordisk; REDEFINE 2 ClinicalTrials.gov number, NCT05394519.)

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Persons with obesity are at increased risk for type 2 diabetes,[1] and overweight or obesity occurs in more than 90% of patients with type 2 diabetes.[2] Thus, successful weight management as a primary treatment goal may improve glycemia, reduce the need for insulin, and result in a reduction in obesity-related complications and an improvement in quality of life.[3,4]

Semaglutide, a once-weekly subcutaneous glucagon-like peptide 1 (GLP-1) agonist, has been approved for weight management. In a phase 3, 68-week study involving adults with overweight or obesity and type 2 diabetes, the use of semaglutide (at a dose of 2.4 mg) resulted in a mean body-weight reduction of 9.6%.[5] Cagrilintide is a long-acting amylin analogue that binds the calcitonin receptor and all three amylin receptors. It has been shown to reduce food intake and induce weight loss.[6-8] A fixed-dose combination of cagrilintide and semaglutide (called CagriSema) is being evaluated for weight management according to the rationale that therapies with distinct but complementary mechanisms of action may provide greater weight loss than that achieved with the individual components.

We performed the phase 3a REDEFINE 2 trial to evaluate the efficacy and safety of once-weekly subcutaneous cagrilintide–semaglutide (at a dose of 2.4 mg each) as compared with placebo as an adjunct to lifestyle interventions for weight management in patients with overweight or obesity and type 2 diabetes, including a subgroup of patients with continuous glucose monitoring.

Methods

Trial Design and Oversight

This was a randomized, double-blind, placebo-controlled trial conducted in 12 countries in Europe, North America, and Asia for 68 weeks (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol and amendments (also available at NEJM.org) were approved by the relevant institutional review or independent ethics committee at each trial site.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.[9,10] The sponsor, Novo Nordisk, was responsible for designing the trial, preparing the protocol and statistical analysis plan, monitoring the trial sites, and performing the statistical analyses. The authors had full access to the data and analysis, interpreted the aggregated data, participated in the drafting of the manuscript, 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. The investigators were responsible for trial-related medical decisions and data collection.

Patients

Eligible patients were adults (≥18 years of age) with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 27 or more, a glycated hemoglobin level of 7 to 10% (53 to 86 mmol per mole), and at least one self-reported unsuccessful dietary effort to lose weight. All the patients had received a diagnosis of type 2 diabetes at least 180 days before screening and had received stable treatment with lifestyle intervention or no more than three oral glucose-lowering drugs for at least 90 days before screening. Exclusion criteria included previous surgical or pharmacologic treatment for obesity within 90 days before screening. Full eligibility criteria and exceptions to the surgical exclusion criterion are described in the Supplementary Appendix. All the patients provided written informed consent.

Procedures

The patients were randomly assigned in a 3:1 ratio to receive cagrilintide–semaglutide or placebo, plus lifestyle intervention, with the use of a Web-based system with stratification according to inclusion in a subgroup receiving continuous glucose monitoring. Cagrilintide–semaglutide — administered as a fixed-dose combination by means of a dual-chamber, single-dose, single-use pen device — was initiated at a once-weekly dose of 0.25 mg of each drug, with dose escalation every 4 weeks (to 0.5 mg, 1.0 mg, and 1.7 mg of each drug) until the maintenance dose of 2.4 mg of each drug was reached after 16 weeks. The maintenance period lasted 52 weeks with a 7-week follow-up period after the end of the trial treatment.

Dose reduction or delay of escalation was permitted if the current dose was associated with unacceptable side effects or if the patient was reported to have a BMI in the lower normal range, according to investigator discretion. Patients were

allowed to continue in the trial while receiving a submaximal dose and were recommended to attempt escalation to the maximum dose at least once. Glucose-lowering medications could be modified at the discretion of the investigator. All the patients at selected sites in the United States underwent continuous glucose monitoring, as described in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The two primary end points were the percent change in body weight and the percentage of patients with a reduction in body weight of 5% or more from baseline to week 68. Confirmatory secondary end points were the percentage of patients who had a reduction in body weight of 20% or more from baseline to week 68, the percent change in body weight from baseline to week 20, and changes from baseline to week 68 in waist circumference, glycated hemoglobin level, systolic blood pressure, and the patients' scores for physical function on the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT) and on the Short Form 36, version 2 (SF-36v2), Health Survey Acute. These last two end points were evaluated both in the overall population and in patients with poor physical function at baseline (Fig. S2). The latter subgroup was defined according to whether patients had reported "poor" function on the Patient Global Impression of Status Physical Function measure. A full list of end points, testing methods, and scoring ranges for patient-reported outcomes is provided in the Supplementary Appendix.

