ORIGINAL ARTICLE

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

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ABSTRACT

BACKGROUND

Retatrutide (LY3437943) is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors. Its dose–response relationships with respect to side effects, safety, and efficacy for the treatment of obesity are not known.

METHODS

We conducted a phase 2, double-blind, randomized, placebo-controlled trial involving adults 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 who had a BMI of 27 to less than 30 plus at least one weight-related condition. Participants were randomly assigned in a 2:1:1:1:1:2:2 ratio to receive subcutaneous retatrutide (1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. The primary end point was the percentage change in body weight from baseline to 24 weeks. Secondary end points included the percentage change in body weight from baseline to 48 weeks and a weight reduction of 5% or more, 10% or more, or 15% or more. Safety was also assessed.

RESULTS

We enrolled 338 adults, 51.8% of whom were men. The least-squares mean percentage change in body weight at 24 weeks in the retatrutide groups was –7.2% in the 1-mg group, –12.9% in the combined 4-mg group, –17.3% in the combined 8-mg group, and –17.5% in the 12-mg group, as compared with –1.6% in the placebo group. At 48 weeks, the least-squares mean percentage change in the retatrutide groups was –8.7% in the 1-mg group, –17.1% in the combined 4-mg group, –22.8% in the combined 8-mg group, and –24.2% in the 12-mg group, as compared with –2.1% in the placebo group. At 48 weeks, a weight reduction of 5% or more, 10% or more, and 15% or more had occurred in 92%, 75%, and 60%, respectively, of the participants who received 4 mg of retatrutide; 100%, 91%, and 75% of those who received 8 mg; 100%, 93%, and 83% of those who received 12 mg; and 27%, 9%, and 2% of those who received placebo. The most common adverse events in the retatrutide groups were gastrointestinal; these events were dose-related, were mostly mild to moderate in severity, and were partially mitigated with a lower starting dose (2 mg vs. 4 mg). Dose-dependent increases in heart rate peaked at 24 weeks and declined thereafter.

CONCLUSIONS

In adults with obesity, retatrutide treatment for 48 weeks resulted in substantial reductions in body weight. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT04881760.)

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*A full list of the Retatrutide Phase 2 Obesity Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Obesity is a chronic, treatable, neurometabolic disease that is projected to affect nearly a quarter of the world population by 2035.[1] Until recently, advances in the development of pharmacotherapeutic agents for the treatment of obesity were modest. With the introduction of semaglutide and tirzepatide (now in phase 3 trials), the obesity treatment landscape appears to be transforming rapidly, with potentially highly effective nutrient-stimulated hormone-based therapeutics in development that target the neuroendocrine mechanisms underlying obesity.[2-7] Such novel medications engage with one or more G-protein–coupled receptor targets, including glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon (GCG), amylin, oxyntomodulin, and peptide YY receptors that appear to affect the regulation of body-fat mass and energy homeostasis.[8] Several GLP-1–GCG and GIP–GLP-1–GCG receptor agonists are currently in clinical development, given the premise that incorporating GCG receptor agonism may further reduce energy intake, increase energy expenditure, or both, thus potentially enhancing efficacy.[9-11]

Retatrutide (LY3437943; Eli Lilly) is a single peptide conjugated to a fatty diacid moiety and has agonism toward the GIP, GLP-1, and GCG receptors. As compared with the endogenous receptor ligands, retatrutide is less potent at the human GCG and GLP-1 receptors (by a factor of 0.3 and 0.4, respectively) and is more potent at the human GIP receptor (by a factor of 8.9).[12] The pharmacokinetics of retatrutide are considered dose-proportional; it has a half-life of approximately 6 days,[13] which enables weekly administration. In a phase 1b trial involving participants with type 2 diabetes, treatment with retatrutide resulted in a placebo-adjusted least-squares mean weight reduction of 8.96 kg (approximately 10%) in the highest-dose (12-mg) group after 12 weeks.[13] In the phase 2 trial described here, we investigated the efficacy, side effects, and safety of retatrutide at various doses and dose-escalation regimens in persons with obesity who did not have type 2 diabetes.

Methods

Trial Design

We conducted this phase 2, multicenter, randomized, double-blind, placebo-controlled trial in the United States (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol is available 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. All the participants provided written, informed consent before participation. The sponsor (Eli Lilly) designed and oversaw the conduct of the trial, investigators at the trial sites were responsible for data collection, and the sponsor undertook site monitoring, data collation, and data analysis. The first draft of the manuscript was written by the first author (one of the academic authors) and the last author (an employee of the sponsor). All the authors participated in interpretation of the data and critical review of the submitted manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

Participants

Persons who were 18 to 75 years of age and either had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 to 50 or had a BMI of 27 to less than 30 in addition to at least one weight-related condition were eligible to participate. Key exclusion criteria were diabetes, previous or planned surgical treatment for obesity, and treatment with medication that promotes weight loss or gain or a change in body weight of more than 5 kg within 3 months before screening. Enrollment was actively managed to achieve approximately equal percentages of women and men. A full list of the eligibility criteria is provided in the Supplementary Appendix.

