ORIGINAL ARTICLE

Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity — A Phase 2 Trial

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ABSTRACT

BACKGROUND

Maridebart cafraglutide (known as MariTide) is a long-acting peptide–antibody conjugate that combines glucagon-like peptide-1 receptor agonism and glucose-dependent insulinotropic polypeptide receptor antagonism and that is intended for the treatment of obesity.

METHODS

We conducted a phase 2, double-blind, randomized, placebo-controlled, dose-ranging trial that included 11 groups as two cohorts. Participants with obesity (obesity cohort) were randomly assigned in a 3:3:3:2:2:2:3 ratio to receive maridebart cafraglutide subcutaneously at a dose of 140, 280, or 420 mg every 4 weeks without dose escalation; 420 mg every 8 weeks without dose escalation; 420 mg every 4 weeks with 4-week dose escalation; 420 mg every 4 weeks with 12-week dose escalation; or placebo. Participants with obesity with type 2 diabetes (obesity–diabetes cohort) were randomly assigned in a 1:1:1:1 ratio to receive maridebart cafraglutide at a dose of 140, 280, or 420 mg every 4 weeks (all without dose escalation) or placebo. The primary end point was the percent change in body weight from baseline to week 52.

RESULTS

We enrolled 592 participants. In the obesity cohort (465 participants; female sex, 63%; mean age, 47.9 years; mean body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 37.9), the mean percent change in body weight from baseline to week 52 on the basis of the treatment policy estimand (intention-to-treat approach) ranged from –12.3% (95% confidence interval [CI], –15.0 to –9.7) to –16.2% (95% CI, –18.9 to –13.5) with maridebart cafraglutide, as compared with –2.5% (95% CI, –4.2 to –0.7) with placebo. In the obesity–diabetes cohort (127 participants; female sex, 42%; mean age, 55.1 years; mean BMI, 36.5), the mean percent change in body weight from baseline to week 52 on the basis of the treatment policy estimand ranged from –8.4% (95% CI, –11.0 to –5.7) to –12.3% (95% CI, –15.3 to –9.2) with maridebart cafraglutide, as compared with –1.7% (95% CI, –2.9 to –0.6) with placebo. The mean change in the glycated hemoglobin level on the basis of the treatment policy estimand in this cohort was –1.2 to –1.6 percentage points in the maridebart cafraglutide groups and 0.1 percentage points in the placebo group. Gastrointestinal adverse events were common with maridebart cafraglutide, although less frequent with dose escalation and a lower starting dose. No unexpected safety signals emerged.

CONCLUSIONS

In this phase 2 trial, once-monthly maridebart cafraglutide resulted in substantial weight reduction in participants with obesity with or without type 2 diabetes. (Funded by Amgen; ClinicalTrials.gov number, NCT05669599.)

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

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Once-monthly therapeutics for obesity may offer sustainable treatment for persons with this highly prevalent, chronic disease.[1] Once-weekly nutrient-stimulated hormone receptor modulators,[2,3] such as semaglutide and tirzepatide, target the neurometabolic pathophysiological pathways of obesity,[4] resulting in substantial weight reduction[5] while also addressing obesity-related complications.[6,7] However, access and adherence remain barriers to treatment.[8-11] Medication at less frequent intervals may improve adherence and reduce barriers, potentially facilitating improvements in long-term health outcomes.[12,13]

Maridebart cafraglutide (known as MariTide or AMG133; Amgen) is a long-acting molecule that combines glucagon-like peptide-1 (GLP-1) receptor agonism and glucose-dependent insulinotropic polypeptide (GIP) receptor antagonism. Although both GIP receptor agonism and antagonism lead to weight reduction, especially when combined with GLP-1 receptor agonism,[14] genetic evidence indicates that GIP receptor variants that are linked to reduced receptor signaling are associated with a lower body-mass index (BMI, the weight in kilograms divided by the square of the height in meters).[15] Maridebart cafraglutide, composed of two identical GLP-1 peptide analogues conjugated to a single monoclonal antibody antagonist to the GIP receptor,[16] has a half-life of approximately 21 days (approximately 3 times as long as the longest-acting Food and Drug Administration–approved once-weekly medications for obesity), which supports monthly or less frequent administration.[16] In phase 1, the safety and the side-effect profile of maridebart cafraglutide were acceptable, and dose-dependent weight reduction (mean change, up to −14.5% at 12 weeks) was maintained for up to 150 days after the last dose.[16] The present phase 2 trial evaluated the efficacy, side-effect profile, and safety of maridebart cafraglutide at various doses, with and without dose escalation, in adults with obesity with or without type 2 diabetes.

METHODS

TRIAL DESIGN

This phase 2, multinational, double-blind, randomized, placebo-controlled, dose-ranging trial included two cohorts: persons with obesity (obesity cohort; protocol cohort A) and persons with obesity with type 2 diabetes (obesity–diabetes cohort; protocol cohort B) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by an independent ethics committee or institutional review board at each trial site. The sponsor (Amgen) designed and oversaw the trial conduct. The first author wrote the first draft. All the authors participated in data interpretation and critical review of the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). This phase 2 trial has two parts. Part 1 (52 weeks), discussed here, investigated dose range, dose escalation, and no dose escalation. Part 2 (an additional 52 weeks) is investigating various maintenance-dose strategies. In this article, we also describe a phase 1 pharmacokinetics low-dose initiation (PK-LDI) study designed to inform the initial dose and dose escalation for the phase 3 program (Fig. S13).

PARTICIPANTS

Participants were 18 years of age or older. The obesity cohort included participants with a BMI of 30 or more, or 27 or more with at least one obesity-related complication, and a glycated hemoglobin level of less than 6.5%. The obesity–diabetes cohort included participants with a BMI of 27 or more and an established diagnosis of type 2 diabetes (glycated hemoglobin level, 7 to ≤10%) that had been managed with lifestyle modifications alone or with stable treatment with metformin, a sodium–glucose cotransporter 2 inhibitor, or a sulfonylurea (combination or monotherapy). Key exclusions were a history of pancreatitis, recent change in body weight, previous or planned surgery for weight loss, or use of medications that promote weight gain or weight loss. (For full eligibility criteria, see the Supplementary Appendix.)