We conducted mental health assessments throughout the trial using the Patient Health Questionnaire-9 and the Columbia–Suicide Severity Rating Scale questionnaire. Safety end points included the number of adverse events and serious adverse events during treatment and the number of severe and clinically significant episodes of hypoglycemia, according to the 2018 American Diabetes Association classification.[11] An independent external event-adjudication committee performed ongoing blinded adjudication of selected adverse events and deaths.

STATISTICAL ANALYSIS

We calculated that the enrollment of 1200 patients would provide the trial with a power of more than 99% for the two primary end points. The primary end points and confirmatory secondary end points were tested in a prespecified hierarchical order. Efficacy end points were analyzed in the full analysis population (all the patients who had undergone randomization), and safety end points were analyzed in the safety analysis population (all the patients in the full analysis population who had received at least one dose of cagrilintide–semaglutide or placebo).

Efficacy end points were assessed over two observation periods: the in-trial period, defined as the time from randomization to the patient's last contact with a trial site regardless of discontinuation of cagrilintide–semaglutide or placebo or rescue intervention, and the on-treatment period, defined as the period from the first administration of cagrilintide–semaglutide or placebo to the first discontinuation (defined as no dose for 14 days) without rescue intervention.

Two estimands were used to assess efficacy from different perspectives, as described previously.[12] The treatment-policy estimand assessed the effect of the prescription of cagrilintide–semaglutide or placebo regardless of discontinuation or rescue intervention (consistent with the intention-to-treat principle) and was based on data from the in-trial period. The trial-product estimand assessed the effect of taking cagrilintide–semaglutide or placebo as intended (at any dose level) without discontinuation or rescue intervention and was based on data from the on-treatment period. All reported results are from the treatment-policy estimand, unless otherwise stated.

All the results of the statistical analyses are reported with two-sided 95% confidence intervals. Corresponding P values are provided for the two primary and confirmatory secondary end points, with significance defined as a P value of less than 0.05. P values are not provided for end points that were not included in the testing hierarchy, because these analyses were not controlled for multiplicity. Missing data were imputed with the use of a multiple-imputation approach, similar to a method described previously.[13] Additional details regarding estimands, analysis methods, and modeling for continuous and binary end points are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From February 1 to August 11, 2023, a total of 1606 patients underwent screening, and 1206 were

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

Characteristic	Cagrilintide–Semaglutide (N=904)	Placebo (N=302)
Age — yr	55.9±11.8	56.5±10.7
Female sex — no. (%)	429 (47.5)	140 (46.4)
Race or ethnic group — no. (%)†		
White	597 (66.0)	204 (67.5)
Asian	262 (29.0)	84 (27.8)
Black	33 (3.7)	10 (3.3)
Other‡	12 (1.3)	4 (1.3)
Body weight — kg	101.9±22.6	103.3±23.5
Body-mass index	36.1±6.7	36.4±7.1
Waist circumference — cm	115.6±14.7	116.4±15.2
Glycated hemoglobin level — %	8.0±0.8	8.0±0.8
Fasting plasma glucose level — mmol/liter	9.3±2.4	9.5±2.8
Blood pressure — mm Hg		
Systolic	130.2±14.0	130.2±13.8
Diastolic	80.4±9.6	80.4±9.3
Estimated glomerular filtration rate — ml/min/per 1.73 m^2	94.2±19.3	93.4±17.2
Duration of diabetes — yr	8.5±6.3	8.7±5.9
Oral glucose-lowering medication — no. (%)		
Metformin	773 (85.5)	263 (87.1)
SGLT2 inhibitor	305 (33.7)	98 (32.5)
Sulfonylurea	238 (26.3)	87 (28.8)
Thiazolidinedione	41 (4.5)	15 (5.0)
None	64 (7.1)	18 (6.0)
Physical function		
IWQOL-Lite-CT score§	59.0±24.3	59.7±24.0
SF-36v2 score¶	44.8±9.8	44.6±9.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. SGLT2 denotes sodium–glucose cotransporter 2.
† Race or ethnic group was reported by the patients.
‡ Other race or ethnic group includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple groups, and not reported.
§ The physical-function score on the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT) ranges from 0 to 100, with higher scores indicating better functioning.
¶ The physical-function score on the Short Form 36, version 2 (SF-36v2), Health Survey Acute ranges from 19.0 to 57.6, with higher scores indicating better functioning.