Procedures

Participants were randomly assigned in a 2:1:1:1:1:2:2 ratio (with stratification according to sex and BMI [<36 or ≥36]) to receive retatrutide at a dose of 1 mg, 4 mg with an initial dose of 2 mg, 4 mg with an initial dose of 4 mg, 8 mg with an initial dose of 2 mg, 8 mg with an initial dose of 4 mg, or 12 mg with an initial dose of 2 mg or to receive placebo — all administered subcutaneously once weekly for 48 weeks. For participants who were assigned to receive a retatrutide dose of 4 mg or higher, treatment was initiated with a retatrutide dose of either 2 mg

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

Characteristic	Placebo Group (N=70)	Retatrutide Groups						Overall (N=338)
		1 mg (N=69)	4 mg (ID, 2 mg) (N=33)	4 mg (ID, 4 mg) (N=34)	8 mg (ID, 2 mg) (N=35)	8 mg (ID, 4 mg) (N=35)	12 mg (ID, 2 mg) (N=62)	
Age — yr	48.0±12.5	50.6±13.3	50.8±11.9	46.8±14.1	46.1±13.5	48.7±11.1	45.8±12.2	48.2±12.7
Female sex — no. (%)	34 (49)	33 (48)	16 (48)	16 (47)	17 (49)	17 (49)	30 (48)	163 (48)
Race or ethnic group — no. (%)†								
American Indian or Alaska Native	0	0	0	1 (3)	0	0	1 (2)	2 (1)
Asian	2 (3)	0	0	0	1 (3)	0	1 (2)	4 (1)
Black	8 (11)	6 (9)	4 (12)	2 (6)	4 (11)	1 (3)	2 (3)	27 (8)
White	59 (84)	61 (88)	29 (88)	30 (88)	30 (86)	33 (94)	56 (90)	298 (88)
Native Hawaiian or other Pacific Islander	0	1 (1)	0	0	0	0	0	1 (<1)
Multiple	1 (1)	0	0	1 (3)	0	1 (3)	2 (3)	5 (1)
Hispanic or Latino ethnic group — no. (%)†	22 (31)	23 (33)	9 (27)	14 (41)	15 (43)	12 (34)	22 (35)	117 (35)
Duration of obesity — yr	11.7±9.3	13.7±12.9	15.6±12.5	11.5±8.2	12.8±9.6	15.2±12.3	12.1±9.7	13.0±10.8
Body weight — kg	109.2±20.9	106.4±19.8	108.0±26.3	107.0±21.3	106.5±21.6	108.6±20.9	108.0±21.7	107.7±21.4
BMI‡	37.3±5.9	37.5±5.9	37.3±5.9	37.4±4.7	37.4±6.0	37.0±5.5	37.4±6.0	37.3±5.7
BMI category — no. (%)‡								
<30	5 (7)	3 (4)	0	0	2 (6)	2 (6)	2 (3)	14 (4)
≥30 to <35	24 (34)	26 (38)	15 (45)	16 (47)	11 (31)	14 (40)	24 (39)	130 (38)
≥35 to <40	20 (29)	20 (29)	7 (21)	8 (24)	12 (34)	9 (26)	16 (26)	92 (27)
≥40	21 (30)	20 (29)	11 (33)	10 (29)	10 (29)	10 (29)	20 (32)	102 (30)
Waist circumference — cm	115.1±13.9	114.8±14.7	117.2±16.6	115.2±14.2	114.3±14.3	115.6±12.7	116.5±16.4	115.5±14.7
Prediabetes — no. (%)§	26 (37)	27 (39)	15 (45)	10 (29)	11 (31)	15 (43)	19 (31)	123 (36)
Hypertension — no. (%)	40 (57)	30 (43)	15 (45)	12 (35)	12 (34)	13 (37)	22 (35)	144 (43)
Dyslipidemia — no. (%)	23 (33)	22 (32)	14 (42)	12 (35)	11 (31)	9 (26)	19 (31)	110 (33)

* Plus–minus values are means ±SD. ID denotes initial dose.
† Race and ethnic group were reported by the participants.
‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. The range of BMIs at baseline in this trial was 27.3 to 50.6.
§ Prediabetes was defined as a glycated hemoglobin level of 5.7% to less than 6.5%.

or 4 mg, followed by gradual dose escalation every 4 weeks for up to 12 weeks. After the 48-week treatment period, participants proceeded to a 4-week safety follow-up period (Fig. S1 in the Supplementary Appendix). All the participants received a lifestyle intervention, including regular counseling sessions that were delivered by a dietitian or qualified health care professional and were based on U.S. government guidelines for a healthy diet and physical activity.[14,15] The protocol did not require a specific energy deficit for the diet.

END POINTS AND ASSESSMENTS

The primary end point was the percentage change in weight from baseline to 24 weeks, an early assessment of efficacy. Trial-site personnel and trial team members responsible for oversight remained unaware of the trial-group assignments after the interim 24-week analyses until all participants had completed the trial and the database was locked. The secondary end points were the percentage change in weight from baseline to 48 weeks, a weight reduction of 5% or more, 10% or more, and 15% or more at 24 and 48 weeks; and the change from baseline at 24 and 48 weeks in weight, BMI, and waist circumference. Prespecified exploratory end points included a weight reduction of 20% or more, 25% or more, and 30% or more at 24 and 48 weeks; the change from baseline to 24 and 48 weeks in the glycated hemoglobin level, fasting glucose level, insulin and lipid levels, and the domain scores on the 36-Item Short Form Health Survey (SF-36), version 2, acute form; and the change from baseline to 24 and 36 weeks in the heart rate and systolic and diastolic blood pressure, as assessed by 24-hour ambulatory blood-pressure monitoring. Changes in antihypertensive medications over the entire duration of the trial period were noted. Safety assessments included assessments of adverse events and serious adverse events and laboratory assessments in accordance with the protocol.