PROCEDURES

Participants in the obesity cohort were randomly assigned in a 3:3:3:2:2:2:3 ratio to receive 52 weeks of maridebart cafraglutide subcutaneously at a dose of 140, 280, or 420 mg every 4 weeks without dose escalation; or 420 mg every 8 weeks without dose escalation; or 420 mg every 4 weeks with a 4-week dose escalation; or 420 mg every 4 weeks with a 12-week dose escalation; or pla-

cebo, respectively. Participants in the obesity–diabetes cohort were randomly assigned in a 1:1:1:1 ratio to receive 52 weeks of maridebart cafraglutide at a dose of 140, 280, or 420 mg every 4 weeks (all without dose escalation) or placebo, respectively. Randomization was stratified according to sex. In the obesity cohort, enrollment of women was capped at 70%. In the PK-LDI study, participants were randomly assigned in a 1:1:1 ratio to receive maridebart cafraglutide at lower starting doses of 21, 35, or 70 mg on day 1, followed by 70 mg on day 15 and 350 mg on day 29. In addition to standard (unsolicited) adverse-event reporting, we used a modified patient-reported outcome tool used in chemotherapy trials (Modified Index of Nausea, Vomiting, and Retching [M-INVR]) (Fig. S2)[11] to assess the incidence, duration, and frequency of nausea, vomiting, and retching (dry heaves) in the obesity cohort (daily for 7 days after each dose up to week 12) and the PK-LDI study (daily on days 1 through 43).

END POINTS

End points were measured from baseline to week 52. The primary end point was the percent change in body weight. Key secondary end points included weight reduction of at least 5%, at least 10%, at least 15%, or at least 20%; the change in the glycated hemoglobin level; the pharmacokinetics of maridebart cafraglutide; and measures of glucose metabolism. Body composition was explored in a subgroup of participants. Safety assessment included adverse events and serious adverse events.

STATISTICAL ANALYSIS

Power analyses to determine the sample size for each cohort are detailed in the Supplementary Appendix. Efficacy and safety end points were analyzed with data from all randomly assigned participants who received at least one dose of maridebart cafraglutide or placebo. Two estimands were used to assess the primary and key secondary end points: a treatment policy estimand (intention-to-treat approach) used for proof of concept in which differences in the percent change in body weight from baseline to week 52 were estimated regardless of adherence to the trial regimen and data on body weight for participants assigned to receive maridebart cafraglutide who discontinued the drug were imputed with the use of data from participants assigned to receive placebo[17]; and an efficacy estimand (hypothetical approach) that assumed adherence to the trial regimen and no use of glycemic rescue medications (glycemic end points) and assumed the same trajectories for participants who discontinued the trial regimen and those who continued it. Efficacy analyses were performed separately according to cohort. Statistical analyses of continuous end points for the treatment policy estimand were conducted with the use of an analysis-of-covariance model, and the efficacy estimand used a mixed model for repeated measures. Confidence intervals are not adjusted for multiplicity and should not be used for hypothesis testing. (Additional details are provided in the Supplementary Appendix.)

RESULTS

PARTICIPANTS

Part 1 of the trial (conducted from January 2023 through September 2024) included 592 participants (465 in the obesity cohort and 127 in the obesity–diabetes cohort). The demographic and clinical characteristics of the participants at baseline were similar across the trial groups for each cohort (Table 1). The representativeness of the trial population is shown in Table S1. Overall, 72% of the participants completed Part 1 while receiving maridebart cafraglutide or placebo (in the obesity cohort, 67 to 82% across the maridebart cafraglutide groups and 62% in the placebo group; in the obesity–diabetes cohort, 59 to 81% across the maridebart cafraglutide groups and 69% in the placebo group) (Fig. S3). For the PK-LDI study, the demographic and clinical characteristics of the participants are shown in Table S10, and participant disposition is shown in Figure S14.

BODY WEIGHT

In the obesity cohort, the mean percent change in body weight from baseline to week 52 on the basis of the treatment policy estimand ranged from –12.3% (95% confidence interval [CI], –15.0 to –9.7) to –16.2% (95% CI, –18.9 to –13.5) with maridebart cafraglutide, as compared with –2.5% (95% CI, –4.2 to –0.7) with placebo (Table 2, Fig. 1A, and Fig. S4A). The mean percent change on the basis of the efficacy estimand ranged from –16.3% (95% CI, –17.5 to –15.2) to –19.9% (95% CI, –21.4 to –18.4) with maridebart cafraglutide, as compared with –2.6% (95% CI, –3.6 to –1.5) with placebo (Table 2, Fig. 1A, and Fig. S4B).