randomly assigned to receive cagrilintide–semaglutide (904 patients) or placebo (302 patients) (Fig. S3). The mean age of the patients was 56.0 years, 637 (52.8%) were men, 801 (66.4%) were White, and 346 (28.7%) were Asian. The mean body weight was 102.2 kg, the mean BMI was 36.2, and the mean waist circumference was 115.8 cm. The mean glycated hemoglobin level was 8.0%. The mean duration of diabetes was 8.5 years, and 41.3% and 39.9% of patients were receiving treatment with one or two oral glucose-lowering medications, respectively. The most common glucose-lowering medications were metformin (in 85.9% of the patients), sodium–glucose cotransporter 2 inhibitors (in 33.4%), and sulfonylureas (in 26.9%). Baseline characteristics were

Table 2. Primary and Confirmatory Secondary End Points.*

End Point	Cagrilintide–Semaglutide (N=904)	Placebo (N=302)	Treatment Difference (95% CI)	P Value
Primary end points				
Percent change in body weight	–13.7	–3.4	–10.4 (–11.2 to –9.5)	<0.001
Patients with body-weight reduction of ≥5% — %	83.6	30.8	52.8 (46.7 to 58.9)	<0.001
Confirmatory secondary end points				
Patients with body-weight reduction of ≥20% — %	22.9	0.5	22.4 (19.5 to 25.3)	<0.001
Percent change in body weight from baseline to week 20	–10.1	–2.3	–7.8 (–8.3 to –7.3)	<0.001
Change in waist circumference — cm	–11.9	–3.6	–8.3 (–9.3 to –7.3)	<0.001
Change in glycated hemoglobin level — percentage points	–1.8	–0.4	–1.4 (–1.6 to –1.2)	<0.001
Change in systolic blood pressure — mm Hg	–6.5	–2.4	–4.1 (–6.0 to –2.1)	<0.001
Change in IWQOL-Lite-CT physical-function score				
All patients	16.1	10.4	5.8 (3.2 to 8.4)	<0.001
Patients with poor physical function at baseline†	21.8	12.0	9.8 (2.1 to 17.6)	0.01
Change in SF-36v2 physical-function score				
All patients	5.0	3.1	1.9 (0.9 to 3.0)	<0.001
Patients with poor physical function at baseline†	7.6	3.8	3.8 (0.5 to 7.1)	0.02

* All end points were assessed from baseline to week 68 unless otherwise stated on the basis of the treatment-policy estimand. All data are estimated mean changes or estimated percentages for the in-trial period. The corresponding data for the on-treatment period and trial-product estimand are provided in Table S4 in the Supplementary Appendix.
† The number of patients with poor physical function at baseline was 136 (15.0%) in the cagrilintide–semaglutide group and 39 (12.9%) in the placebo group. This subgroup was defined according to whether patients reported "poor" function on the Patient Global Impression of Status Physical Function measure.

balanced between the two trial groups (Table 1 and Table S1). The representativeness of the trial population is described in the Supplementary Appendix.

Continuous glucose monitoring was performed in 149 of 904 patients (16.5%) in the cagrilintide–semaglutide group and in 50 of 302 patients (16.6%) in the placebo group; baseline characteristics for this subgroup are shown in Table S2. Overall, 1146 patients (95.0%) completed the trial; 1033 (85.7%) completed the trial while receiving cagrilintide–semaglutide or placebo. In the cagrilintide–semaglutide group, 61.9% of the patients were receiving the 2.4-mg dose at the end of the treatment period, as compared with 80.5% in the placebo group. The maximum dose was received at some point in the trial by 75.9% of the patients in the cagrilintide–semaglutide group, as compared with 91.7% in the placebo group (Table S3 and Fig. S4).

BODY WEIGHT

For the treatment-policy estimand, the estimated mean change in body weight from baseline to week 68 (the first primary end point) was –13.7% with cagrilintide–semaglutide, as compared with –3.4% with placebo (estimated difference, –10.4 percentage points; 95% confidence interval [CI], –11.2 to –9.5; P<0.001) (Table 2 and Fig. 1A). For the trial-product estimand, the change in body weight was –15.7% with cagrilintide–semaglutide and –3.1% with placebo (estimated difference, –12.6 percentage points; 95% CI, –13.4 to –11.7) (Table S4 and Fig. 1B).