STATISTICAL ANALYSIS

We estimated that a sample of 300 participants would provide at least 97% power to show the superiority of each retatrutide dose to placebo with respect to the primary end point at a two-sided significance level of 0.05. For the sample-size calculation, we assumed at least an 8-percentage-point difference in the mean percentage weight change from baseline to week 24 between each retatrutide group and the placebo group, a common standard deviation of 10%, and a dropout rate of 20%.

Efficacy end points were analyzed with data from all the participants who underwent randomization, excluding those who discontinued treatment because of inadvertent enrollment (i.e., those who underwent randomization but did not fully meet inclusion criteria or met exclusion criteria), and safety end points were analyzed with data from all the participants who underwent randomization and took at least one dose of retatrutide or placebo. The estimand used to assess treatment efficacy was an "efficacy" estimand, representing the mean treatment effect of retatrutide relative to placebo for all participants who had undergone randomization, if the treatment was administered as intended (according to the hypothetical strategy in the International Council for Harmonisation E9 [R1] addendum).[16] A "hybrid" estimand was also used in supplementary efficacy analyses. Details regarding the estimands, the handling of missing values, and the statistical analysis methods are provided in the Supplementary Appendix. All reported results are for the efficacy estimand unless stated otherwise. No adjustment for multiplicity was performed when calculating the sample size or reporting hypothesis test results and confidence intervals, and therefore the confidence intervals should not be used to infer definitive treatment effects.

RESULTS

PARTICIPANT CHARACTERISTICS

The trial was conducted from May 2021 through November 2022 and included 338 participants. The demographic and baseline clinical characteristics of the participants were generally similar among the treatment groups (Table 1 and Table S1). The representativeness of the trial population and sex-specific demographic characteristics are shown in Tables S2 and S3; 52% of the participants were men. Overall, 81% of the participants completed the 52-week trial (76% to 87% across the retatrutide groups and 71% in the placebo group), and 78% of the participants completed the course of retatrutide or placebo in the 48-week treatment period (74% to 88% across retatrutide groups and 71% in the placebo group) (Fig. S2).

Table 2. Primary and Secondary End Points.*

End Point	Placebo Group (N=70)	Retatrutide Groups					
		1 mg (N=69)	4 mg (ID, 2 mg) (N=33)	4 mg (ID, 4 mg) (N=34)	8 mg (ID, 2 mg) (N=35)	8 mg (ID, 4 mg) (N=35)	12 mg (ID, 2 mg) (N=62)
Primary end point (at 24 wk)							
Least-squares mean percentage change in body weight (95% CI)	−1.6 (−2.7 to −0.5)	−7.2 (−8.5 to −5.9)	−11.8 (−13.3 to −10.2)	−13.9 (−15.9 to −11.9)	−16.7 (−18.4 to −15.1)	−17.9 (−19.7 to −16.1)	−17.5 (−18.8 to −16.1)
Least-squares mean difference from placebo (95% CI) — percentage points	—	−5.6 (−7.3 to −3.9)	−10.1 (−12.0 to −8.3)	−12.3 (−14.6 to −10.0)	−15.1 (−17.1 to −13.2)	−16.3 (−18.3 to −14.2)	−15.8 (−17.6 to −14.1)
Secondary end points (at 48 wk)							
Least-squares mean percentage change in body weight	−2.1 (−3.5 to −0.7)	−8.7 (−10.5 to −6.8)	−16.3 (−19.4 to −13.2)	−17.8 (−20.8 to −14.8)	−21.7 (−24.5 to −19.0)	−23.9 (−26.8 to −20.9)	−24.2 (−26.6 to −21.8)
Least-squares mean difference from placebo (95% CI) — percentage points	—	−6.6 (−8.9 to −4.2)	−14.2 (−17.6 to −10.8)	−15.7 (−19.1 to −12.4)	−19.6 (−22.7 to −16.5)	−21.8 (−25.1 to −18.5)	−22.1 (−24.9 to −19.3)
Weight reduction of ≥5% — % of participants†	27	64	87	97	100	100	100
Weight reduction of ≥10% — % of participants†	9	27	73	76	90	91	93
Weight reduction of ≥15% — % of participants†	2	16	55	64	73	77	83
Least-squares mean change in weight from baseline (95% CI) — kg	−1.8 (−3.5 to −0.2)	−9.4 (−11.4 to −7.3)	−17.3 (−20.8 to −13.8)	−19.1 (−22.7 to −15.6)	−23.5 (−26.7 to −20.4)	−25.9 (−29.2 to −22.6)	−26.2 (−28.8 to −23.6)
Least-squares mean change in BMI from baseline (95% CI)	−0.7 (−1.3 to −0.2)	−3.2 (−3.9 to −2.5)	−6.1 (−7.4 to −4.9)	−6.7 (−7.8 to −5.5)	−8.1 (−9.2 to −7.0)	−9.0 (−10.1 to −7.9)	−9.1 (−10.0 to −8.2)
Least-squares mean change in waist circumference from baseline (95% CI) — cm	−2.6 (−4.6 to −0.7)	−6.5 (−8.7 to −4.3)	−14.6 (−17.6 to −11.5)	−14.9 (−18.2 to −11.5)	−18.5 (−21.4 to −15.7)	−18.5 (−21.5 to −15.5)	−19.6 (−22.1 to −17.1)

* Efficacy end points were analyzed with data from all the participants who underwent randomization, excluding those who discontinued treatment because of inadvertent enrollment.
† Percentages were calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.