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

Characteristic	Obesity Cohort								Obesity–Diabetes Cohort				
	Maridebart Cafraglutide, No Dose Escalation			Maridebart Cafraglutide, Dose Escalation (DE)			Placebo (N=78)	Total (N=465)	Maridebart Cafraglutide, No Dose Escalation			Placebo (N=32)	Total (N=127)
	140 mg Every 4 Wk (N=77)	280 mg Every 4 Wk (N=77)	420 mg Every 4 Wk (N=79)	420 mg Every 8 Wk (N=51)	420 mg Every 4 Wk, with 4-Wk DE (N=51)	420 mg Every 4 Wk, with 12-Wk DE (N=52)			140 mg Every 4 Wk (N=31)	280 mg Every 4 Wk (N=32)	420 mg Every 4 Wk (N=32)		
Age — yr	45.6±12.2	49.4±12.6	49.1±13.0	47.6±11.0	49.0±11.4	48.2±12.5	47.0±12.9	47.9±12.3	54.9±12.8	56.8±11.7	55.3±10.3	53.5±10.2	55.1±11.2
Female sex — no. (%)	48 (62)	48 (62)	50 (63)	33 (65)	31 (61)	33 (64)	49 (63)	292 (63)	13 (42)	14 (44)	13 (41)	13 (41)	53 (42)
Race or ethnic group — no. (%)†													
American Indian or Alaska Native	0	0	0	0	0	1 (2)	1 (1)	2 (<0.5)	0	0	0	0	0
Asian	13 (17)	20 (26)	15 (19)	11 (22)	14 (27)	16 (31)	14 (18)	103 (22)	6 (19)	6 (19)	9 (28)	10 (31)	31 (24)
Black	6 (8)	4 (5)	4 (5)	3 (6)	6 (12)	2 (4)	7 (9)	32 (7)	2 (6)	2 (6)	0	5 (16)	9 (7)
White	53 (69)	52 (68)	59 (75)	33 (65)	30 (59)	32 (62)	51 (65)	310 (67)	23 (74)	24 (75)	22 (69)	17 (53)	86 (68)
Native Hawaiian or other Pacific Islander	1 (1)	1 (1)	0	1 (2)	0	0	1 (1)	4 (1)	0	0	0	0	0
Multiple	2 (3)	0	0	2 (4)	0	0	1 (1)	5 (1)	0	0	0	0	0
Other	2 (3)	0	1 (1)	1 (2)	1 (2)	1 (2)	3 (4)	9 (2)	0	0	1 (3)	0	1 (1)
Hispanic or Latino ethnic group — no. (%)†	6 (8)	8 (10)	9 (11)	4 (8)	7 (14)	9 (17)	19 (24)	62 (13)	6 (19)	4 (12)	3 (9)	4 (12)	17 (13)
Body weight — kg	109.9± 26.7	103.4± 18.3	108.6± 25.3	106.9± 28.4	109.3± 21.9	102.3± 19.7	110.1± 31.7	107.4± 25.2	106.0± 24.6	101.0± 16.8	106.7± 26.5	101.8± 18.0	103.9± 21.7
Mean BMI	38.3±7.6	36.6±5.8	38.8±7.8	38.0±8.7	38.3±6.9	36.2±6.2	38.9±8.9	37.9±7.5	36.5±6.8	35.8±6.6	37.1±8.5	36.4±6.3	36.5±7.0
BMI category — no. (%)													
<30	6 (8)	8 (10)	7 (9)	7 (14)	1 (2)	6 (12)	7 (9)	42 (9)	5 (16)	7 (22)	7 (22)	6 (19)	25 (20)
30 to <35	25 (32)	25 (32)	20 (25)	14 (27)	18 (35)	21 (40)	28 (36)	151 (32)	9 (29)	8 (25)	7 (22)	8 (25)	32 (25)
35 to <40	20 (26)	24 (31)	22 (28)	14 (27)	15 (29)	13 (25)	12 (15)	120 (26)	9 (29)	10 (31)	9 (28)	11 (34)	39 (31)
≥40	26 (34)	20 (26)	30 (38)	16 (31)	17 (33)	12 (23)	31 (40)	152 (33)	8 (26)	7 (22)	9 (28)	7 (22)	31 (24)

Waist circumference — cm	114.9±16.3	113.1±13.2	117.3±16.4	114.4±18.4	117.4±14.8	112.0±12.8	116.8±19.6	115.2±16.2	117.8±15.7	116.4±11.8	119.7±16.2	115.0±13.8	117.2±14.4
Prediabetes — no. (%)‡	26 (34)	27 (35)	24 (30)	18 (35)	23 (45)	11 (21)	24 (31)	153 (33)	NA	NA	NA	NA	NA
Glycated hemoglobin — %	5.5±0.4	5.5±0.4	5.5±0.4	5.5±0.4	5.5±0.4	5.5±0.4	5.5±0.4	5.5±0.4	7.8±0.6	7.8±0.7	7.8±0.6	8.0±0.9	7.9±0.7
Systolic blood pressure — mm Hg	125.0±14.3	126.3±16.1	128.6±14.8	126.6±14.1	130.0±13.1	126.2±11.9	125.9±13.7	126.8±14.2	128.3±13.2	131.3±15.6	131.0±19.5	133.9±16.0	131.1±16.2
Diastolic blood pressure — mm Hg	80.5±10.5	79.0±11.4	80.4±10.3	80.9±8.9	82.4±9.9	81.2±8.6	81.9±9.3	80.8±10.0	81.8±8.6	84.5±8.5	80.1±10.5	83.6±9.2	82.5±9.3

* Plus–minus values are means ±SD. The obesity cohort included participants with obesity, and the obesity–diabetes cohort included participants with obesity with type 2 diabetes. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants.
‡ Prediabetes was defined as a glycated hemoglobin level of 5.7% to less than 6.5%.

In the obesity–diabetes cohort, the mean percent change in body weight from baseline to week 52 on the basis of the treatment policy estimand ranged from −8.4% (95% CI, −11.0 to −5.7) to −12.3% (95% CI, −15.3 to −9.2) with maridebart cafraglutide, as compared with −1.7% (95% CI, −2.9 to −0.6) with placebo (Table 2, Fig. 1B, and Fig. S4C). The mean percent change on the basis of the efficacy estimand ranged from −12.1% (95% CI, −14.2 to −10.1) to −17.0% (95% CI, −18.8 to −15.3) with maridebart cafraglutide, as compared with −1.4% (95% CI, −2.5 to −0.3) with placebo (Table 2, Fig. 1B, and Fig. S4D).

The proportions of participants with weight reductions of at least 5%, at least 10%, at least 15%, and at least 20% were numerically higher with maridebart cafraglutide than with placebo (Fig. S6 and Table S3). Waterfall plots of percent change in body weight are shown in Figure S7. Weight change in the PK-LDI study is shown in Figure S15.

ANTHROPOMETRIC AND CARDIOMETABOLIC VARIABLES

From baseline to week 52, treatment with maridebart cafraglutide was associated with greater improvements in glycated hemoglobin levels than placebo (Fig. 1C and 1D, Table 2, and Table S2) in both cohorts. Apparent improvements were observed with respect to other key (Table 2) and additional secondary end points (Table S4 and Fig. S8 through S11), including waist circumference, BMI, systolic blood pressure, diastolic blood pressure, high-sensitivity C-reactive protein (hs-CRP), and select lipid variables. Body composition was assessed by means of dual-energy x-ray absorptiometry (DXA) in a substudy (191 participants in the obesity cohort and 46 participants in the obesity–diabetes cohort) as an exploratory end point, and the analysis showed a greater reduction in fat mass than in lean mass.

Reductions in fat mass ranged from −26.2% to −36.8% in the maridebart cafraglutide groups in the obesity cohort (vs. −9.1% in the placebo group), and reductions in lean mass ranged from −8.6% to −11.6% (vs. −2.1% in the placebo group). Reductions in fat mass ranged from −17.4% to −33.7% in the maridebart cafraglutide groups in the obesity–diabetes cohort (vs. −4.3% in the placebo group), and reductions in lean mass ranged from −6.8% to −9.6% (vs. −2.3% in the placebo group).