A weight reduction of 5% or more (the second primary end point) was reported in 83.6% of the

patients in the cagrilintide–semaglutide group and in 30.8% of those in the placebo group (P<0.001). In addition, a weight reduction of 10% or more occurred in 65.6% of the patients in the cagrilintide–semaglutide group and in 10.3% of those in the placebo group; a weight reduction of 15% or more in 43.8% and 2.4%, respectively; and a weight reduction of 20% or more in 22.9% and 0.5%, respectively (P<0.001 for the last comparison) (Table 2, Fig. 1C, and Table S5). Results for the trial-product estimand were similar to those for the treatment-policy estimand (Fig. 1D). Treatment with cagrilintide–semaglutide also led to a greater mean reduction in waist circumference from baseline to week 68 than placebo (estimated difference, –8.3 cm; 95% CI, –9.3 to

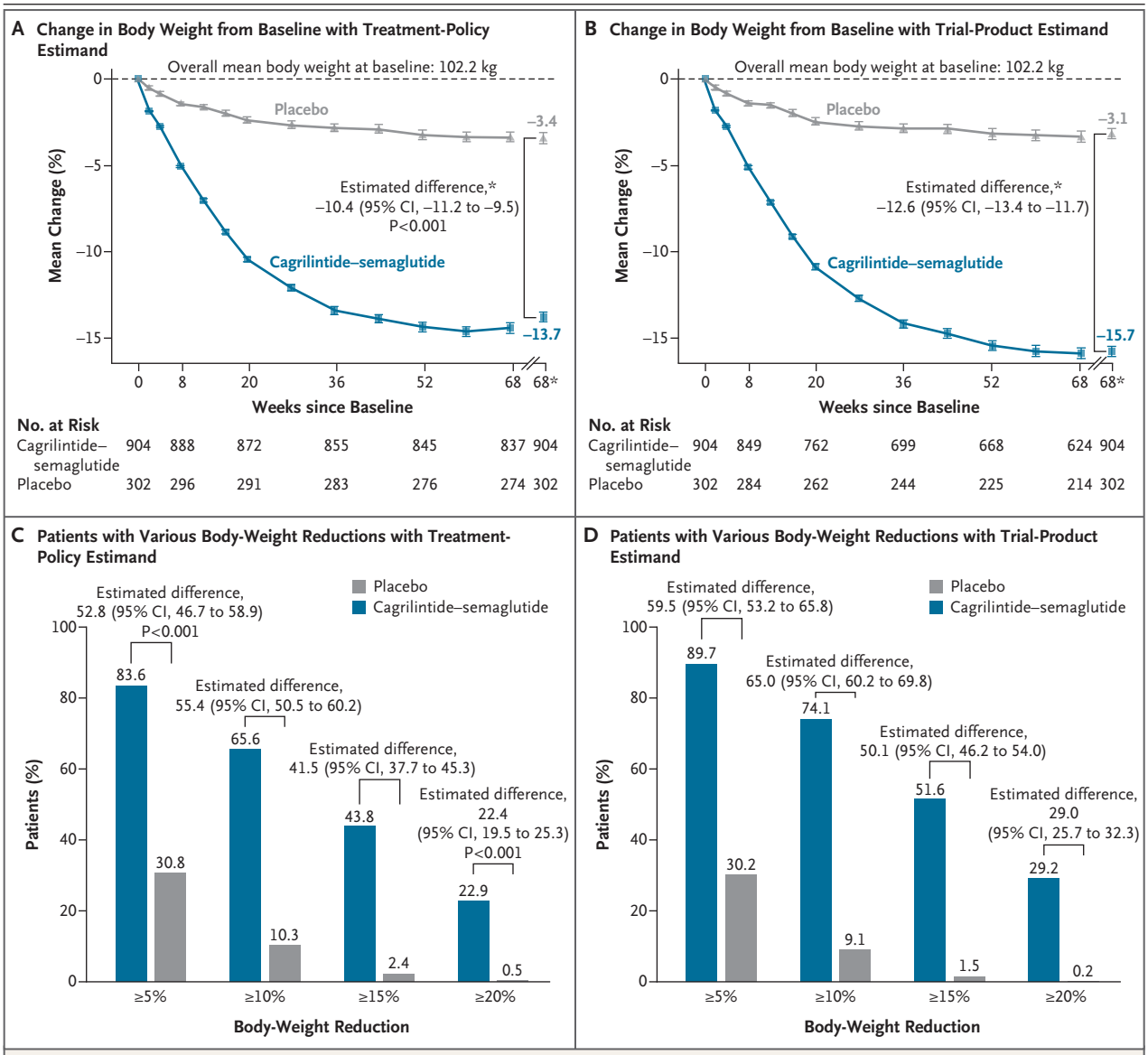

Figure 1. Effect of Once-Weekly Cagrilintide–Semaglutide, as Compared with Placebo, on Body Weight.