CHANGES IN BODY WEIGHT

In the analysis of the primary end point, the least-squares mean change in weight at week 24 was –7.2% in the 1-mg group, –11.8% in the 4-mg group with an initial dose of 2 mg, –13.9% in the 4-mg group with an initial dose of 4 mg, –16.7% in the 8-mg group with an initial dose of 2 mg, –17.9% in the 8-mg group with an initial dose of 4 mg, and –17.5% in the 12-mg group with an initial dose of 2 mg, as compared with –1.6% in the placebo group (Table 2 and Table S4; results of an analysis of a hybrid estimand are shown in Table S5). In the combined 4-mg group (i.e., including participants who received either initial dose), the change was –12.9%; in the combined 8-mg group, the change was –17.3%.

The least-squares mean percentage change in weight at 48 weeks (secondary end point) was –8.7% in the 1-mg group, –16.3% in the 4-mg group with an initial dose of 2 mg, –17.8% in the 4-mg group with an initial dose of 4 mg, –21.7% in the 8-mg group with an initial dose of 2 mg, –23.9% in the 8-mg group with an initial dose of 4 mg, and –24.2% in the 12-mg group with an initial dose of 2 mg, as compared with –2.1% in the placebo group (Fig. 1A and

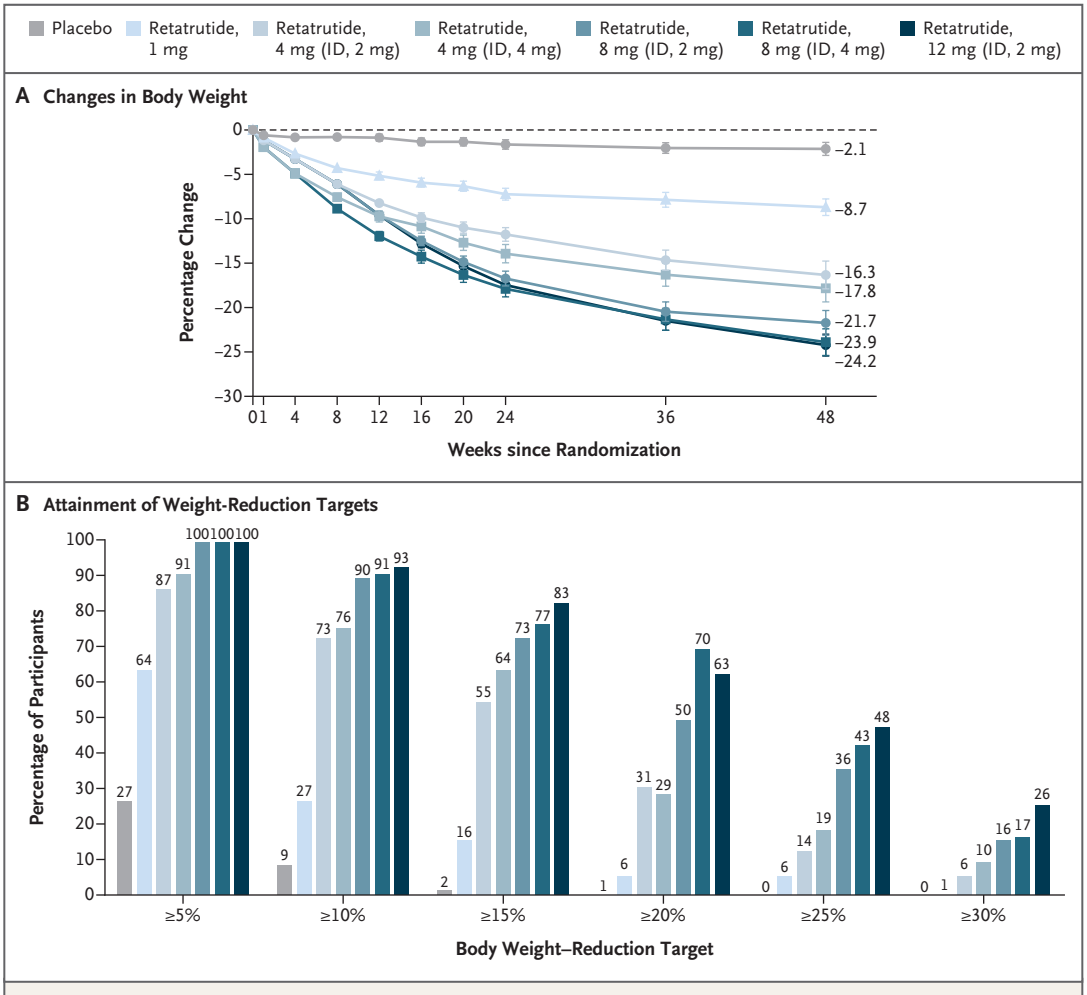

Figure 1. Changes in Body Weight with Retatrutide as Compared with Placebo.

Panel A shows the percentage change in body weight from baseline to week 48, derived from a mixed model for repeated measures (MMRM) analysis for the efficacy estimand. The values shown are least-squares means; I bars indicate standard errors. Panel B shows the percentages of participants with percentage body-weight reductions of at least 5%, 10%, 15%, 20%, 25%, and 30% from baseline to week 48. Efficacy end points were analyzed with data from all the participants who underwent randomization, excluding those who discontinued treatment because of inadvertent enrollment. ID denotes initial dose.