Table 2. Primary and Select Key Secondary End Points.*

End Point	Obesity Cohort							Obesity–Diabetes Cohort			
		Maridebart Cafraglutide, No Dose Escalation			Maridebart Cafraglutide, Dose Escalation (DE)		Placebo (N=76)	Maridebart Cafraglutide, No Dose Escalation			Placebo (N=32)
	140 mg Every 4 Wk (N=77)	280 mg Every 4 Wk (N=77)	420 mg Every 4 Wk (N=79)	420 mg Every 8 Wk (N=51)	420 mg Every 4 Wk, with 4-Wk DE (N=51)	420 mg Every 4 Wk, with 12-Wk DE (N=52)		140 mg Every 4 Wk (N=31)	280 mg Every 4 Wk (N=32)	420 mg Every 4 Wk (N=32)	
	estimate (95% CI)										
Treatment policy estimand											
Primary end point											
Mean percent change in body weight	−13.6 (−15.5 to −11.7)	−15.5 (−17.7 to −13.4)	−14.6 (−16.8 to −12.4)	−12.3 (−15.0 to −9.7)	−14.1 (−16.2 to −12.1)	−16.2 (−18.9 to −13.5)	−2.5 (−4.2 to −0.7)	−10.3 (−13.2 to −7.4)	−8.4 (−11.0 to −5.7)	−12.3 (−15.3 to −9.2)	−1.7 (−2.9 to −0.6)
Mean difference vs. placebo — percentage points	−11.1 (−13.6 to −8.7)	−13.1 (−15.6 to −10.6)	−12.2 (−14.8 to −9.5)	−9.9 (−12.8 to −6.9)	−11.7 (−14.3 to −9.1)	−13.8 (−16.8 to −10.7)	NA	−8.6 (−11.6 to −5.6)	−6.6 (−9.3 to −3.9)	−10.5 (−13.6 to −7.4)	NA
Key secondary end points											
Change in glycated hemoglobin — percentage points	−0.3 (−0.4 to −0.3)	−0.4 (−0.5 to −0.3)	−0.3 (−0.3 to −0.2)	−0.3 (−0.4 to −0.2)	−0.3 (−0.4 to −0.3)	−0.3 (−0.4 to −0.3)	0.0 (−0.1 to 0.1)	−1.6 (−1.9 to −1.2)	−1.2 (−1.7 to −0.7)	−1.5 (−1.9 to −1.0)	0.1 (−0.4 to 0.5)
Change in mean fasting serum insulin — μIU/ml	−1.7 (−4.0 to 0.7)	−4.0 (−5.6 to −2.4)	−3.8 (−5.4 to −2.2)	−2.0 (−4.1 to 0.1)	−4.2 (−6.0 to −2.4)	−5.1 (−6.6 to −3.7)	0.0 (−3.4 to 3.4)	−1.7 (−4.7 to 1.3)	0.4 (−2.9 to 3.6)	−2.2 (−5.7 to 1.4)	0.1 (−2.6 to 2.9)
Change in mean fasting plasma glucose — mg/dl	−8.6 (−10.8 to −6.5)	−9.2 (−11.2 to −7.2)	−9.0 (−11.5 to −6.5)	−7.7 (−10.2 to −5.3)	−10.6 (−12.9 to −8.2)	−9.1 (−12.3 to −5.9)	−0.6 (−3.7 to 2.6)	−33.9 (−48.7 to −19.2)	−25.5 (−42.5 to −8.5)	−35.1 (−52.7 to −17.5)	9.2 (−16.8 to 35.1)
Efficacy estimand											
Primary end point											
Mean percent change in body weight	−16.3 (−17.5 to −15.2)	−19.9 (−21.1 to −18.6)	−18.9 (−20.2 to −17.6)	−17.7 (−19.3 to −16.1)	−16.7 (−18.0 to −15.4)	−19.9 (−21.4 to −18.4)	−2.6 (−3.6 to −1.5)	−12.3 (−14.1 to −10.4)	−12.1 (−14.2 to −10.1)	−17.0 (−18.8 to −15.3)	−1.4 (−2.5 to −0.3)
Mean difference vs. placebo — percentage points	−13.8 (−15.3 to −12.2)	−17.3 (−18.9 to −15.7)	−16.3 (−18.0 to −14.6)	−15.1 (−17.1 to −13.2)	−14.2 (−15.8 to −12.5)	−17.4 (−19.2 to −15.6)	NA	−10.9 (−13.0 to −8.7)	−10.7 (−13.1 to −8.4)	−15.7 (−17.8 to −13.6)	NA

Key secondary end points											
Change in glycated hemoglobin — percentage points	−0.4 (−0.5 to −0.3)	−0.4 (−0.5 to −0.4)	−0.4 (−0.4 to −0.3)	−0.4 (−0.5 to −0.3)	−0.4 (−0.5 to −0.3)	−0.4 (−0.5 to −0.3)	0.0 (−0.1 to 0.1)	−1.9 (−2.1 to −1.6)	−2.0 (−2.2 to −1.8)	−2.2 (−2.4 to −2.0)	0.1 (−0.4 to 0.6)
Change in mean fasting serum insulin — μIU/ml	−1.4 (−4.1 to 1.2)	−5.2 (−6.4 to −4.0)	−5.0 (−6.9 to −3.1)	−2.7 (−5.2 to −0.3)	−6.0 (−8.0 to −3.9)	−6.1 (−7.1 to −5.1)	−0.5 (−3.2 to 2.2)	−2.0 (−5.4 to 1.4)	−0.1 (−4.8 to 4.5)	−3.1 (−8.4 to 2.3)	1.2 (−1.6 to 3.9)
Change in mean fasting plasma glucose — mg/dl	−11.4 (−13.3 to −9.5)	−12.3 (−13.8 to −10.9)	−12.7 (−15.1 to −10.3)	−11.7 (−14.0 to −9.5)	−13.0 (−15.3 to −10.7)	−11.7 (−15.3 to −8.1)	−0.5 (−3.7 to 2.7)	−43.6 (−56.1 to −31.0)	−46.4 (−56.5 to −36.4)	−58.2 (−67.4 to −49.0)	22.0 (−8.9 to 53.0)

* End points were measured from baseline to week 52. Values are derived from an analysis of variance for the treatment policy estimand (top part of table) and a mixed-model-for-repeated-measures analysis for the efficacy estimand (bottom part of table). The 95% confidence intervals are not adjusted for multiplicity and should not be used for hypothesis testing.