Shown is the observed mean percent change in body weight from baseline to week 68 for the patients in the full analysis population during the in-trial period (Panel A) and during the on-treatment period (Panel B). I bars represent standard errors. Asterisks indicate the estimated means and estimated treatment differences according to the treatment-policy estimand (Panel A) and the trial-product estimand (Panel B). Estimated percentages of patients with body-weight reductions of at least 5%, 10%, 15%, and 20% from baseline at week 68 in the full analysis population are shown according to the treatment-policy estimand (Panel C) and the trial-product estimand (Panel D).

–7.3) (Table 2 and Fig. S5). Changes in BMI categories also favored cagrilintide–semaglutide (Table S6).

GLYCEMIC-RELATED END POINTS

For the treatment-policy estimand, cagrilintide–semaglutide led to a greater mean reduction in the glycated hemoglobin level from baseline to week 68, as compared with placebo (–1.8 percentage points vs. –0.4 percentage points; estimated difference, –1.4; 95% CI, –1.6 to –1.2; P<0.001) (Table 2 and Fig. 2A). For the trial-product estimand, the estimated difference was –2.0 (95% CI, –2.2 to –1.8) (Fig. S6).

The percentage of patients who had a glycated hemoglobin level of 6.5% or less was 73.5% in the cagrilintide–semaglutide group and 15.9% in the placebo group. Decreases in levels of fasting plasma glucose and fasting serum insulin also appeared greater with cagrilintide–semaglutide than with placebo.

Of the 794 patients who received oral glucose-lowering medication between baseline and week 68 in the cagrilintide–semaglutide group, 5.8% had an increase in medication intensity and 35.3% had a decrease. In the placebo group, of the 269 patients who received medication, 34.2% had an increase in medication intensity and 7.8% had a decrease. Changes in the use of glucose-lowering medications are summarized in Table S7.

Among the 199 patients in the continuous-glucose-monitoring subgroup, increases in the percentage of time spent in the glycemic target range (70 to 180 mg per deciliter [3.9 to 10 mmol per liter]) and time spent in a tight glycemic range (70 to 140 mg per deciliter [3.9 to 7.8 mmol per liter]) appeared to be larger with cagrilintide–semaglutide than with placebo. In the cagrilintide–semaglutide group, the mean observed percentage of time spent in the glycemic target range was 43.6% at baseline and 86.8% at week 68; in the placebo group, the corresponding values were 41.3% and 50.2%. In addition, the percentage of time spent below range at week 68 was less than 1% in both trial groups (Fig. 2B). The 24-hour glucose profiles are shown in Figure 2C.

ADDITIONAL END POINTS

Treatment with cagrilintide–semaglutide led to a greater mean reduction from baseline to week 68 than placebo in systolic blood pressure (estimated difference, –4.1 mm Hg; 95% CI, –6.0 to –2.1; P<0.001) (Table 2 and Fig. S7). Changes favoring cagrilintide–semaglutide were observed for diastolic blood pressure, C-reactive protein, and lipids. Greater improvements were observed for cagrilintide–semaglutide as compared with placebo in the physical-function score on the IWQOL-Lite-CT and on the SF-36v2 in the overall population (P<0.001 for both), including in those with poor physical function at baseline (P<0.05 for both) (Figs. S8 and S9). Changes in additional IWQOL-Lite-CT and SF-36v2 scores are shown in Figures S10, S11, and S12.

SAFETY

Adverse events were reported in 815 patients (90.2%) in the cagrilintide–semaglutide group and in 258 patients (85.4%) in the placebo group; serious adverse events were reported in 94 patients (10.4%) and 39 patients (12.9%), respectively (Table 3 and Table S8). The most frequently reported adverse events in the cagrilintide–semaglutide group were gastrointestinal disorders, which occurred in 72.5% of patients, as compared with 34.4% in the placebo group (Table 3 and Table S9). Overall, gastrointestinal adverse events were mild to moderate in severity, with few reports of severe events. The prevalence of nausea, vomiting, and diarrhea was highest during the dose-escalation phase, whereas the prevalence of constipation remained stable throughout the trial (Fig. S13).

More patients in the cagrilintide–semaglutide group than in the placebo group discontinued treatment because of an adverse event (8.4% vs. 3.0%) (Table 3). Gastrointestinal disorders were the most frequent type of adverse events leading to the discontinuation of cagrilintide–semaglutide, which was reported in 43 patients (4.8%), as compared with 2 patients (0.7%) with placebo. Cases of pancreatitis were reported in 3 patients (0.3%) in the cagrilintide–semaglutide group and injection-site reactions in 44 patients (4.9%), as compared with no such events in the placebo group. Malignant neoplasms that were confirmed by the event-adjudication committee were reported in 14 patients (1.5%) in the cagrilintide–semaglutide group and in 4 patients (1.3%) in the placebo group. Overall, there was little difference between the trial groups with respect to mental health assessments according to the Patient Health Questionnaire-9 and the Columbia–Suicide Severity Rating Scale (Tables S10 and S11).