Table 2 and Figs. S4 and S5). In the combined 4-mg group, the change at 48 weeks was –17.1%; in the combined 8-mg group, the change was –22.8%. The estimated difference from placebo in the percentage change in weight at 48 weeks ranged from –6.6 to –22.1 percentage points in the retatrutide groups (Table 2).

At 48 weeks, 64 to 100% of participants in the retatrutide groups had body-weight reductions of 5% or more, as compared with 27% of the participants in the placebo group. Higher percentages of participants had reductions in body weight of 10% or more and 15% or more with retatrutide (all doses) than with placebo (Fig. 1B and Table 2). At 48 weeks, a weight reduction of 5% or more, 10% or more, and 15% or more had been reached in 92%, 75%, and 60%, respectively, of the participants who received 4 mg of retatrutide (at either starting dose); in 100%, 91%, and 75% of those who received 8 mg (at either starting dose); and in 100%, 93%, and 83% of those who received 12 mg. The mean changes in waist circumference with retatrutide ranged from –6.5 cm to –19.6 cm, as compared with –2.6 cm with placebo (Table 2 and Fig. S6). The results for secondary end points at 24 weeks are shown in Table S4.

Body-weight reductions of 20% or more and 25% or more were more common among the participants who received retatrutide at a dose of at least 4 mg than among those who received placebo. In the 12-mg retatrutide group, 26% of the participants had a body-weight reduction of 30% or more (Fig. 1B and Table S6). Prespecified analyses showed that greater percentage reductions in weight were attained with retatrutide among participants with a BMI of 35 or more than among those with a BMI of less than 35 and among female participants than among male participants (Fig. 2 and Table S7).

CARDIOMETABOLIC RISK FACTORS AND PARTICIPANT-REPORTED OUTCOMES

Treatment with retatrutide was associated with improvements in cardiometabolic measures (exploratory end points) including systolic and diastolic blood pressure and levels of glycated hemoglobin, fasting glucose, insulin, and lipids (with the exception of high-density lipoprotein [HDL] cholesterol) at weeks 24 and 48 (Tables S6 and S8 and Figs. S7 and S8). At week 48, 72% of the participants who had prediabetes at baseline in the retatrutide groups had reverted to normoglycemia (glycated hemoglobin level, <5.7%), as compared with 22% of the participants in the placebo group. Improvements in blood pressure within the 48-week treatment period resulted in discontinuation of at least one antihypertensive medication in 41% of the participants in the combined 8-mg group and in 30% of the participants in the 12-mg group. At week 48, improved scores on five of the eight domains on the SF-36 (exploratory end point) and the physical component summary score were noted in some retatrutide dose groups, without a clear dose–response relationship (Table S9).

SAFETY

Overall, adverse events during the treatment period were reported in 70% of the participants in the placebo group and in 73 to 94% of the participants in the retatrutide groups, with the highest incidence in the 8-mg and 12-mg groups (Table 3 and Table S10). Discontinuation of retatrutide or placebo due to adverse events occurred in 6 to 16% of the participants who received retatrutide and in none of the participants who received placebo (Table 3). The most frequently reported adverse events were gastrointestinal (nausea, diarrhea, vomiting, and constipation) and occurred more frequently with retatrutide than with placebo. Gastrointestinal adverse events in the retatrutide groups occurred primarily during dose escalation, were predominantly mild to moderate in severity, were more frequent in higher-dose groups, were partially mitigated by the use of a lower starting dose (2 mg vs. 4 mg), and were the most common adverse events leading to treatment discontinuation (Table 3 and Fig. S9). Fourteen participants had a decrease in BMI to 22 or lower (1 in the placebo group and 13 in the retatrutide groups); 8 participants who received retatrutide had protocol-driven dose reductions because of decreased BMI, but none of these participants met the criteria for treatment discontinuation. No participant had a decrease in BMI to 19 or lower.

Fifteen serious adverse events occurred in 13 participants, with similar frequencies in the retatrutide group and the placebo group (4% in both groups) (Table 3 and Table S11). One death due to drowning occurred in a participant who received retatrutide and was assessed by the site investigator as not related to retatrutide. Transient