SIDE-EFFECT PROFILE AND SAFETY

In the obesity cohort, 90 to 99% of participants who received maridebart cafraglutide reported at least one adverse event, irrespective of causality, as compared with 68% with placebo (Table 3). In the obesity–diabetes cohort, 91 to 97% of participants who received maridebart cafraglutide reported at least one adverse event, as compared with 81% with placebo (Table 3). A total of 35 participants reported at least one serious adverse event (Table 3 and Table S5). Two deaths were reported in participants who received maridebart cafraglutide; both deaths were assessed as being unrelated to maridebart cafraglutide by site investigators (Table 3).

Reporting of gastrointestinal adverse events in the electronic data-capture system included unsolicited reporting (without prompt or specific questionnaire), but participants in the phase 2 obesity cohort and the PK-LDI study were additionally solicited to complete the M-INVR patient-reported outcome tool. Whether to include the data captured by the M-INVR tool in the reporting of adverse events in the electronic data-capture system was at the investigator's discretion. The most frequently reported adverse events were gastrointestinal; most were mild to moderate, including nausea, vomiting, constipation, retching (dry heaves), and diarrhea, with a higher incidence in the no-dose-escalation groups and a lower incidence in the groups that included dose escalation and a lower starting dose (Figs. S12 and S16 and Tables S6 and S11). The incidence of discontinuation of maridebart cafraglutide due to gastrointestinal adverse events in the dose-escalation groups was 8% (obesity cohort); by comparison, the incidence in the no-dose-escalation groups was 12 to 27% (obesity cohort) and 6 to 16% (obesity–diabetes cohort). The gastrointestinal adverse events that most frequently led to discontinuation of maridebart cafraglutide were vomiting and nausea (Table 3). No discontinuations of maridebart cafraglutide due to gastrointestinal adverse events occurred in the PK-LDI study; this study was shorter than the phase 2 trial and was not powered to detect the potential differences between study groups.

The incidence of other adverse events was generally balanced across groups in the phase 2 trial. Among predefined adverse events of interest (Table 3), hypersensitivity events were mild or moderate (all nonserious) and included injec-

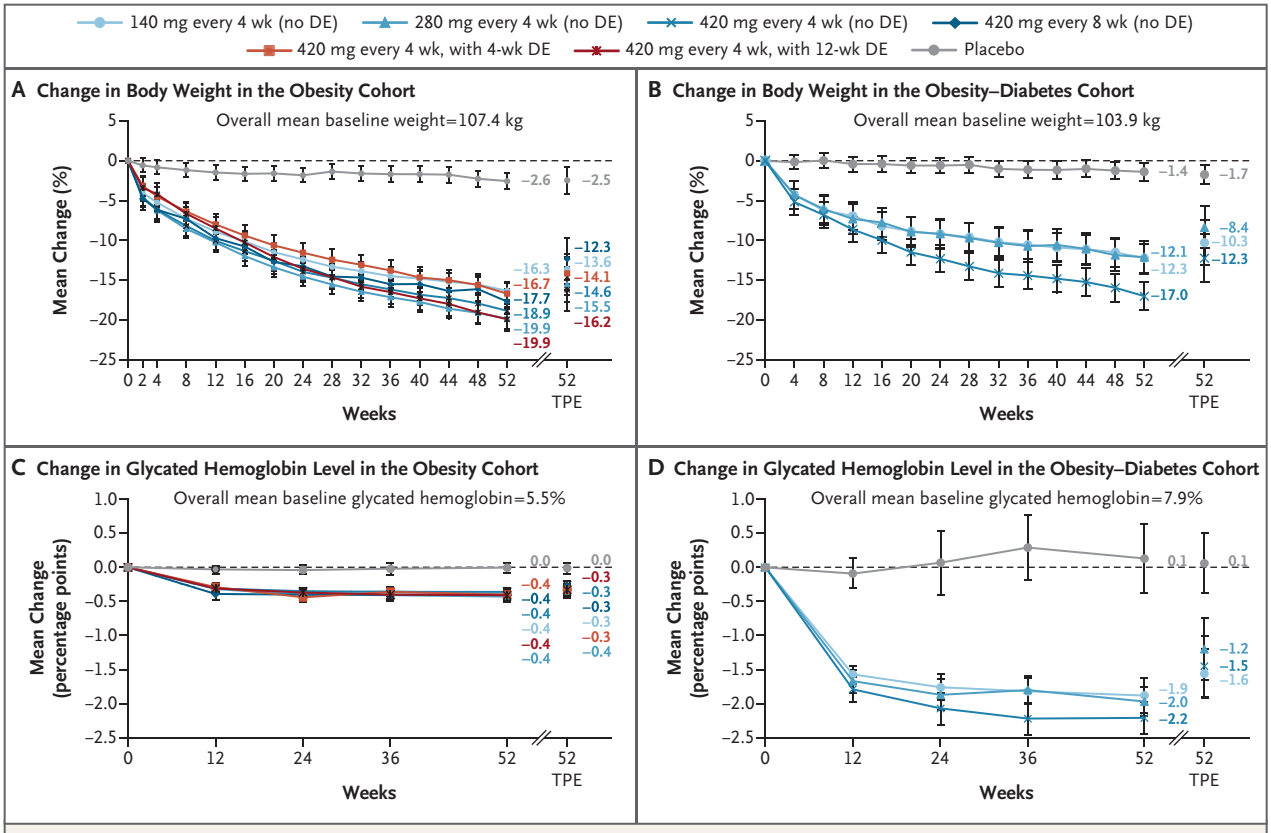


Figure 1. Changes in Body Weight and Glycated Hemoglobin Level with Maridebart Cafraglutide as Compared with Placebo.