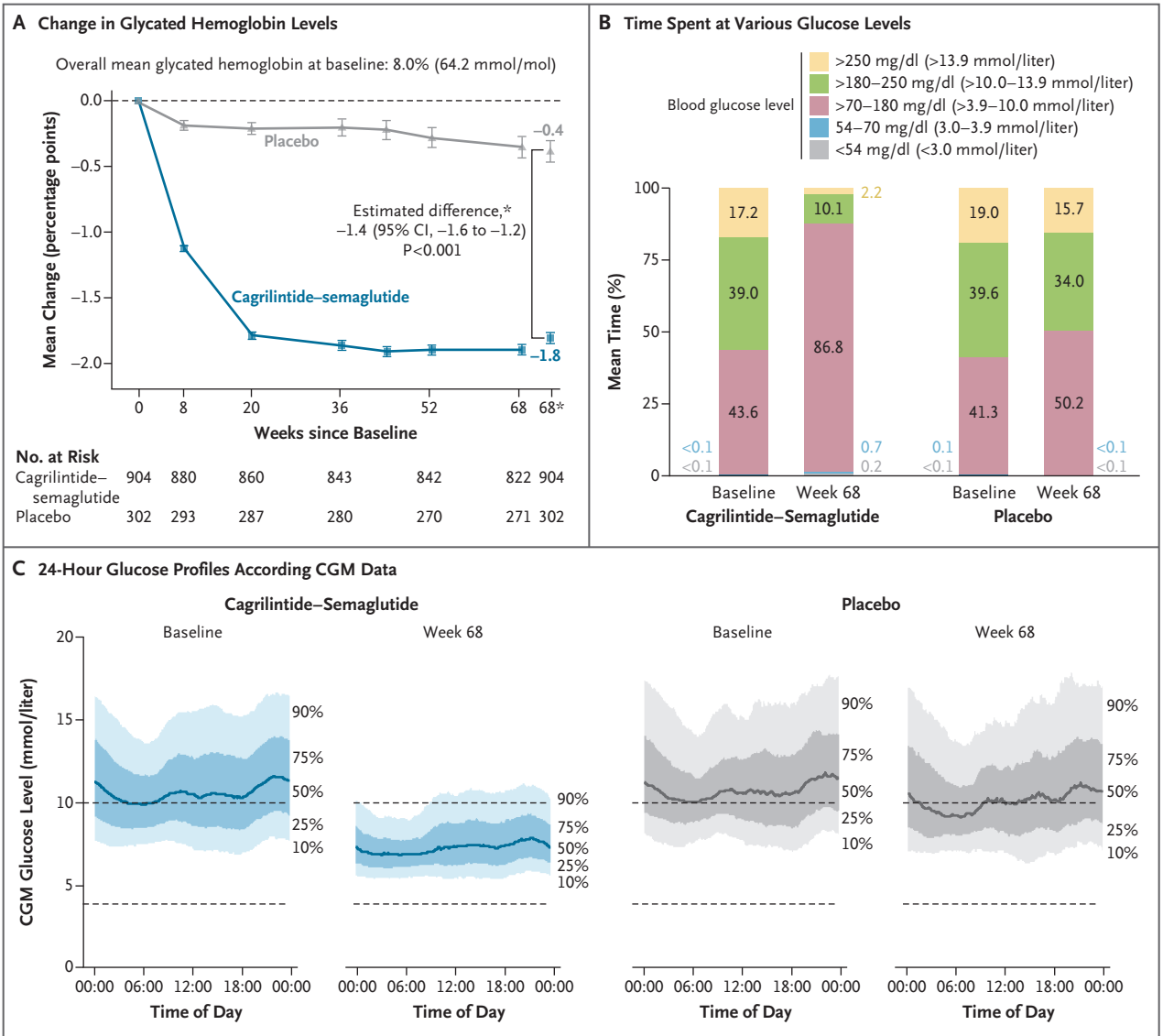

Figure 2. Effect of Once-Weekly Cagrilintide–Semaglutide, as Compared with Placebo, on Glycemic Control.

Panel A shows the observed mean change in glycated hemoglobin levels from baseline to week 68 among patients in the full analysis set during the in-trial observation period. I bars represent standard errors. Asterisks indicate the estimated means and estimated differences according to the treatment-policy estimand. Panel B shows the mean percentage of observed time spent at various glucose levels at baseline and week 68 as measured by continuous glucose monitoring (CGM). The target glycemic range was 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter). Panel C shows 24-hour glucose profiles in the two trial groups among the patients who were receiving CGM. In each group, the dark curves represent the median, the shaded bands show the percentiles of patients' glucose measurements ranging from 10 to 90%, and the dashed lines indicate the target glycemic range.