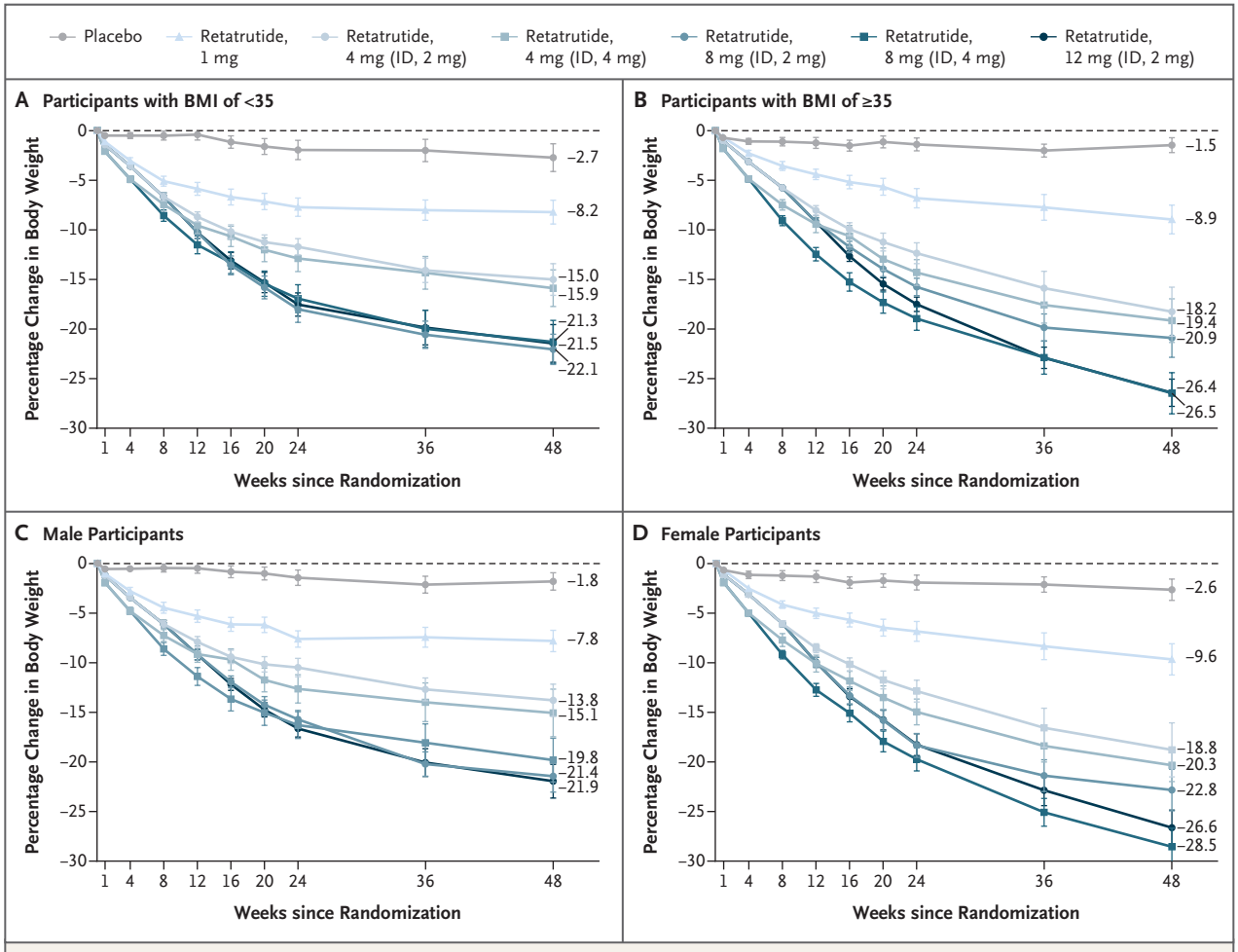

Figure 2. Changes in Body Weight with Retatrutide as Compared with Placebo in Prespecified Exploratory Subgroups.

The values shown are least-squares mean percentage changes in body weight from baseline to week 48, derived from an MMRM analysis for the efficacy estimand; I bars indicate standard errors. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Efficacy end points were analyzed with data from all the participants who underwent randomization, excluding those who discontinued treatment because of inadvertent enrollment.

increases in alanine aminotransferase (ALT) levels to more than 3 times the upper limit of the normal range occurred in 1% of the participants who received retatrutide; the mean ALT and aspartate aminotransferase (AST) levels were unchanged or had decreased at week 48. Increases in amylase and lipase levels were asymptomatic with the exception of one serious adverse event (acute pancreatitis) (Table S12). The heart rate increased in a dose-dependent manner with retatrutide up to 24 weeks and then declined thereafter (Tables S6 and S8 and Fig. S10). Reported cardiac arrhythmias were mild to moderate in severity with the exception of one severe adverse event (prolonged QT syndrome) in a participant treated with ondansetron (Table S13). No cases of clinically significant hypoglycemia (i.e., level 2 [glucose level, <54 mg per deciliter] or level 3 [severe event characterized by altered mental or physical status and necessitating assistance for treatment of hypoglycemia]), medullary thyroid cancer, or C-cell hyperplasia were reported. Cutaneous hyperesthesia and skin sensitivity adverse events were reported in 7% of the participants who received retatrutide and 1% of those who received placebo (Table 3 and Table S14). None of these events were severe or serious or were associated with overt skin findings, and none led to discontinuation of retatrutide or placebo. (A summary of the doses being taken at