The relative change in body weight from baseline to week 52 is shown for participants with obesity (obesity cohort; Panel A) and participants with obesity and type 2 diabetes (obesity–diabetes cohort; Panel B). Pooled values for all maridebart cafraglutide 420-mg dose groups are shown in Figure S5 in the Supplementary Appendix. The absolute change in the glycated hemoglobin level from baseline to week 52 is shown for the obesity cohort (Panel C) and the obesity–diabetes cohort (Panel D). Time-course results are derived from a mixed-model-for-repeated-measures analysis for the efficacy estimand, with week 52 results derived from an analysis of covariance for the treatment policy estimand (52 TPE) overlaid on the right. The values shown are estimated marginal means, with results presented as weeks since the first dose of maridebart cafraglutide or placebo; I bars indicate 95% confidence intervals. The 95% confidence intervals are not adjusted for multiplicity and should not be used for hypothesis testing. DE denotes dose escalation.

tion-site reactions, rash, and urticaria; hypersensitivity events occurred in 5% of participants who received maridebart cafraglutide and 4% of those who received placebo (obesity cohort) and in 3% and 0%, respectively (obesity–diabetes cohort). Gallbladder events were more frequent in the maridebart cafraglutide groups than in the placebo groups (Table 3). Level 2, laboratory-confirmed hypoglycemia (glucose level, <54 mg per deciliter) was reported in 2 participants in the obesity cohort and 3 participants in the obesity–diabetes cohort (who were taking oral glucose-lowering medications) (Table S7). Bone mineral density was measured by DXA in a substudy (191 participants in the obesity cohort and 46 participants in the obesity–diabetes cohort) as an exploratory end point. There were no substantial changes in bone mineral density at the spine, and changes at the hip were not dose-related and were consistent with studies of diet-induced weight loss (Table S8).[17-19] Mood events (e.g., depressive disorder) were infrequent and were mild to moderate in severity; such events led to discontinuation of the trial regimen in 2 participants (1 who received maridebart cafraglutide and 1 who received placebo) (Table 3). In the maridebart cafraglutide groups, heart rate and levels of calcitonin, amylase, and lipase all increased, with mean values remaining within the normal range, whereas liver aminotransferase levels decreased (Table S9). No cases of pancreatitis, diabetic retinopathy, or C-cell hyperplasia were reported.

PHARMACOKINETICS

Plasma levels of maridebart cafraglutide were higher at higher doses (Table S12 and Fig. S17). Plasma levels of the drug were also higher at higher frequencies of administration.

DISCUSSION

This phase 2 dose-ranging trial investigating the efficacy and safety of maridebart cafraglutide, a long-acting GLP-1 receptor agonist and GIP receptor antagonist administered once monthly or less frequently, showed substantial weight reduction and no new or unexpected safety signals, supporting advancement to phase 3. Participants with obesity without type 2 diabetes had mean weight reduction of up to 16.2% (treatment policy estimand [intention-to-treat approach], with imputation of results for participants who discontinued maridebart cafraglutide as if they received placebo, which may result in underestimation of benefits) at 52 weeks without reaching a weight plateau. Participants with obesity and type 2 diabetes had a mean weight reduction of up to 12.3% (treatment policy estimand), accompanied by a mean reduction in the glycated hemoglobin level of up to 1.6 percentage points (treatment policy estimand). On the basis of the efficacy estimand (with imputation of results for participants who discontinued the trial regimen as if they had continued it as intended, which may result in overestimation of benefits), participants in the obesity cohort had a mean weight reduction of up to 19.9%, and participants in the obesity–diabetes cohort had a mean weight reduction of up to 17.0%, accompanied by a mean reduction in the glycated hemoglobin level of up to 2.2 percentage points (Table 2). This degree of weight reduction and glycemic improvement with a once-monthly therapy is otherwise lacking. The safety and the side-effect profile of maridebart cafraglutide were consistent with those of currently available GIP–GLP-1 or GLP-1 receptor agonists,[5,14,18,19] albeit nausea and vomiting were more frequent when no dose escalation was used. Although the findings are not conclusive and require confirmation in a larger, longer trial, the use of a lower starting dose and dose escalation resulted in fewer gastrointestinal adverse events, as shown in the PK-LDI study, which is informing the phase 3 approach to improve the side-effect profile.

Efficacy with respect to weight reduction of at least 15% and at least 20% has been associated with clear improvements in health outcomes.[7,20-25] In this trial, half the participants had a weight reduction of at least 15% with the highest dose (regardless of cohort) on the basis of the treatment policy estimand, and three quarters of the participants had such a reduction on the basis of the efficacy estimand. Approximately 80% of the participants (on the basis of the treatment policy estimand) or nearly all the participants (on the basis of the efficacy estimand) had a weight reduction of at least 5% at 1 year. A weight plateau was not reached at 52 weeks, with weight continuing a downward trajectory; therefore, longer-term trials are needed to assess the full weight efficacy of this agent. Part 2 of this trial will help to determine the weight plateau and nadir and whether weight reduction is maintained with lower doses or less frequent administration.

The evolution of nutrient-stimulated hormone receptor modulators (e.g., semaglutide and tirzepatide) has partly focused on mode of delivery (injectable or oral) and on extending the half-life of therapeutics beyond that of native hormones.[26] The subcutaneous therapeutics have evolved from twice-daily administration[27] to once daily,[28] weekly,[5,14] and now monthly[12,16] — a defining advance for the obesity field.[27] Monthly or potentially less frequent administration of maridebart cafraglutide is enabled by the monoclonal antibody backbone targeting the GIP receptor.[16] Less frequent administration[12,13,29] can potentially mitigate treatment burden[30,31] and improve adherence, persistence, and long-term weight maintenance, factors that could promote improvements in health outcomes for people living with obesity.[9,10]

The antagonism of the GIP receptor by maridebart cafraglutide introduces a new mechanistic insight given that tirzepatide, a GIP receptor agonist and GLP-1 receptor agonist, also leads to substantial weight reduction.[14] Recent preclinical studies using tissue-specific knockout of the central GIP receptor in murine models support the contribution of GIP pathway inhibition to weight reduction with maridebart cafraglutide.[32] Nevertheless, the mechanisms by which both GIP receptor antagonism and agonism, when combined with GLP-1 receptor agonism, are effective at reducing weight have yet to be fully elucidated; several hypotheses have been proposed[8,33,34] and are beyond the scope of this article. This enigma has existed in preclinical mod-