Level 2 hypoglycemic episodes were reported in 6.0% of the patients in the cagrilintide–semaglutide group and in 3.3% of those in the placebo group; level 3 episodes were reported in 2 patients (0.2%) in the cagrilintide–semaglutide group, both of whom were being concomitantly treated with sulfonylureas, and in no patients in the placebo group (Table S12). Hypoglycemic events according to sulfonylurea treatment status are summarized in Table S13.

Four deaths were reported in the cagrilintide–semaglutide group (from suicide, cancer, sudden cardiac death, and other noncardiovascular causes), as determined by the event-adjudication commit-

Table 3. Adverse Events.*

Adverse Events	Cagrilintide–Semaglutide (N=904)			Placebo (N=302)		
	Patients	Events	Event Rate†	Patients	Events	Event Rate†
	no. (%)	*no.*		*no. (%)*	*no.*	
Any	815 (90.2)	6088	477.4	258 (85.4)	1275	301.6
Serious	94 (10.4)	138	10.8	39 (12.9)	51	12.1
Leading to permanent discontinuation						
Any adverse event	76 (8.4)	97	7.6	9 (3.0)	13	3.1
Gastrointestinal adverse event	43 (4.8)	49	3.8	2 (0.7)	3	0.7
Fatal event‡	4 (0.4)	4	0.3	0	—	—
Hypoglycemic episode§						
Alert value: level 1¶	108 (11.9)	328	27.8	24 (7.9)	61	15.6
Clinically significant: level 2¶	54 (6.0)	85	7.2	10 (3.3)	11	2.8
Severe: level 3¶	2 (0.2)	2	0.2	0	—	—
Selected safety event						
Gastrointestinal disorder¶	655 (72.5)	2742	232.4	104 (34.4)	227	58.0
Retinal disorder	75 (8.3)	94	7.4	24 (7.9)	29	6.9
Neoplasm	63 (7.0)	80	6.3	20 (6.6)	26	6.1
Allergic reaction¶	46 (5.1)	55	4.7	18 (6.0)	19	4.9
Injection-site reaction¶	44 (4.9)	65	5.5	0	—	—
Gallbladder-related disorder¶	18 (2.0)	24	2.0	2 (0.7)	2	0.5
Malignant neoplasm‖	14 (1.5)	16	1.3	4 (1.3)	4	0.9
Pancreatitis¶	3 (0.3)	3	0.3	0	—	—
Suicidal ideation or behavior**	8 (0.9)	—	—	4 (1.4)	—	—

* Data are from the safety analysis set from the in-trial period unless otherwise stated.
† The event rate is the number of events per 100 patient-years of observation (for in-trial period) or exposure (for on-treatment period).
‡ Causes of death were exocrine and endocrine pancreatic cancer, sudden cardiac death, suicide, and other noncardiovascular causes, as defined by the event-adjudication committee.
§ Hypoglycemic episodes were defined according to the American Diabetes Association 2018 classification for blood glucose: level 1, less than 70 mg per deciliter (3.9 mmol per liter) but at least 54 mg per deciliter (3.0 mmol per liter); level 2, less than 54 mg per deciliter (3.0 mmol per liter); and level 3, requiring assistance from another person for recovery.
¶ Data are for the on-treatment period.
‖ Malignant neoplasms were confirmed by the event-adjudication committee. Malignant neoplasms recorded for the cagrilintide–semaglutide group were cutaneous squamous-cell carcinoma and other cutaneous carcinomas (in 5 patients), colon and rectal cancer (in 2 patients), corpus uteri cancer (in 2 patients), and (in 1 patient each) distal bile-duct cancer, exocrine and endocrine pancreatic cancer, prostate cancer, melanoma of the skin, and papillary thyroid carcinoma. Malignant neoplasms recorded in the placebo group (in 1 patient each) were kidney cancer, prostate cancer, corpus uteri cancer, and "other."
** The presence of suicidal ideation or behavior was assessed with the use of the Columbia–Suicide Severity Rating Scale at any visit after randomization. Included in this assessment were 878 patients in the cagrilintide–semaglutide group and 296 patients in the placebo group.

tee (Table 3). No deaths were reported in the placebo group.