Table 3. Adverse Events and Safety.*

Adverse Event	Placebo Group (N = 70)	Retatrutide Groups					Overall (N = 337)
		1 mg (N = 69)	4 mg (ID, 2 mg) (N = 33)	4 mg (ID, 4 mg) (N = 33)	8 mg (ID, 2 mg) (N = 35)	8 mg (ID, 4 mg) (N = 35)	12 mg (ID, 2 mg) (N = 62)	
	number of participants (percent)							
Any adverse event during treatment	49 (70)	58 (84)	24 (73)	28 (85)	28 (80)	33 (94)	57 (92)	277 (82)
Serious adverse event	3 (4)	3 (4)	0	2 (6)	1 (3)	2 (6)	2 (3)	13 (4)
Death†	0	0	0	1 (3)	0	0	0	1 (<1)
Adverse events leading to discontinuation of retatrutide or placebo‡								
Any event	0	5 (7)	2 (6)	3 (9)	5 (14)	2 (6)	10 (16)	27 (8)
Nausea	0	0	0	0	1 (3)	0	3 (5)	4 (1)
Vomiting	0	1 (1)	0	1 (3)	0	0	1 (2)	3 (1)
Diarrhea	0	0	0	0	1 (3)	0	1 (2)	2 (1)
Dyspepsia	0	0	1 (3)	0	0	0	1 (2)	2 (1)
Increase in lipase level	0	1 (1)	1 (3)	0	0	0	0	2 (1)
Adverse events during treatment that occurred in ≥5% of total participants								
Nausea	8 (11)	10 (14)	6 (18)	12 (36)	6 (17)	21 (60)	28 (45)	91 (27)
Covid-19	14 (20)	13 (19)	4 (12)	6 (18)	6 (17)	12 (34)	15 (24)	70 (21)
Decreased appetite	6 (9)	9 (13)	6 (18)	8 (24)	4 (11)	11 (31)	18 (29)	62 (18)
Diarrhea	8 (11)	6 (9)	4 (12)	4 (12)	7 (20)	7 (20)	9 (15)	45 (13)
Vomiting	1 (1)	2 (3)	4 (12)	4 (12)	2 (6)	9 (26)	12 (19)	34 (10)
Constipation	2 (3)	5 (7)	5 (15)	2 (6)	4 (11)	4 (11)	10 (16)	32 (9)
Fatigue	3 (4)	3 (4)	4 (12)	2 (6)	1 (3)	3 (9)	6 (10)	22 (7)
Early satiety	4 (6)	3 (4)	1 (3)	1 (3)	0	2 (6)	6 (10)	17 (5)
Increase in lipase level	2 (3)	2 (3)	3 (9)	2 (6)	1 (3)	2 (6)	5 (8)	17 (5)

Adverse events of special interest§								
Hypersensitivity	2 (3)	7 (10)	1 (3)	2 (6)	3 (9)	7 (20)	8 (13)	30 (9)
Antidrug antibodies during treatment¶	1 (1)	3 (4)	4 (12)	5 (16)	5 (16)	2 (6)	11 (18)	31 (9)
Hyperesthesia or related adverse event	1 (1)	1 (1)	2 (6)	2 (6)	1 (3)	5 (14)	8 (13)	20 (6)
Cardiac arrhythmia‖	2 (3)	3 (4)	0	2 (6)	0	5 (14)	7 (11)	19 (6)
Hepatic disorder	2 (3)	5 (7)	1 (3)	0	1 (3)	2 (6)	2 (3)	13 (4)
Biliary disorder**	0	0	0	0	1 (3)	2 (6)	0	3 (1)
Severe gastrointestinal adverse event	0	0	0	1 (3)	1 (3)	1 (3)	4 (6)	7 (2)
Injection-site reaction	0	1 (1)	0	1 (3)	0	1 (3)	5 (8)	8 (2)
Major depressive disorder or suicidal ideation	1 (1)	0	0	0	0	0	0	1 (<1)
Renal event	1 (1)	1 (1)	1 (3)	0	0	1 (3)	0	4 (1)
Major adverse cardiovascular event††	0	2 (3)	0	0	0	0	0	2 (1)
Pancreatitis††	0	0	0	0	0	0	1 (2)	1 (<1)

* Safety end points were analyzed with data from all the participants who underwent randomization and took at least one dose of retatrutide or placebo. Covid-19 denotes coronavirus disease 2019.

† An external committee of physicians was responsible for determining whether any death that occurred during the trial was cardiovascular-related; the single death in this trial was adjudicated as undetermined. The death (from drowning) was assessed by the site investigator as not related to retatrutide.

‡ Adverse events that led to discontinuation in two or more participants are shown here.

§ With the exception of antidrug antibodies, the 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.

¶ Data on antidrug antibodies were not available for 10 participants (2 in the placebo group, 1 in the 1-mg group, 1 in the 4-mg group with an initial dose of 4 mg, 3 in the 8-mg group with an initial dose of 2 mg, 1 in the 8-mg group with an initial dose of 4 mg, and 2 in the 12-mg group).

‖ This category includes supraventricular arrhythmias and cardiac conduction disorders.

** This category includes cholecystitis (in one participant), and cholelithiasis (in two participants).

†† These events were confirmed by an independent clinical end-point committee. Adverse events of special interest that did not occur in any participants are described in the text.

the end of the treatment period is provided in Table S15.)

DISCUSSION

In this phase 2 trial involving persons with obesity, treatment with the 12-mg dose of retatrutide, a GIP–GLP-1–GCG receptor triple agonist, resulted in a mean weight reduction of 24.2% after 48 weeks. Furthermore, participants who were receiving retatrutide continued to lose weight until treatment was stopped at 48 weeks, and the trajectory of the weight-reduction curves indicated that a plateau had not yet been reached (Figs. 1A and 2). Data are lacking from randomized clinical trials of 1 year or less in duration reporting this degree of weight reduction with antiobesity pharmacotherapeutics.[17,18] The safety and side-effect profile of retatrutide was similar to that observed with GLP-1 and GIP–GLP-1 receptor agonists.[3,4]