Table 3. Safety and Adverse Events.*

Event	Obesity Cohort							Obesity–Diabetes Cohort			
	Maridebart Cafraglutide, No Dose Escalation			Maridebart Cafraglutide, Dose Escalation (DE)			Placebo (N=76)	Maridebart Cafraglutide, No Dose Escalation			Placebo (N=32)
	140 mg Every 4 Wk (N=77)	280 mg Every 4 Wk (N=77)	420 mg Every 4 Wk (N=79)	420 mg Every 8 Wk (N=51)	420 mg Every 4 Wk, with 4-Wk DE (N=51)	420 mg Every 4 Wk, with 12-Wk DE (N=52)		140 mg Every 4 Wk (n=31)	280 mg Every 4 Wk (N=32)	420 mg Every 4 Wk (N=32)	
	number of participants (percent)										
Overall											
Any adverse event	73 (95)	75 (97)	78 (99)	49 (96)	46 (90)	49 (94)	52 (68)	29 (94)	29 (91)	31 (97)	26 (81)
Serious adverse event	4 (5)	4 (5)	5 (6)	7 (14)	0	3 (6)	5 (7)	1 (3)	2 (6)	4 (12)	0
Death†	0	0	0	0	0	1 (2)	0	0	1 (3)	0	0
Adverse events leading to discontinuation of trial regimen	11 (14)	11 (14)	17 (22)	15 (29)	5 (10)	6 (12)	1 (1)	4 (13)	6 (19)	5 (16)	1 (3)
GI adverse event leading to discontinuation	10 (13)	9 (12)	13 (16)	14 (27)	4 (8)	4 (8)	0	2 (6)	5 (16)	4 (12)	0
Most frequent adverse events leading to discontinuation‡											
Vomiting	9 (12)	8 (10)	12 (15)	12 (24)	3 (6)	1 (2)	0	1 (3)	3 (9)	4 (12)	0
Nausea	6 (8)	7 (9)	11 (14)	8 (16)	3 (6)	1 (2)	0	1 (3)	2 (6)	1 (3)	0
Retching	2 (3)	1 (1)	1 (1)	3 (6)	0	0	0	0	0	0	0
Headache	1 (1)	1 (1)	2 (3)	2 (4)	0	0	0	0	0	0	0
Diarrhea	0	1 (1)	3 (4)	0	1 (2)	0	0	1 (3)	1 (3)	0	0
Fatigue	1 (1)	1 (1)	2 (3)	1 (2)	0	0	0	0	0	0	0
Constipation	2 (3)	1 (1)	1 (1)	0	0	0	0	0	0	0	0
GERD	2 (3)	0	0	1 (2)	0	0	0	0	0	0	0
Injection-site reaction	1 (1)	0	1 (1)	0	1 (2)	0	0	0	0	0	0
Malaise	0	2 (3)	1 (1)	0	0	0	0	0	0	0	0
Most frequent adverse events§											
Nausea	59 (77)	60 (78)	69 (87)	42 (82)	36 (71)	38 (73)	19 (25)	18 (58)	13 (41)	19 (59)	3 (9)
Vomiting	52 (68)	56 (73)	69 (87)	47 (92)	22 (43)	23 (44)	2 (3)	14 (45)	16 (50)	24 (75)	2 (6)
Constipation	23 (30)	19 (25)	19 (24)	18 (35)	12 (24)	11 (21)	4 (5)	4 (13)	3 (9)	6 (19)	0
Retching	13 (17)	11 (14)	18 (23)	11 (22)	5 (10)	8 (15)	1 (1)	1 (3)	2 (6)	2 (6)	0

Diarrhea	8 (10)	5 (6)	17 (22)	6 (12)	7 (14)	10 (19)	4 (5)	3 (10)	5 (16)	5 (16)	3 (9)
Headache	11 (14)	8 (10)	13 (16)	10 (20)	3 (6)	5 (10)	5 (7)	1 (3)	1 (3)	3 (9)	4 (12)
GERD	8 (10)	8 (10)	8 (10)	7 (14)	4 (8)	7 (13)	0	2 (6)	2 (6)	2 (6)	0
Adverse events of special interest¶											
Hypersensitivity	3 (4)	4 (5)	2 (3)	3 (6)	4 (8)	4 (8)	3 (4)	1 (3)	1 (3)	1 (3)	0
Injection-site reactions	10 (13)	5 (6)	8 (10)	0	8 (16)	6 (12)	2 (3)	2 (6)	3 (9)	1 (3)	2 (6)
Severe or serious GI events	6 (8)	2 (3)	9 (11)	5 (10)	1 (2)	1 (2)	0	0	1 (3)	3 (9)	0
Acute renal events	0	0	0	1 (2)	0	0	0	0	0	0	0
Diabetic retinopathy	0	0	0	0	0	0	0	0	0	0	0
Acute pancreatitis	0	0	0	0	0	0	0	0	0	0	0
Acute gallbladder diseases	1 (1)	1 (1)	5 (6)	1 (2)	0	2 (4)	0	0	1 (3)	0	0
C-cell hyperplasia or thyroid cancer	0	0	0	0	0	0	0	0	0	0	0
Heart-rate increase	0	4 (5)	0	1 (2)	1 (2)	0	1 (1)	0	2 (6)	0	2 (6)
Depressive disorder or suicidal behavior or ideation‖	1 (1)	0	4 (5)	5 (10)	1 (2)	0	0	0	0	0	1 (3)
Severe or serious adverse event	0	0	0	1 (2)	0	0	0	0	0	0	0

* Shown are adverse events during the treatment period regardless of causality. GERD denotes gastroesophageal reflux disease, and GI gastrointestinal.

† Two deaths were reported in participants who received maridebart cafraglutide; both deaths were assessed as being unrelated to maridebart cafraglutide by the site investigator. A participant in the obesity cohort died of traumatic intracranial hemorrhage 2 months after starting maridebart cafraglutide. A participant in the obesity–diabetes cohort had sudden cardiac death 8 months after starting maridebart cafraglutide, with underlying cardiovascular risk factors (Table S5).

‡ Shown are adverse events that led to discontinuation in 3 or more participants who received maridebart cafraglutide, including both cohorts.

§ Shown are adverse events that were reported in 10% or more of the participants in the maridebart cafraglutide groups (combining all dose groups within a cohort) in either the obesity cohort or the obesity–diabetes cohort.