DISCUSSION

We found that once-weekly treatment with subcutaneous cagrilintide–semaglutide led to substantial and clinically meaningful weight loss in adults with overweight or obesity and type 2 diabetes. Patients who received cagrilintide–semaglutide had near-normoglycemic control, along with improvements in cardiovascular risk factors and physical function. These findings support the use of cagrilintide–semaglutide as a promising treatment option in this population with type 2 diabetes.

Preclinical evidence suggests that the effects of cagrilintide–semaglutide on weight loss are mediated by the direct and complementary effects of the two drug molecules on brain regions known to be involved in homeostatic and hedonic appetite regulation[14,15]; clinical evidence suggests that both molecules have beneficial effects on regulation of appetite and improved control of eating.[8,16-18] In addition, the mode of action of semaglutide to improve glycemic control includes increased insulin secretion and decreased glucagon secretion in a glucose-dependent manner.[19]

The magnitude of weight loss with cagrilintide–semaglutide (–13.7%) was consistent with the result for tirzepatide at doses of 10 mg (–12.8%) and 15 mg (–14.7%) in a similar study population.[20] A greater proportion of patients in the cagrilintide–semaglutide group reached weight-loss thresholds (≥5%, ≥10%, ≥15%, and ≥20%) than those in the placebo group. Achievement of substantial weight loss is more difficult in persons with diabetes than in those without diabetes owing to multiple factors, including the use of medications that can cause weight gain.[21]

The weight-loss efficacy of cagrilintide–semaglutide was particularly encouraging, given that a considerable percentage of the patients were receiving treatment with sulfonylureas or thiazolidinediones, both agents associated with weight gain.[22] The finding that weight-loss percentages appeared to be lower in this trial than those reported for other GLP-1 agonists among participants without diabetes is in alignment with the findings in other weight-management studies.[20,23-25] In addition, the higher proportion of Asian patients in this trial than in similar studies may have reduced values for weight-loss efficacy.[20,24] Long-term treatment will probably be required to sustain the observed clinical benefits of cagrilintide–semaglutide, as is the case for other GLP-1–based therapies, with which treatment discontinuation has been associated with weight regain and deterioration in glycemic control.[26]

Cagrilintide–semaglutide improved glycemic control and was associated with a low incidence of hypoglycemia. Almost three quarters of the patients had a glycated hemoglobin target of 6.5% or less at the end of the trial, which exceeded the proportion that was previously reported for a 2.4-mg dose of semaglutide (67.5% of the patients).[24] In addition, the results in the subgroup that received continuous glucose monitoring showed that the patients in the cagrilintide–semaglutide group spent substantially longer in the target glycemic range than those in the placebo group. Overall, improvements in glycemic control were observed with cagrilintide–semaglutide despite the finding of a larger percentage of patients in the placebo group who increased their use of oral glucose-lowering medications.

Significant improvements in patient-reported physical functioning were observed with cagrilintide–semaglutide as compared with placebo and appeared to be greater than those observed previously with a 2.4-mg dose of semaglutide,[24] with a larger treatment effect observed in those with poor physical function at baseline.

In accordance with protocol-defined options for dose adjustments, patients could remain on their target dose or decrease to a submaximum dose, which probably contributed to the low discontinuation rates. Even though only 61.9% of the patients in the cagrilintide–semaglutide group were receiving the target maintenance dose of 2.4 mg by the end of the trial, 75.9% of the patients had received the maximum dose at some point after randomization. Substantial treatment benefits were observed with cagrilintide–semaglutide, given that just under two thirds of the patients were receiving the target maintenance dose by the end of the trial. These findings may be important for clinical practice, because dose modifications are frequently made at the discretion of health care professionals on the basis of side effects, efficacy, and health goals.[27,28]

The safety profile of cagrilintide–semaglutide was generally consistent with previous data for semaglutide and cagrilintide in combination and as monotherapies.[6,7,24] The most common adverse events for cagrilintide–semaglutide were gastrointestinal disorders, but discontinuation because of such events was low overall (4.8%), with an incidence that was similar to those in other trials enrolling similar populations.[24,29] Cagrilintide–semaglutide treatment was associated with a low incidence of hypoglycemia, which was encouraging, given the level of glycemic control achieved and with approximately a quarter of the patients receiving a sulfonylurea at baseline.

Strengths of the trial include the large population, the protocol-defined options for dose adjustments, and the use of continuous glucose monitoring. Limitations include the lack of separate monotherapy groups for cagrilintide and

semaglutide, the predominantly White population, and the fact that only 16.5% of the trial population was receiving continuous glucose monitoring.

Once-weekly cagrilintide–semaglutide at a dose of 2.4 mg provided clinically meaningful weight reduction in adults with overweight or obesity and type 2 diabetes.

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