Nutrient-stimulated hormone-based pharmacotherapeutics target endogenous mechanisms that regulate body-fat mass and energy homeostasis.[8] We speculate that the efficacy of GLP-1 or GIP–GLP-1 agonism may be enhanced in combination with GCG receptor activation, which may augment effects on energy intake, substrate utilization, and energy expenditure.[12] All the participants treated with retatrutide at a dose of 8 mg or 12 mg in this trial had a weight reduction 5% or more (Fig. 1B), the current minimum threshold for efficacy.[19] With the 12-mg dose of retatrutide, more than 9 of 10 participants lost 10% or more of their baseline weight, nearly two thirds lost 20% or more, nearly half lost 25% or more, and a quarter lost 30% or more. This is an unusually high magnitude of efficacy as compared with findings in clinical trials of other antiobesity agents, although it has been observed with bariatric–metabolic surgery.[20,21] These results may prompt reconsideration of whether a weight reduction of 5% or more[19] remains an optimal goal for obesity treatment or whether treatment goals should be reevaluated within the context of the magnitude and quality (i.e., in terms of body composition) of weight reduction, specific BMI or percentage body fat targets (rather than percentage weight change), and health effects. Given that the participants were continuing to lose weight at the end of the trial, we speculate that greater weight reductions may be observed in the longer-duration phase 3 trial (ClinicalTrials.gov number, NCT05882045), as has been observed in trials of other highly efficacious agents.[3,4]

Most of the participants who received retatrutide lost a substantial amount of weight, although, as expected, there was individual variability, given the heterogeneity of obesity.[18] Because predictors of response are important but have been elusive, we investigated prespecified subgroups based on baseline BMI and sex. Participants with a BMI of 35 or higher had a greater mean percentage weight reduction with retatrutide than did those with a BMI of less than 35. With the 8-mg dose (initial dose, 4 mg) and the 12-mg dose of retatrutide, the mean weight reduction among participants with a BMI of 35 or higher was 26.5% and 26.4%, respectively, as compared with 21.3% and 21.5% among participants with a BMI of less than 35. In these same dose groups, women had a higher mean weight reduction than did men (28.5% and 26.6% vs. 19.8% and 21.9%). Whether these observations are attributable to sex-dependent differences in body composition, adipose distribution, or hormonal milieu remains to be determined. Because post hoc analyses of several studies of GLP-1 receptor agonists showed greater weight reductions among female than among male participants,[22,23] sex differences were considered during the design of this trial, with intentional inclusion of approximately equal numbers of men and women. We note that the inclusion of approximately equal percentages of men and women may have dampened the efficacy results of this trial as compared with those that have enrolled higher percentages of women (67 to 78%).[3,4,24]

Weight reductions among the participants who received retatrutide were accompanied by improvements in cardiometabolic measures, including waist circumference, systolic and diastolic blood pressure, and glycated hemoglobin, fasting glucose, insulin, and lipid levels (with the exception of HDL cholesterol). In addition, 72% of the participants who had prediabetes at baseline reverted to normoglycemia with retatrutide treatment. Several factors were likely to have contributed to these observations, including the substantial degree of weight reduction, the ratio of receptor activation for GCG relative to GIP and GLP-1, and the physiological role of glucagon beyond the historically investigated

counterregulatory response to hypoglycemia (i.e., glucagon secretion in response to protein ingestion,[25] decreases in meal size,[26] and increases in energy expenditure[27,28]). Reductions in the low-density lipoprotein cholesterol level of approximately 20% with retatrutide may reflect the effects of glucagon agonism on PCSK9 (proprotein convertase subtilisin/kexin type 9) degradation.[29] Ongoing trials are investigating whether treating obesity with highly effective pharmacotherapeutics results in reductions in cardiovascular events.[30,31]

The safety profile of retatrutide was consistent with reported phase 1 findings in persons with type 2 diabetes[13] and similar to those of therapies based on GLP-1 or GIP–GLP-1 for the treatment of type 2 diabetes or obesity.[3,4] Transient, mostly mild-to-moderate gastrointestinal events were the most frequently reported adverse events, occurring primarily during dose escalation. The frequency of these adverse events was higher in the 8-mg and 12-mg dose groups than in the other dose groups and was higher among participants who received an initial dose of 4 mg than among those who received an initial dose of 2 mg. Further refinement of the dose-escalation scheme for phase 3 trials may improve the side-effect profile. Glucagon and GLP-1 can exert positive chronotropic and inotropic effects on the heart.[32,33] The heart rate increased with retatrutide treatment in a dose-dependent manner, peaking at 24 weeks, followed by a decline at 36 and 48 weeks; the increases were similar to those reported for GLP-1 receptor agonists.[33] Cases of altered or enhanced skin sensation were mild to moderate in severity and did not lead to discontinuation of treatment; these events did not appear to be related to the magnitude or rate of weight loss.

The strengths of this trial include its extended-duration phase 2 design, which provided outcomes up to 48 weeks of treatment; the approximately equal percentages of men and women in the trial population; a sample size adequate to allow exploration of the effects of treatment on cardiovascular risk measures; and a trial population with 35% of the participants identifying as Hispanic or Latino. Limitations of the trial include the racial and geographic homogeneity of the sample (United States only and majority White). Because only 4% of the participants had overweight (in this trial, a BMI of 27 to <30) plus an obesity-related condition, the results may not be generalizable to this population.

In this phase 2 trial, once-weekly treatment with retatrutide resulted in substantial weight reduction at 24 and 48 weeks, with dose-dependent efficacy. The results warrant further investigation in the planned phase 3 trial to inform the efficacy and safety of retatrutide for the treatment of obesity.

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

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