¶ Adverse events of special interest were evaluated with the use of prespecified standardized *Medical Dictionary for Regulatory Activities* (MedDRA) search queries or customized clusters of MedDRA preferred terms. Mood adverse events include depressive disorder and suicidal behavior or ideation and were evaluated with the prespecified standardized MedDRA search query of MedDRA preferred terms.

‖ The severity of mood changes was mild (in 9 participants) and moderate (in 3 participants); one of the moderate events was a serious adverse event (Table S5). A serious adverse event of suicidal ideation associated with an interrupted suicide attempt resulted in the discontinuation of maridebart cafraglutide in this participant. In addition, 1 participant in the placebo group discontinued the trial regimen owing to suicidal ideation.

els[32,35] for decades and is now addressed here in a well-controlled study showing weight reduction and glycemic improvement in humans with a combined GLP-1 receptor agonist and GIP receptor antagonist.

A consistent observation from clinical trials with nutrient-stimulated hormone receptor modulators is that persons with obesity and type 2 diabetes lose less weight than those without type 2 diabetes[5,14,18,19]; the mechanisms of the response are unknown. We found that participants with type 2 diabetes lost only slightly less weight than those without type 2 diabetes (differences of approximately 3 to 4 percentage points between the obesity cohort and the obesity–diabetes cohort). Participants in the obesity–diabetes cohort lost on average up to 12% of body weight on the basis of the treatment policy estimand (up to 17% on the basis of the efficacy estimand), with few agents to date resulting in such a magnitude of reduction in persons with type 2 diabetes[19,36] and none that are administered once monthly.

Weight reduction with maridebart cafraglutide was accompanied by improvements in prespecified cardiometabolic measures. Participants in the obesity–diabetes cohort had a baseline mean glycated hemoglobin of 7.9%; at 52 weeks, 81 to 87% of the participants in the maridebart cafraglutide groups had a glycated hemoglobin level of 6.5% or less (vs. 9% in the placebo group), and 30 to 70% had normoglycemia with a glycated hemoglobin level of less than 5.7% (none reached this threshold in the placebo group). Among participants in the obesity cohort who had prediabetes at baseline and had data on the glycated hemoglobin level at week 52 (approximately one third), 70 to 95% reverted to normoglycemia with maridebart cafraglutide, as compared with 17% with placebo. Given the contribution of obesity to the development of type 2 diabetes, achieving normoglycemic levels is becoming a treatment goal.[20] Improvements were also observed in systolic blood pressure, diastolic blood pressure, and the hs-CRP level.

The safety profile of maridebart cafraglutide was consistent with phase 1 findings and similar to that of other nutrient-stimulated hormone receptor modulators.[16] A degree of ascertainment bias may have existed for some gastrointestinal adverse events, because the M-INVR was used as an additional, more rigorous way to assess the side-effect profile than standard (unsolicited) adverse event reporting that is conventionally used to assess adverse events in obesity trials. This hypothesis is supported by the unusually high reported incidence of nausea (25%) with placebo (obesity cohort), although the incidence of vomiting is more objective.

As with other nutrient-stimulated hormone (GLP-1, GIP, glucagon, and amylin)[2] receptor modulators, use of dose escalation and lower starting doses (PK-LDI study) resulted in a better side-effect profile than no dose escalation and a higher starting dose. As highlighted in the PK-LDI study, the lowest incidence of gastrointestinal adverse events was observed in the group with the lowest starting dose (21 mg), with an incidence of vomiting of 2% in the first 2 weeks, as compared with 32% with a higher starting dose (70 mg). In the groups that received a high initial dose (with or without dose escalation), most of the nausea and vomiting occurred with the first dose, and the incidence markedly decreased with each subsequent dose. Accordingly, the incidence of discontinuation of maridebart cafraglutide due to gastrointestinal adverse events was lower in the dose-escalation groups than in the no-dose-escalation groups (phase 2 trial) and lowest in groups with lower starting doses (PK-LDI study). Of note, the use of a lower starting dose or dose escalation did not appear to affect overall efficacy with respect to weight reduction as assessed (at week 52 in the phase 2 trial or day 36 in the PK-LDI study). Taken together, the results support initiation of maridebart cafraglutide at a lower starting dose and with more gradual dose escalation. In phase 3 trials (ClinicalTrials.gov numbers, NCT06858839 and NCT06858878), dose escalation is being implemented in all the trial groups with a more gradual approach than that used in the phase 2 trial or PK-LDI study.

Strengths of this phase 2 trial include the use of sites worldwide to increase generalizability (22 to 24% of the participants in the two cohorts were Asian), the 52-week trial duration (relatively long for early-phase obesity trials), assessment of monthly (or less frequent) treatment, and the use of the M-INVR to more precisely assess gastrointestinal adverse events. The latter may also be considered a limitation, given the potential for ascertainment bias (and the results are not directly comparable to those in other obesity trials), but the M-INVR does provide data to better inform phase 3 design. Limitations also includ-

ed several groups that did not use dose escalation, which substantially increased the likelihood of gastrointestinal adverse events, and although Part 1 of the trial spanned 1 year, it was of insufficient duration to determine maximum weight reduction; Part 2 will help address this question. Additional limitations include a relatively small size, given the number of groups, which limits the power to detect differences among groups; the limited number of escalation schemes (to assess their usefulness in reducing the gastrointestinal adverse events); and limited comparability between the PK-LDI study and the phase 2 trial. Finally, although the efficacy estimand involves a hypothetical approach to estimate the treatment effect under the assumption of optimal circumstances — including full adherence to treatment, regardless of the occurrence of intercurrent events, such as adverse events — and thus may overestimate the results, the treatment policy estimand in this trial imputed missing end-point data for participants who discontinued maridebart cafraglutide or placebo with the use of data from participants assigned to receive placebo and disregards any observed long-lasting weight reduction in the phase 1 study[16] (i.e., 150 days of durable weight reduction and maintenance after the last dose) and thus may underestimate the results. Ongoing phase 3 trials are assessing the efficacy and safety of maridebart cafraglutide as a potential once-monthly or less frequent medicine for obesity.

In this phase 2 trial, once-monthly maridebart cafraglutide resulted in substantial, clinically important weight reduction in participants with obesity with or without type 2 diabetes.

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